Andres Costa ♦ Eugenio Villalba
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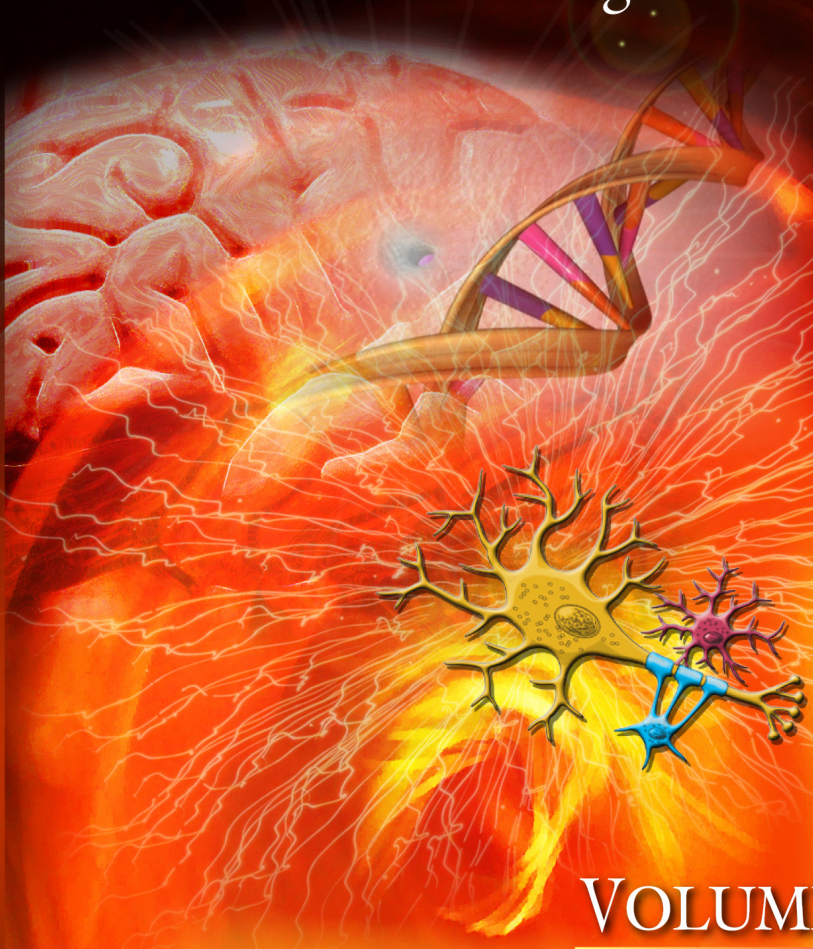

VOLUME 39

HORIZONS IN NEUROSCIENCE RESEARCH

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VOLUME 39

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HORIZONS IN NEUROSCIENCE RESEARCH

VOLUME 39

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AND
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CONTENTS

PREFACE

Horizons in Neuroscience Research. Volume 39 first presents a study wherein the gravitational noise of the brain at different ages within the same family was studied by gravitational mass spectroscopy.

The authors explore the resources for community integration for individuals that have acquired a traumatic brain injury, highlighting areas that need further investigation.

In a subsequent study, the gravitational mass spectroscopy method was used for the fast diagnosis of human brain states at long-range order.

Various routes for ischaemic stroke management are also discussed, including hyper acute management, acute management and long-term management.

Continuing, the newer technologies and approaches currently being applied in the field of neurosurgery are reviewed.

The authors summarize the reported cases and observational studies regarding nonconvulsive status epilepticus in neurosurgical subspecialties of emergency and perioperative care, cerebrovascular diseases, neurotrauma, brain tumor, and stereotactic and functional neurosurgery.

The associations between different brain inflammatory mediators and epileptogenesis are explored in an effort to affirm the idea that targeting the inflammatory pathway may be an effective therapeutic strategy to prevent or treat epilepsy.

The major issue in glycemic control in neurocritical care patients is addressed: tight glycemic control using intensive insulin therapy is associated with higher rates of hypoglycemia without an improvement in survival rate. On these bases, adequate nutrition before and during insulin infusion is recommended.

This compilation goes on to discuss evoked potentials, electrical responses of the brain to light, sound, or electrical stimuli. Depending on the type of stimulus, they emerge as visual, auditory, or somatosensorial evoked potentials.

Chapter 1 - The gravitational noise (GN) of the brain of different ages of the same family was studied by gravitational mass spectroscopy (GMS). The signals from the mass concentration of atomic nuclei clusters were selected in the mass range from 200 Daltons (Da) to 3.4 billion Da. The authors analyze the dynamics of tubulin coils oscillations inside the tubulin nanotubes and albumin coils connecting by cytolinker Cas2L1 and MACF1, as well as HDAC6 involved in the formation of nanotubes. Age-related differences were found in the cytoskeletons of the right and left parts of the brain inside the member of one family (2 ... 67 years old). Quick diagnostics of long-range order (LRO) in the cytoskeleton of some parts of the brain at the level of its domain (molecular clusters, domains, micelles and super micelles) constructs was proposed. An understanding of the forced change in LRO in the brain by artificial GN was given.

Chapter 2 - The gravitational mass spectroscopy method (GMS) was used for the fast diagnostic (10 s) of human brain states at long-range order (LRO, molecular mass range from 200 to 3E9 Daltons). Gravitational noises (GN) from the right, left and small brains of probants of 11, 41, 67 and 69 years old (grandson, son, grandfather and grandmother) were studied in the area of tubulin oscillations, cytolinkers (Gas2L1, MACF1) and herpes simplex virus type 1 (HSV-1, plasmid). A different structure of GN was found on the right and left spheres of the brain by both probants, as well as on the cerebellum. The fundamental possibility of analysis, according to the GN data, of the domain structure inside the brain cytoskeleton and the effect of surgical intervention on it and viral infections was proven. A correlation was found between the long-range order (LRO) at the molecular domains

level and conformational changes in some protein coils/domains that bind tubulin nanotubes to actin. The mechanism of destruction of tubulin nanotubes by virus plasmid attack was discussed.

Chapter 3 - In the current chapter the authors explore the options and resources for community integration for individuals that have acquired a traumatic brain injury (TBI). The goal of this chapter is to evaluate community integration resources and influences to highlight what is being done well and areas that need further investigation. Traumatic brain injuries can result in lifelong difficulties in areas of mental health, cognition, physical ability, and more. The term TBI lacks specificity as the injuries are typically measured on a continuum of severity from mild, moderate, to severe. Recovery rates, similar to all other aspects of TBI, vary by degree of severity. Given the major impact of TBI, it is important to assess the opportunities available for successful community integration after injury.

Community integration can be broken down to three main components: social integration, return to productivity, and independence. Social integration is considered to be the most important component of community integration. Despite the benefits of social support, researchers have shown that individuals with a TBI do not get adequate social support. Social support has been shown to have a significant positive impact on engaging in various health behaviors, specifically, for engaging in physical activity. Physical activity has shown to provide many benefits to this population and may provide an opportunity to encourage community engagement by the individual with a TBI and their various support systems. Informing individuals about social support resources and opportunities can help to further promote community integration following a TBI. Returning to work or school and independence following injury are also important components of community integration after injury. Researchers have suggested that an individualized approach is most effective for preparing individuals to engage in these various activities within the community. More research is needed to determine how to effectively generate a comprehensive rehabilitation program to impact all areas of community integration. Additionally, programs are needed to continue enhancing community integration efforts after individuals have been discharged from rehabilitation programs.

Individuals with TBI can live a productive and satisfying life when provided with effective programming and resources.

Chapter 4 - In this chapter, the various management of ischaemic stroke will be discussed. The management of ischaemic stroke can be divided into hyper acute management, acute management and long term management of stroke. In addition, the updates of hyperacute management of acute ischaemic stroke such as thrombolysis with intravenous alteplase and mechanical thrombectomy will be discussed. The acute management in stroke unit is also very important. The control of blood pressure is essential. A multidisciplinary team consisting stroke neurologists, rehabilitation doctors, physiotherapists, occupational therapists, speech therapists, dietitians and staff nurses, is essential in the management of stroke. Moreover, the long term management which includes rehabilitation and follow-up in clinics will be discussed. The identification and optimization of vascular risk factors, such as atrial fibrillation, diabetes mellitus, hypertension and hyperlipidaemia, need to be emphasized.

Chapter 5 - As the scientists continue to make new innovations with each passing day,wider coverage of information technology, better imaging techniques, use of neuro-navigation and more refined surgical instruments now allow the operating surgeons to attempt surgeries and approaches which were not possible earlier. In this article, the authors attempt to review the newer technologies and approaches being applied in the field of neurosurgery and which have the potential to cause major changes in the treatment of neurosurgical illnesses.

Chapter 6 - Nonconvulsive status epilepticus (NCSE) is a clinically cumbersome entity to cope with; however, accumulating cases suggest that it is much more pervasive than previously considered. This may also apply to neurosurgical cases, wherein common operative procedures, such as craniotomy or transient placement of subdural grid electrodes, are now regarded as potential candidates for NCSE. These cases, while few in number, raise questions about the potential underdiagnosis of NCSE, which might have been left untreated merely because intracranial lesions could not be identified. Furthermore, given that the use of intracranial electrodes or devices is becoming popular through technological development, caution

must be practiced due to the potentially increased opportunities for NCSE. Although cutting-edge knowledge in the relevant field is currently limited to observational studies, basic knowledge on NCSE seems essential for neurosurgeons. This chapter summarizes the reported cases and observational studies of nonconvulsive SE in neurosurgical subspecialties of emergency and perioperative care, cerebrovascular diseases, neurotrauma, brain tumor, and stereotactic and functional neurosurgery. These papers strongly suggest the importance of obtaining relevant knowledge and making an accurate diagnosis of NCSE in the neurosurgical setting.

Chapter 7 - Epilepsy is considered one of the major serious chronic neurological disorders, characterized by recurrent seizures. It is usually associated with history of lesion in the nervous system. Irregular activation of inflammatory molecules in the injured tissue is an important factor in epilepsy development. Although, it is unclear how the imbalanced regulation of inflammatory mediators contribute to epilepsy. So, recent goal in research is the identification of interconnected inflammation pathways which may develop epilepsy. *The available drugs for epilepsy treatment have low effect and high adverse effects*. So developing recent drugs which modulate epilepsy through recent mechanisms other than the traditional is a must. Alternative therapies and diet have recently reported positive outcome in epilepsy treatment. So the aim of this chapter is to review the associations between different brain inflammatory mediators and epileptogenesis, to strengthen the idea that targeting inflammatory pathway may be another effective therapeutic strategy to prevent or treat epilepsy.

Chapter 8 - Diabetes-induced hypoglycemia occurs because of inadequate insulin therapy. It is the main factor leading to brain biochemical dysfunctions, and neuronal death or oxidative damage-associated cognitive impairment. Some consistent evidences have shown that calcium plays a vital role in reducing the risk of diabetes and some neurological disorders have been implicated in dysregulation of Ca^{2+} homeostasis, and negatively affect high-affinity Ca^{2+} transport ATPase which plays a crucial role in controlling cytosolic Ca^{2+}. Besides, studies on the activity of enzymes, including ATPase enzyme have demonstrated changes in their actions when Ca^{2+} homeostasis is dysregulated. The impact of this dysregulation event on

ATPase enzyme activity has been implicated in neurotoxicity and are possibly related to the pathogenesis in some clinical disorders. Currently, the major issue in glycemic control in neurocritical care patients is that tight glycemic control using intensive insulin therapy is associated with higher rates of hypoglycemia without an improvement in survival rate. On these bases, some authors have recommended adequate nutrition before and during insulin infusion. In fact, conventional pharmacotherapies have been associated with hypoglycemic state in old adult patients. However, the molecular metabolisms of these conventional drugs are still unclear. Therefore, it is necessary to carry out studies that could explain the molecular metabolisms of this common drugs that offer new treatment alternatives with trace elements for diabetic population as is described in this document.

Chapter 9 - Evoked potentials are electrical responses of the brain to light, sound, or electrical stimuli. Depending on the type of stimulus, they emerge as visual, auditory, or somatosensorial evoked potentials. Visual evoked potentials (VEPs) are electrophysiological signals taken from the electroencephalographic activity of the visual cortex and recorded the scalp over the cortex. VEPs depend on the functional integrity of the visual pathways at any level including optic components of the eyes, retina, optic nerve, optic chiasm, optic radiations, and the visual cortex. On the pattern VEP recordings, 3 main components are observed which are called N75, P100 and N145. There are two types of recordings, known as pattern VEP and flash VEP. The presence of dopamine in the inner plexiform layer of the retina in mammals including humans and the fact that dopamine is not known to be an important transmitter anywhere in the visual system except for the retina, suggests that VEP abnormality is of retinal origin. Factors affecting VEP latency and amplitude include inflammation, hypoxia, and atherosclerosis. The authors have several publications on this topic on different groups of patients. This chapter of the book was intended to be written in order to explain and comment on the authors' studies as well as the others on the definitions, types, recordings, waves, commenting normal and abnormal responses. Physiology and the pathophysiological mechanisms underlying abnormal VEPs will also be discussed.

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Chapter 1

NEW FAST NON INVASIVE DIAGNOSTIC OF HUMAN BRAIN AT MOLECULAR LEVEL: BRAIN TREATMENT

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ABSTRACT

The gravitational noise (GN) of the brain of different ages of the same family was studied by gravitational mass spectroscopy (GMS). The signals from the mass concentration of atomic nuclei clusters were selected in the mass range from 200 Daltons (Da) to 3.4 billion Da. We analyze the dynamics of tubulin coils oscillations inside the tubulin nanotubes and albumin coils connecting by cytolinker Cas2L1 and MACF1, as well as HDAC6 involved in the formation of nanotubes. Age-related differences were found in the cytoskeletons of the right and left parts of the brain inside the member of one family (2 ... 67 years old). Quick diagnostics of long-range order (LRO) in the cytoskeleton of some parts of the brain at the level of its domain (molecular clusters, domains, micelles and super

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micelles) constructs was proposed. An understanding of the forced change in LRO in the brain by artificial GN was given.

Keywords: brain, domains, tubulins, Cas2L1, MACF1, HDAC6, *in vivo*, GMS method, gravity

1. INTRODUCTION

Previously, we have shown that molecules as ensembles of atomic nuclei, secondary and higher structures LRO in polymers (domain concentrations) and clusters in liquids are formed under the influence of local GN that are resulted from gravitational fluctuations in the sun system and in our galaxy [1…4].

Clusters of atomic nuclei (ANC) in biological tissues generate neutrino fields, halos, whose intensity is proportional to the dynamics of movement of the ANC. The more intense the movement of ANC, the stronger and more pronounced their signals are in the bio field, such as the brain [2]. This discovery has become a platform for creating a quick non-invasive method for diagnosing the LRO of the human brain after glioblastoma surgery [2], as well as *in vivo* operation of the heart muscle [3] at the level of domain interaction of myosin heads with those of actin. It was of interest to understand the dynamics of the development of LRO at the level of the domain structure of the cytoskeleton of the human brain of different age members of the same family. It was the aim of this work.

2. MATERIAL AND METHOD

As an object of study, the cytoskeletal structures of the human brain without pathologies were selected. The GN from the brain of 5 probants aged 2 to 67 years were studied. The gravitational sensor was located in the ear canal of the left and right ears of the probants and was applied to the occipital part in the area close to the small brain (cerebellum), Figure 1. A GMS

sensor recorded GN from ANC in the mass range from 200 Daltons to 3 billion Daltons. GMS spectra were obtained using the first Zubow equation [4], the Zubow force constant was taken for ANC in tubulin equal to 6.55E-15 N/m [4], positive Δf values were characteristic of expanded clusters and domains, they reflected the energy fraction of the domain in the entire ensemble of studied masses, negative values Δf reflected the same thing, but for the collapsed coils, Δf - the difference between the current value of f_t for time t and the average for the entire scan time f_{av}. The average mass of the ANC, $M_{GMS} = \sum \text{abs}(f \cdot m)$. Scan time 10 s. Figure 2 showed the GMS spectrum of GN from the brain in the right part of the probant 4, for understanding. Further, the studies focused on the areas of tubulin oscillations in nanotubes, the Gas2L1 domains (growth arrest-specific 2-like, https://en.wikipedia.org/wiki/GAS2L1), MACF1 (https://en.wikipedia.org/wiki/MACF1) linking nanotubes with albumin [5] and HDAC6. The high activity of tubulin indicates an abnormal cell division and growth, for example, in glioblastoma, and the dynamics of changes in the conformations of the binding domains about the imbalance of internal stresses and pressures in the brain cytoskeleton and, as a result, the loss of electrical signal conductivity via tubulin nanotubes. The latter is demonstrated in a loss of sensitivity (paralysis) of organs, impaired motor skills and coordination.

3. Results and Its Discussion

Consider the structure of GN emanating from the ANC dynamics in both parts of the brain, Figure 3. As can be seen, for all probes, GN in the right part of brain was much more intense and more diverse than in the left. Since the right half of the brain is an evolutionary continuation of the neural network of the intestine, GN activity in it should be understood precisely from these positions [6]. Almost all priorities of the right side of the brain are given to the process of controlling digestion and movement. With eyes closed, GN in the left part of brain was significantly weakened due to the absence of irritation factors. However, here was not all clear. It could be noted that with age, the GN spectrum was became simpler, that is, for logical

operations, the left side of the brain is trained and least needed, while young probants even in the “idle” mode of operation significant energy resources were necessary.

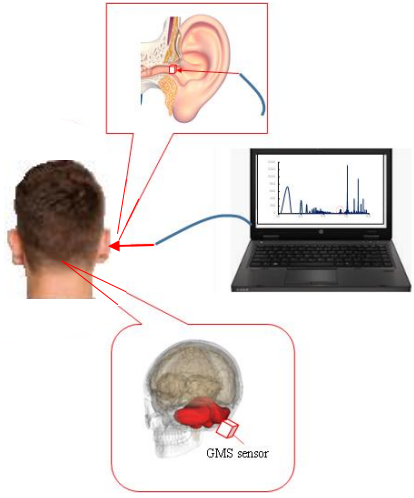

Figure 1. Schematic illustration of the GN scanning from the ANC in the cytoskeletal structure of the brain.

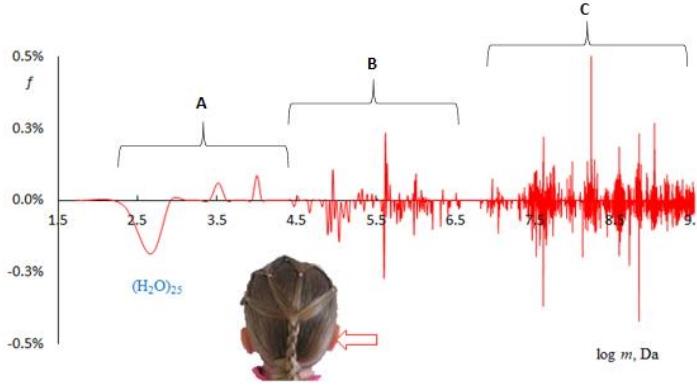

Figure 2. The GMS spectrum of the GN in the right ear of the probant 4. N = 4045, M_{GMS} = 1.016.267.413 Da, D_c = 72%. **A** is the region of oscillations of water clusters, solvate clusters of ion pairs of salts and ANC in biopolymers and in fats, **B** is the region of oscillations of domains, subdomains, and coils, **C** is the region of oscillations of sub micellar, micellar, and super micellar structures [4].

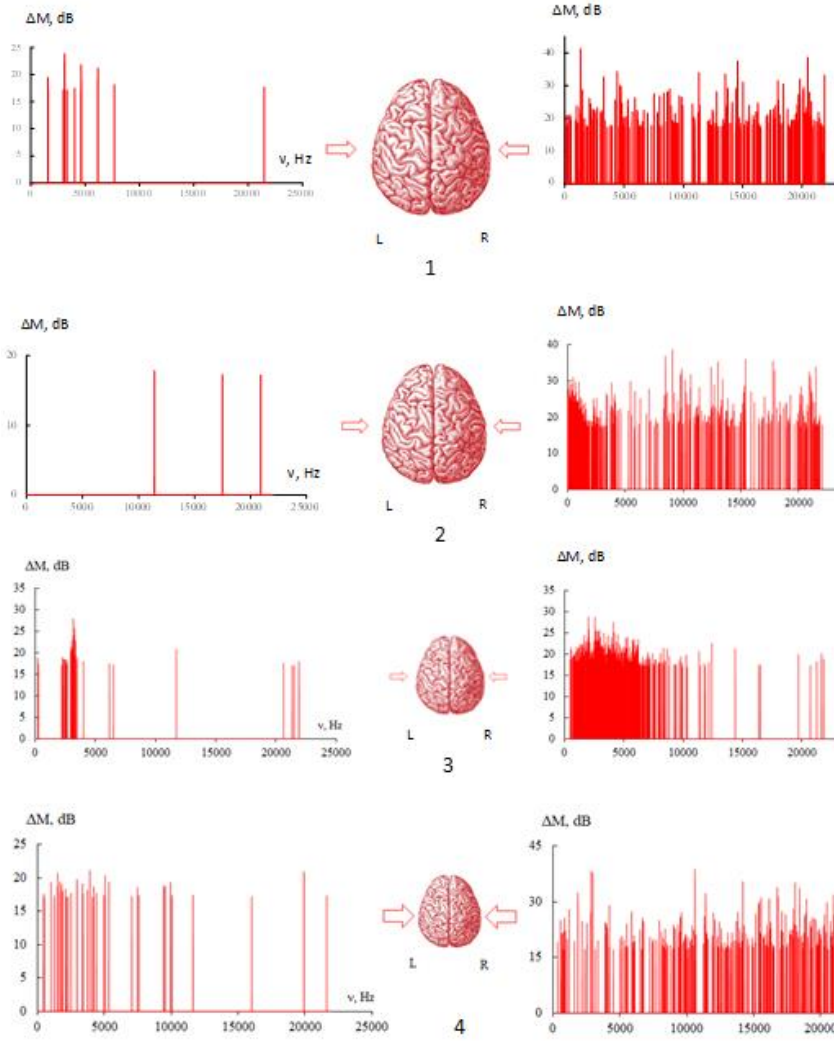

Figure 3. GN of both parts in a calm state (eyes closed): 1 - probant 67, 2 - probant 41, 3 - probant 11, 4 - probant 4. ΔM > 17.

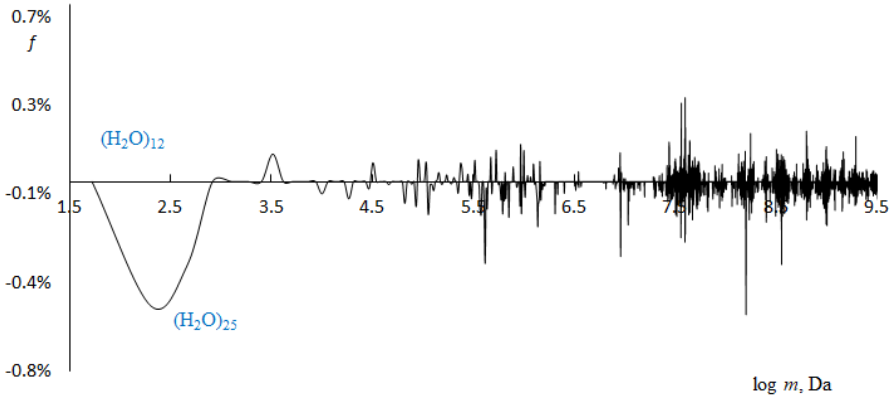

Figure 4. The GMS spectrum of the left (right was shown in Figure 2) part of the brain of probant 4. 1 - N = 3925, M_{GMS} = 973,821,108 Da, D_c = 74%.

When comparing the GMS spectra of the probants, differences in the activities (signal intensities) of the ANC in the left and right parts of head brain were revealed. So, in the area of small water clusters, cluster of 12 molecules [7] in the collapsed form was in the left brain part of probant 4 (Figure 4), while in the right, in collapses form there was only a cluster of water of 25 molecules. The latter indicated active restructuring processes in this part of the brain. In region **C** (Figures 2 and 4), the dynamics of micellar structures was similar, however it also requires special additional studies.

Figure 5 showed the GMS spectra of the brain of probant 11. In this case, the more intense signal from sub ensembles were visible than those of probant 4. However the dominance of certain small water clusters was different, in the left part of brain, collapsed structures consisting of 12 and 25 molecules were dominated. In the right brain were found of 12 water clusters in dense form only. In probant 11, as in probant 4, water clusters in the collapsed form were found in the brain. The intensities of oscillations of water clusters in probant 11 were much higher than in probant 4. Cluster $(H_2O)_{178}$ in collapsed conformation was found only in probant 11 in the right part. In regions **B** and **C**, the situation was more complicated and it required special additional research. In general, the average molecular mass of ANC in the both brain parts of both probants was directly opposite. In the 11-year-old probant in the left brain the value of $M_{GMS}10\%$ was higher than in the

right one, and in the 4-year-old probant vice versa. The concentration of dense ANCs (D_c, rich in potential energy) was the same and lie within ~ 70%.

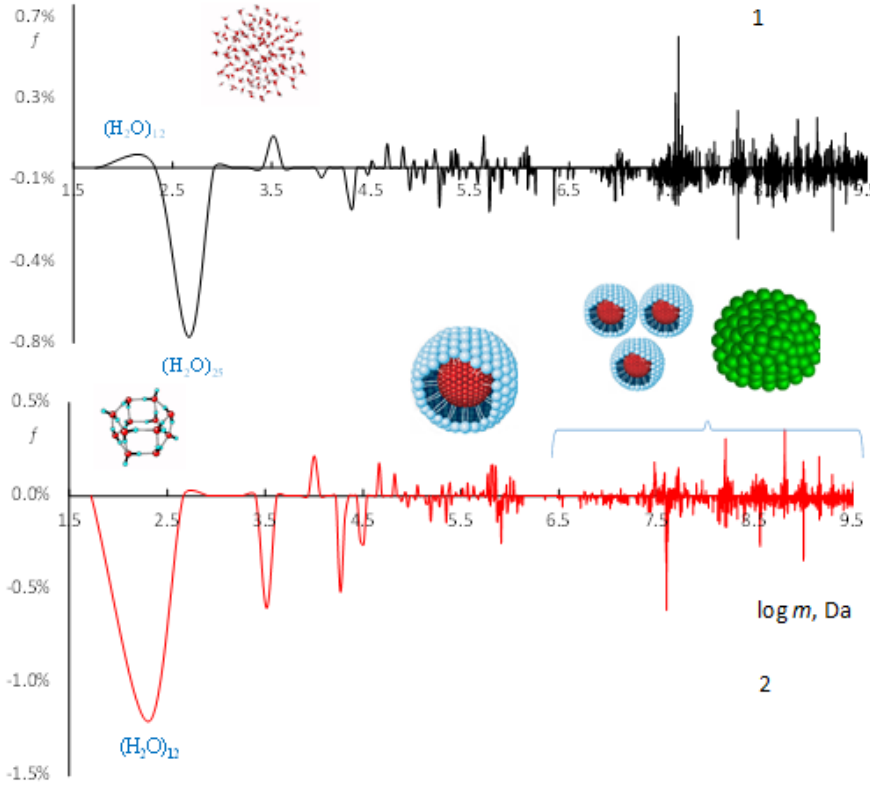

Figure 5. GMS spectra of the left (1) and right (2) parts of the brain of probant 11. 1- N = 3574, M_{GMS} = 1.015.696.815 Da, D_c = 69%; 2 - N = 3935, M_{GMS} = 942,092,933 Da, D_c = 70%. The area of micellar and super micellar structures (**C**) is indicated by a curly bracket. The water cluster model $(H_2O)_{12}$ was kindly provided by prof. Lenz [8]. A water cluster model $(H_2O)_{25}$ can be found here http://www1.lsbu.ac.uk/water/icosahedral_water_clusters.html.

The micellar structures were mainly represented by coil associations (dimers, trimers, etc.) that oscillated as a single spherical pendulums. The coil associations, in turn, formed the next generation of associates — micellar and super micellar structures. The latter formed the elements of

biological tissues that could be observed in optical microscopes in which the ANC are subjected to less energy impacts than in an electron microscope. Therefore, in the GMS method, passive observation of GN from super micellar structures reflected their real state in the cytoskeletons.

The GMS spectra of the brain of probant 41 in region **A** were different from younger probants (Figure 6). So, in the left part there was a clear equilibrium of collapsed-expanded in the conformations of the base water cluster in the cytoskeleton. In the right part, expanded structures dominated in this cluster wherein signals from a cluster of 25 molecules were absent in both parts of the brain. A large cluster of water of 178 molecules was in the brain of the probant only in the dense state (*-f*), and the M_{GMS} values in the left part are approx. 10% higher than in the right, but they were lower than in younger probants. In the brain, in general, the activity of collapsed ANC lie in the range of 75 ... 79%, which was higher than in young probants 4 and 11. In interval **B**, one could be separated strong differences in both parts of brain. So in the right, a number of unusual signals from dense structures were shown (marked by arrows), which were not expressed in the left or were represented by loose structures. Apparently, their appearance was somehow related to the physical load of the probant (15 minutes before the measurements).

Figure 7 showed the GMS spectra of GN in the brain of probant 67. Here could be notice the proximity of the basic parameters of the LRO in both parts of brain. The spectra were very similar. Some differences could be seen only in area **B**.

It was investigated the area in the spectra in which exhibits activity tubulin coil oscillations, tubulins involved in the formation and growth of nano tubes with a diameter of 25 nm. As could be seen from Figures 8, 9, and 10, young probants had active tubulin coils of the similar species, with masses 46,184 Da (https://de.wikipedia.org/wiki/Tubuline). At grandfather (probant 67, Figure 11), at least 2 types of tubulins with masses of 46,184 and 55,883 Da were already active. It could be also notice that in young probants (Figures 8, 9 and 10), both expanded and collapsed forms dominated in tubulin coils, and in different parts of the brain, dominance was the same. Differences were observed only in signal intensities. The

probants 11 and 41 had a clear dominance of expanded forms of coils (46,184 Da) in the right part over those in the left one. In contrary, at probant 4 had, the coils were represented mainly by collapsed forms. Such forms were inactive and indicated a slow cell division [9]. In this time, actually took place some retardation in the development of conversational probant 4, as a result of brain loading bilingual communication between parents.

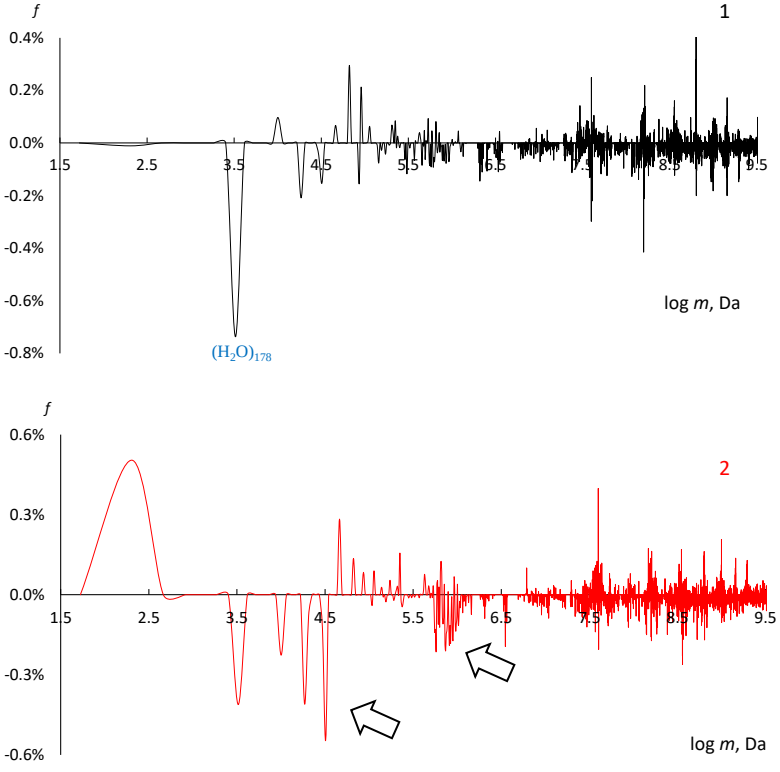

Figure 6. GMS spectra of the left (1) and right (2) parts of the brain of probant 41. 1 - N = 4512, M_{GMS} = 977,954,445 Da, D_c = 79%; 2 - N = 4491, M_{GMS} = 889,240,958 Da, D_c = 75%.

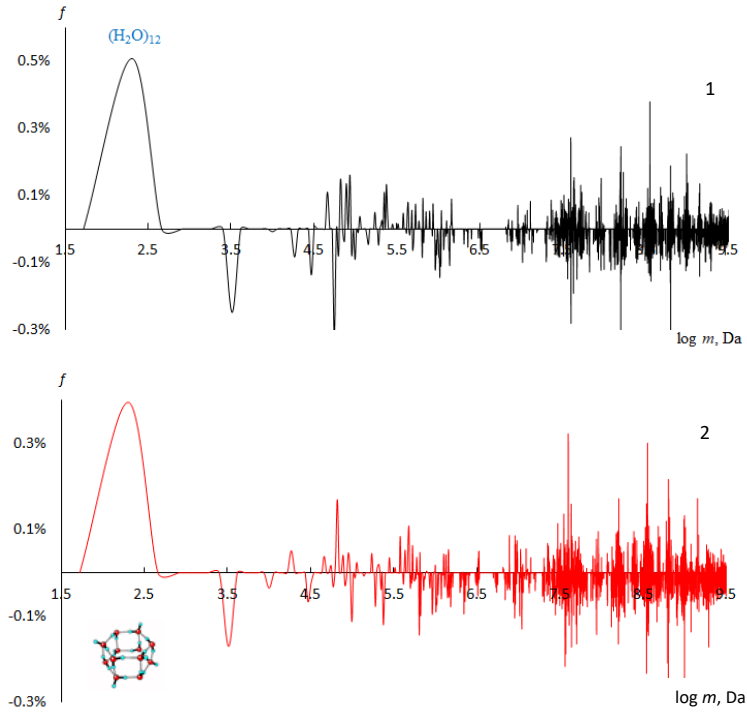

Figure 7. GMS spectra of the left (1) and right (2) parts of the brain of probant 67. 1 - N = 3623, M_{GMS} = 1,014,831,180 Da, D_c = 70%; 2 - N = 4037, M_{GMS} = 1,027,885,515 Da, D_c = 74%.

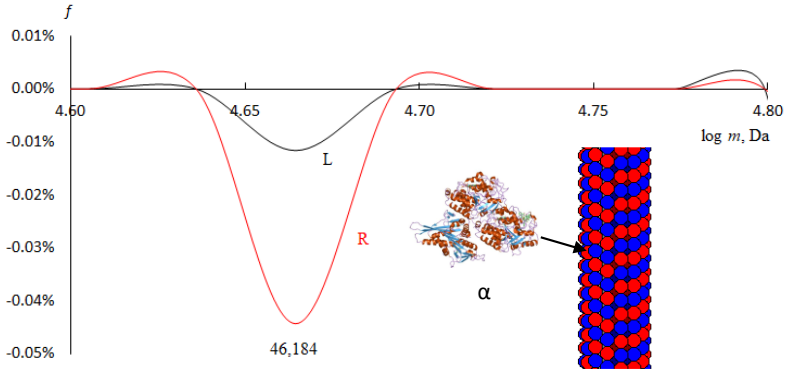

Figure 8. GMS spectra of the left (L) and right (R) parts of the brain of probant 4 in the area of tubulins oscillations. A model of a tubulin nanotube with identical coils and α - tubulin model were taken from: https://de.wikipedia.org/wiki/Mikrotubulus.

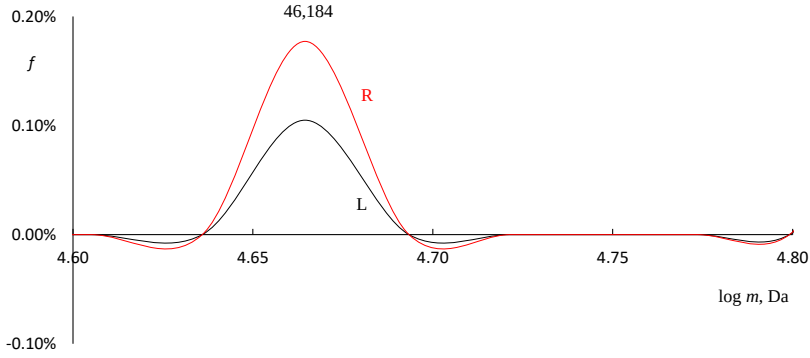

Figure 9. GMS spectra of the left (L) and right (R) parts of the brain of probant 11 in the area of tubulins oscillations.

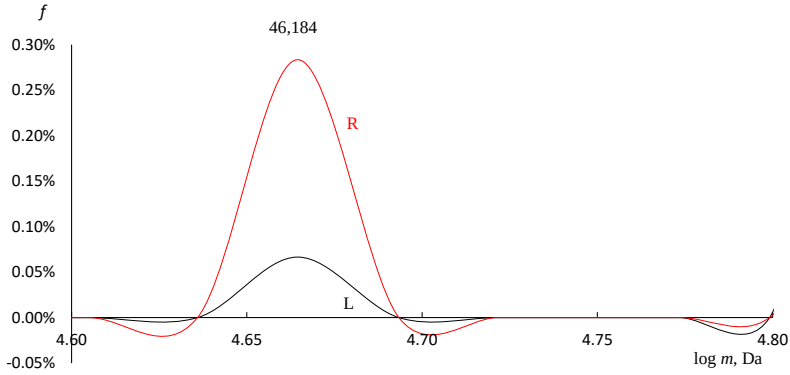

Figure 10. GMS spectra of the left (L) and right (R) parts of the brain of probant 41 in the area of tubulins oscillations.

It is believed that α- and β-tubulins have similar masses and form dimers from which the nanotubes are built using bundles of histone deacetylase HDAC6.

The appearance of probant 67 signals from coils in collapsed conformations with the masses 55,883 Da (Figure 11A), and only in the left part of brain was phenomenal, and may be indicative of a fundamentally new building the cytoskeleton in new forms of axons. It was difficult to attribute them to the processes of natural aging of the brain due to the higher masses of coils, which usually decrease during aging. The difference here was 9,699

Da. It should be noted here that probant 67 was exposed for 3 months to the inhabitants of the planet Uranus remotely (their dispatch satellite over probant 67), from the Earth orbit, while in the left part of the brain he recorded this effect in the form of constantly changing signals of different frequencies, which he understood as a forced rearrangement of the cytoskeleton [10] and preparation brain to the new working conditions of the probant as a pilot upon the arrival of guests on planet Earth (Figure 11B). It could be imagine the appearance of the signal 55,883 Da, as an attempt to rejuvenate the cytoskeleton of the brain, to prepare the probant 67 for active and healthy work with guests. A comparison of the spectra in Figures 11A and 11B revealed striking differences. So, the signals of tangles with masses of 49.362 Da disappeared, and the remaining 46.184 and 55.883 changed their conformations to the opposite. After that, the probant noted a significant improvement in his mental abilities. A certain harmony and calm reigned in the left part of the brain.

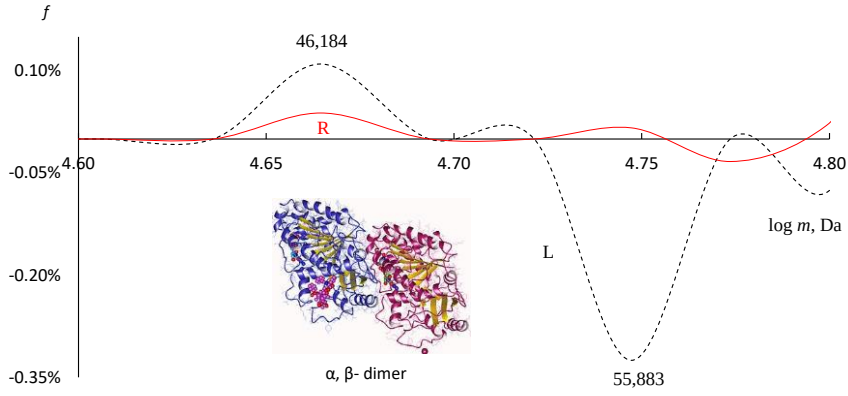

Figure 11A. GMS spectra of the left (L) and right (R) parts of the brain of probant 67 in the area of tubulin coil oscillations (after multi-frequency effects from August to November on the left side of the brain, 2019). The structure of α, β-dimer was taken from https://de.wikipedia.org/wiki/Tubuline.

The state of the brain cytoskeleton strongly depends on the quality of crosslinking of tubulin nanotubes with actin proteins of the MACF1 type (https://en.wikipedia.org/wiki/MACF1), [2]. The signals of MACF1 coils appeared in the GMS spectra in the mass area of $5.47 < \log m < 5.55$. They

reflected the totality of internal stresses in the cytoskeleton, the dynamics of its pathology and development. A brief look at the state of these coils in different brain parts of probants (Figures 12.... 15).

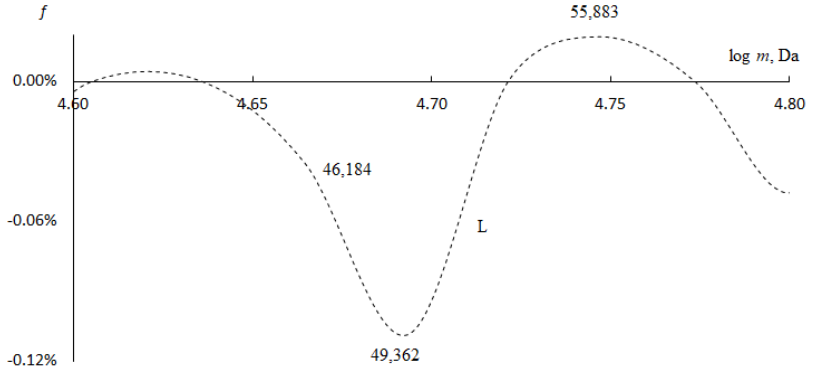

Figure 11B. GMS spectrum of the left (L) part of the brain (probant 67) in the area of tubulin coil oscillations (bevor multi-frequency effects on the left side of the brain, 2015).

In probant 4 (Figure 12) the state conformations MACF1 coils in both parts of the brain were very different. In the right part, there was no pronounced dominance of the collapsed or expanded MACF1 coil conformations. Here, apparently, the collapsed-expanded thermodynamic equilibrium took place, in which the oscillation signals from collapsed coils were mutually compensated from expanded or, most likely, there were simply no coils of MACF1 with masses of 304,485 Da.

In the left part, 2 types of signals were detected for the MACF1 masses 304,485 and 328,664 Da. Moreover, dense (*-f*) dominated in low molecular mass ANC, and expanded conformations (*f*) in high molecular mass ANC (coils). The low molecular mass MACF1 in collapsed form can be represented as an oscillator consisting of a coil of 328,664 Da, from which another, smaller oscillator with a mass of 24,179 Da (328,664 – 304,485 = 24,179) was isolated from the compression. Then, this will indicate the intensive processes of the stressful formation of the cytoskeleton of the left part, its domain structure. Probant 4, in fact, was very concerned about the constant stress at school.

In probants 11 and 67, signals of expanded coils of MACF1 with masses of 328,664 Da were detected and their condition in the cytoskeletons of the brain was identical. However, the MACF1 coil signals from probant 11 were more intense than from his grandfather, probant 67. Moreover the signals from low molecular mass coils of MACF1 304,485 Da in probant 11 were absent in both parts of the brain.

Signals MACF1 of 304,485 and 328,664 Da were reliably detected in probant 41 (Figure 14) in both brain cytoskeletons. Additionally, in the right part of brain they were weakly expressed, and in the left, on the contrary, strongly. It is also seen that the dominance of the collapsed forms of low molecular mass coils 328,664 Da in the left part significantly exceeded their dominance in the right one. This could be understood as a strong increase in internal tensions in the left cytoskeleton. Probant 41 was very concerned about something. The compression of the cytoskeleton led to the convergence of neurons, which means that the time for processing information decreased and thereby increase the efficiency of the brain.

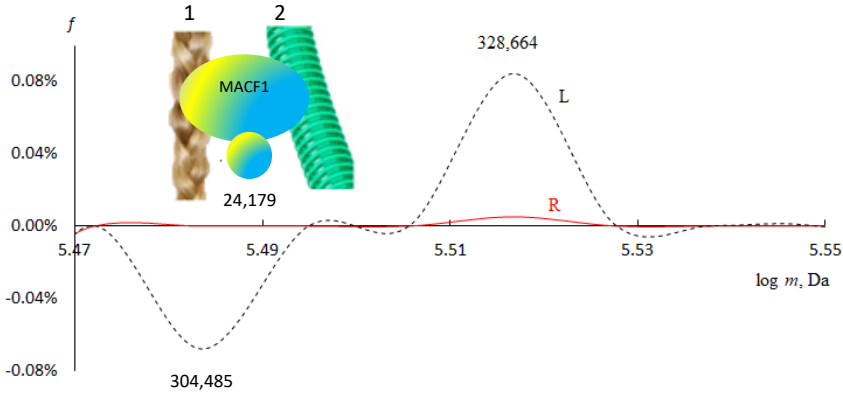

Figure 12. GMS spectra of the left (L) and right (R) parts of the brain of probant 4 in the area of MACF1 coils oscillations. For understanding, a model of the binding of actin (1) and tubulin nanotube (2) by a collapsed coil of MACF1 was presented.

The practical equality of the states of cytoskeletal cross-linking in probant 67 in both brain parts reflected the thermodynamic identity of the

cytoskeletons, their harmony, and the harmony of internal stresses. A similar situation was observed at probant 11, Figure 13.

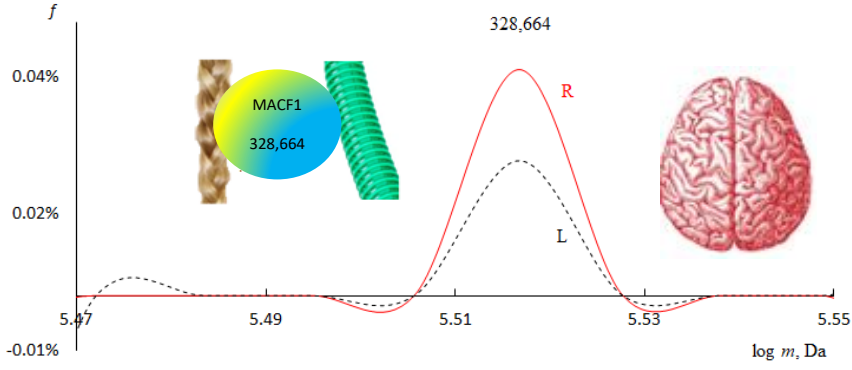

Figure 13. GMS spectra of the left (L) and right (R) parts of the brain of probant 11 in the area of MACF1 coils oscillations. The model of the both cerebral parts in the absence of stress of compression of the cytoskeleton by the collapsed conformations of MACF1 coils was given.

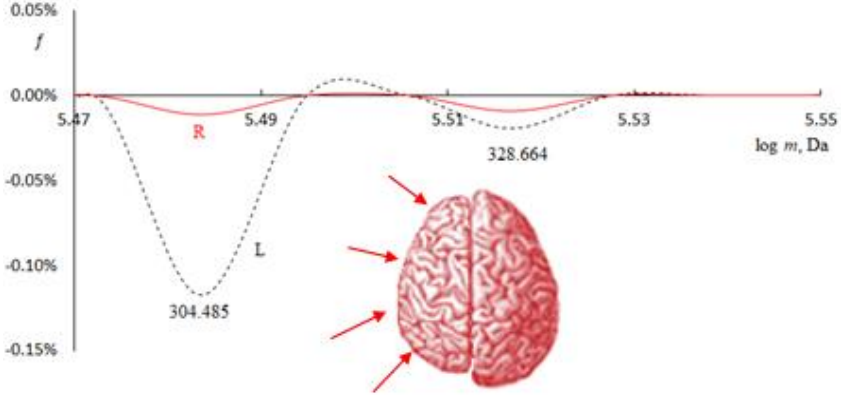

Figure 14. GMS spectra of the left (L) and right (R) parts of the brain of probant 41 in the area of MACF1 oscillations. A model of compression of the cytoskeleton of the left part as a result of the dominance of the collapsed coil conformations of MACF1 was given (stress, Figure 12).

Figures 16 and 17 showed the GMS spectra of the brain of 3 male probands of different ages in comparison (range ***B***, Figure 2). In addition,

each signal in the GMS spectrum of each probant was equal to unity abs(*f*) = 1 and here a search was made for new signals by subtracting the spectra of probants.

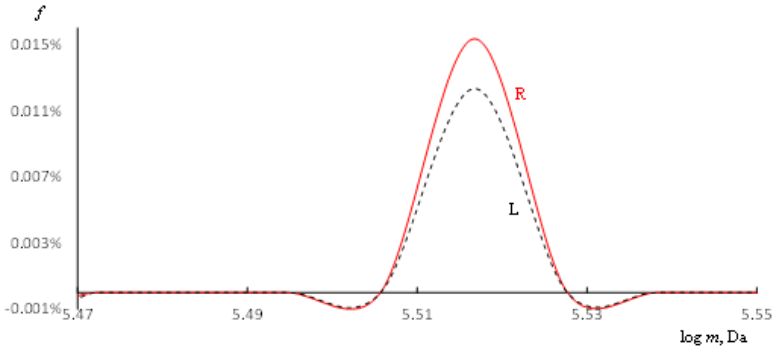

Figure 15. GMS spectra of the left (L) and right (R) parts of the brain of proband 67 in the area of MACF1 coil oscillations.

As could be seen from Figure 16, in comparison with his son, in his father's right part (Probant 41, ***A***) there were many distinctive signals from the new ANCs in the area log *m* > 5.3. But his son (probant 11, ***B***) also showed 7 ANCs signals that were absent from his father, probant 41. However, they were more or less evenly distributed in the range ***B***. The situation changed a lot when searching for new signals from probants 67 (***C***) and 41 (***D***). Probant 67 had 2 regions of new signals in the ranges 4.7 < log m < 5.0 and 6.0 < log m < 6.2, while probe 41 had only one region with log m > 5.2. For probants 67 (***E***) and 11 (***F***), one can notice a similarity with the appearance of new signals like for probants 67 (***C***) and 41 (***D***). Understanding the causes of this phenomenon will require new, deeper research.

Comparison inside the difference GMS spectra of the left and right parts of the brain (Figures 16 and 17) revealed strong differences only for probants 67-41 and 67-11. These spectra for 41–11 (***A***, ***B*** and ***G***, ***H***) were very close and, apparently, reflected the genetic proximity of the father and son. On the other hand (spectra ***I***, ***J*** and ***K***, ***L***) were radically different from all others. They contained signals at the grandson (probant 11) that were absent at his

grandfather (probant 67). This phenomenon could be understood as directed optimization in the development of the mental activity of the brain of probant 67, in it the ANC became inactive, which were not invaded and were not activated by its activity. In younger probants 11 and 41, on the contrary, they were active and demanded by their vital functions.

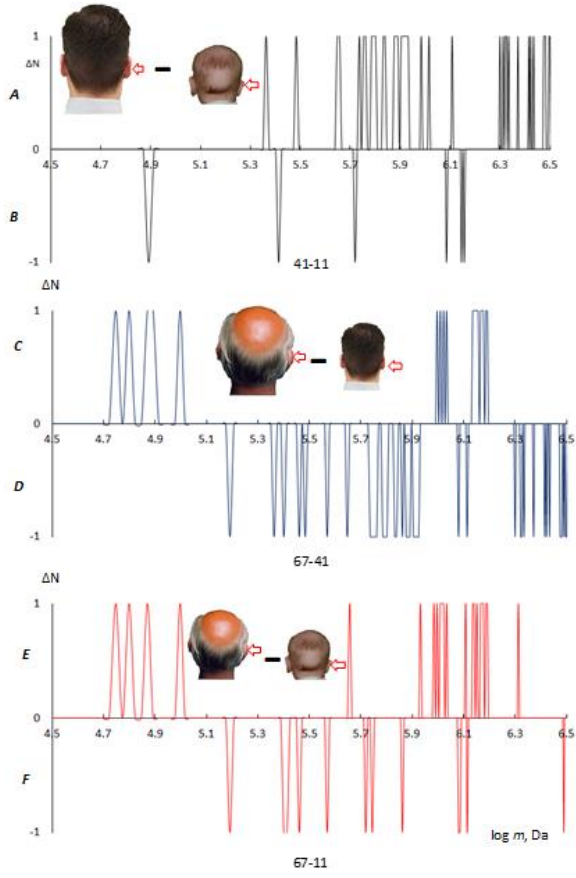

Figure 16. Differential GMS spectra of the right parts of the brain (**B** - the area of subdomains in coils and coil oscillations). 41-11 - father (41) and son (11); 67-41 - grandfathers (67) and son (41) and 67-11 - grandfathers (67) and grandson (11). Each signal was given a conditionally value 1. ΔN was the difference in the numbers of the GN probants signals; each signal in the GMS spectrum was taken as unity regardless of its intensity.

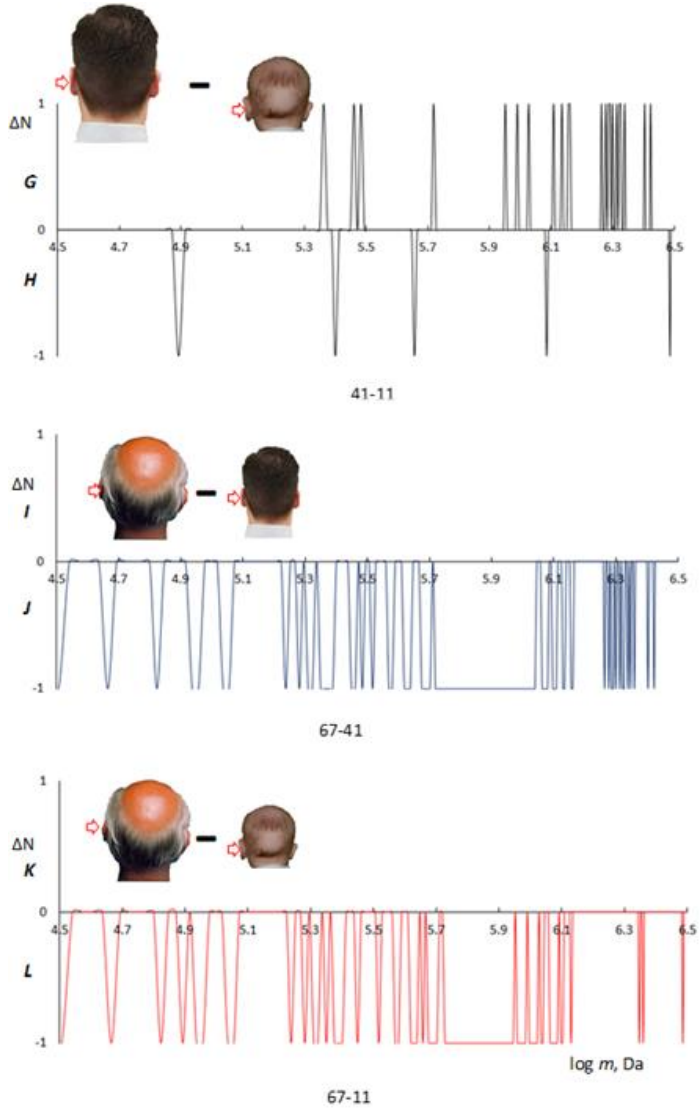

Figure 17. Differential GMS spectra of the left parts (**B** - the area of subdomains in coils and coil oscillations). 41-11 - father (41) and son (11); 67-41 - grandfathers (67) and son (41) and 67-11 - grandfathers (67) and grandson (11). Each signal was given a conditionally value 1. ΔN was the difference in the numbers of the GN probants signals; each signal in the GMS spectrum was taken as unity regardless of its intensity.

It was of interest to understand the quality of the nervous system of probants, for example, the speed of motility or the speed of thinking. The latter should depend on the quality of the tubulin nanotubes in the axons and dendrites (the minimum number of defects in the construction and, as a result, better conductivity of electrical signals). That is, the quality of nanotubes should depend on the quality of the process of their formation. In the process of nano tube growth, HDAC6 protein is involved. Figure 18 showed a model of deacetylation of HDAC6 α- and β-tubulin dimers on the flange during the formation and growth of a nano tube. According to this model, the coil of HDAC6 plays the role of packing dimers (like a working bricklayer) on the flange of a nano tube and its activity, its conformational state can give an answer both to the quality of its work and to the growth of nano tubes, Figures 19 ... 22.

Figure 19 showed a fragment of the GMS spectrum in which HDAC6 signals appear. One can see the differences in the number and forms of HDAC6 in both parts of the brain. In the right part of brain, this protein was represented by collapsed structures of 3 species, with masses of 128,441; 138,837 and 144,307 Da, but in the left one, 128,441 Da in a collapsed and one of 144,307 Da in an expanded state.

It can be assumed that in the right part 3-types of HDAC6 signals reflected their active work in the dendrite structures and axon ends (terminals) (https://en.wikipedia.org/wiki/Neuron). Probant 4 was young and protein activity (its conformation changes) in rapidly growing dendritic structures and axon ends in the right part required their dense state. Since the right part is an evolutionary continuation of the intestinal neural network [6], so the dense state of HDAC6 coils can be understood from these positions. Then, in the left part, HDAC6 with the mass of 144,307 Da, with high probability, worked in growing axons, and coils of HDAC6 with masses of 128,441 Da worked in growing dendritic structures of neurons. This conclusion was based on the diversity and growth rate of nano tubes in dendrites and end nano tubes in axons, https://de.wikipedia.org/wiki/Nervenzelle#/media/Datei:Complete_neuron_cell_diagram_de.svg.

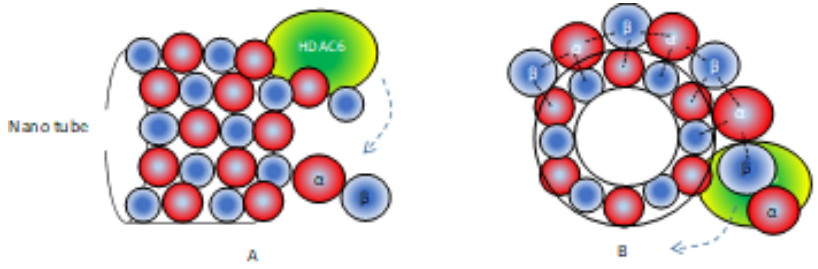

Figure 18. Model of nano tube flange formation by an HDAC6 coil packing tubulin dimers [11]. A - side view, B - top view, at the end of the nano tube.

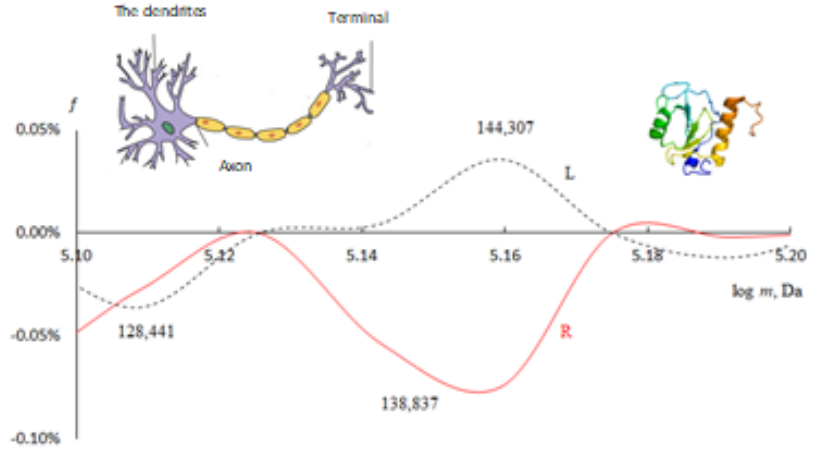

Figure 19. GMS spectra of the left (L) and right (R) parts of the brain at probant 4 in the area of histone deacetylase coil oscillations HDAC6 (https://en.wikipedia.org/wiki/HDAC6). Axon model took from https://de.wikipedia.org/wiki/Dendrit_(Biologie).

With age, the state of HDAC6 coils in the brain changed slightly. At probant 11 (Figure 20) did not found dominance of collapsed or expanded HDAC6 structures with a mass of 128,441 Da, both because of their low activity or, which was unlikely, the collapsed-expanded equilibrium. However, signals appeared from very active coils of HDAC6 in a collapsed state, with large masses of 155,314 Da. The activity of coils in an expanded conformation with masses of 138,837 Da was high in the left part of brain, and in the right, on the contrary, was weakened. HDAC6 were found here in

predominantly dense forms. Probant 11 was an active athlete, but his parents would like to see him as a mathematician and he was forced to do this science.

Father of probant 11, probant 41 is a professor of mathematics and an active athlete, his brain also does not show HDAC6 signals with masses of 128,441 Da, and in the left part of the brain the activity of dense forms of HDAC6 with masses of 144,307 and 155,314 Da was lower (Figure 21). At the same time, the signals from the expanded conformation of HDAC6 coils in the right part of the brain with masses of 138,837 Da were weaker than that at probant 11, but the other two types of coils in collapsed form coincided in character with those at son (144,307 and 155,314 Da). Apparently the coils with small masses of 128,441 Da worked at the ends of tubulin nano tubes in axon terminals, only at the initial stages of brain cytoskeleton development (probant 4).

At probant 67 (Figure 22 A), the character of HDAC6 activity in the right part of the brain was greatly reduced, especially in coils with masses of 138,837 Da. Only one species of HDAC6 with such masses was active in this part of the brain. In the left one can see signals from 2 types of HDAC6 coils with masses of 138,837 and 144,307 Da, dense structures also dominated here, as in the left part of the brain. A decrease in the diversity of active HDAC6 coils in probant 67 indicated stabilization of the development of the neural network of the brain, and high activity in the left cytoskeleton of the brain of the coils with these masses and active mental activity of probant 67 indicated about the normal harmonious formation of tubulin nano tubes in the axon and in dendritic structures of neurons, Figure 19. The result of the 3-month impact of the Uranus Inhabitants on the DP in the left hemisphere of the probant 67 GN was shown in Figure 22B. The spectrum was very similar to the spectrum of HDAC6 tangles in probant 4, Figure 19, except for the signal from dense tangles with masses of 138,837 Da. The mechanism of such an impact is now clear to us, but to implement it in practice, it will take many years to test.

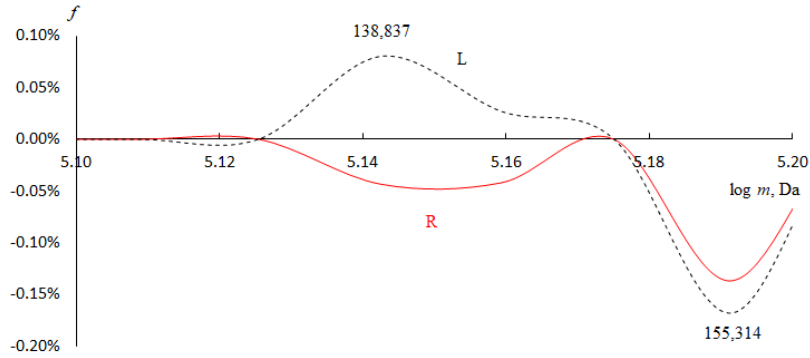

Figure 20. GMS spectra of the left (L) and right (R) parts of the brain at probant 11 in the area of HDAC6 coil oscillations [4, 5] (α-tubulin deacetylase). 175 kDa in [12], 150 ... 160 kDa in [13, 14] and 130 kDa in [15].

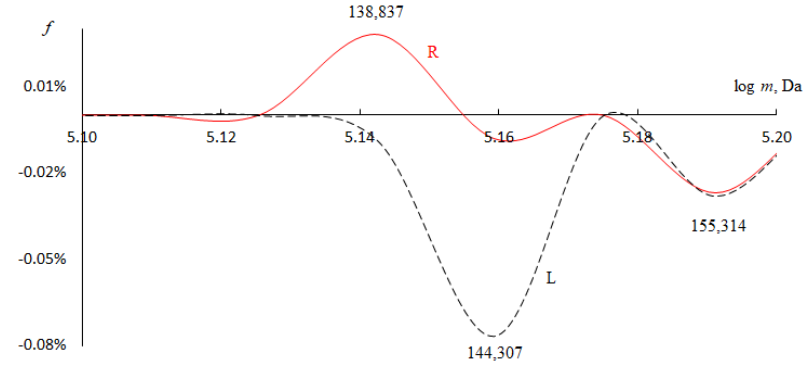

Figure 21. GMS spectra of the left (L) and right (R) parts of the brain of probant 41 in the area of HDAC6 oscillations.

Here it was found very important influence some factors on the process of artificial effects of GN on the brain. Quests, after completing the procedure of remote irradiation of the left part of brain (probant 67), performed a control scan of his nervous system at night, when he observed their spans and exchanged light signals with them. It was expressed in the initiation of very strong pain in the knee of the left leg for 1 hour. At the same time, very strong pains at the junction of the muscle with the bone joint caused forced movements of probant 67 (walking, twisting the body, etc.). This made it possible to fragmentarily register the passage of nerve impulses

in all parts of the body and, after integration, to obtain a complete picture of the quality state of the nervous system of the whole organism. Then the guests made it clear to the probant so that he would sit down and fix his left leg (wireless connection from brain to brain). After this, an impulse followed to a point 10 cm apart from the site of pain. The pulse lasted less than 20 ms (an order of time blinking eyes) and the pain gradually began to disappear. After 2 days, they completely disappeared. In our opinion, such a remote scan of the nervous system was possible only at night from a stationary orbit or with high-precision stabilization of a spacecraft at altitudes not lower than 100 km. Even earlier, the guests "punished" probant 67 for not getting in touch at the appointed time with a GN pulse in the small brain from a distance of about 150 km, paralyzing him for several minutes with animal fear, while the probant was fully conscious. The split of consciousness was short-lived, which was understood by him as the emission of fear hormones, which after 5 minutes were neutralized by the body.

Briefly dwell on age-related differences in the LRO of the cerebellar cytoskeleton. The cerebellum is responsible for motility and coordination of movements, for their accuracy, synchronization and learning movements. It can be involved in functions that reflect attention, the quality of the language, as well as the formation of fear and pleasure [16, 17]. In the GMS spectra are the ANC signals responsible for certain functions of motor activity.

In this work, we have chosen the activity and forms of HDAC6 participation in the formation of high-quality tubulin nano tubes (electrical impulse conductors) in neurons for probants of different ages. Figures 23 and 24 showed the GMS spectra of LRO in the small brain of probants in the area of HDAC6 oscillations. It notice strong differences in the conformations of this coil of all patients. Only at probant 67, the intensity of oscillations of coils in both forms was more than 2 times higher than that of other probants. He also showed the presence of HDAC6 signals with the smallest masses. At probants 11 and 41, 3 type of HDAC6 coils were detected, in the others, only 2 were reliably.

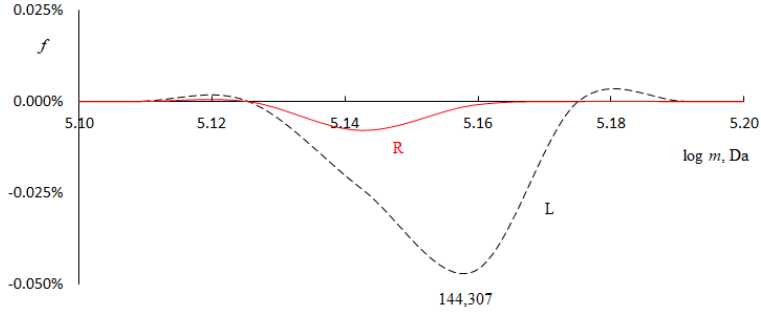

Figure 22A. GMS spectra of the left (L) and right (R) parts of the brain (probant 67) in the area of HDAC6 coil oscillations (after multi-frequency effects from August to November on the left side of the brain, 2019).

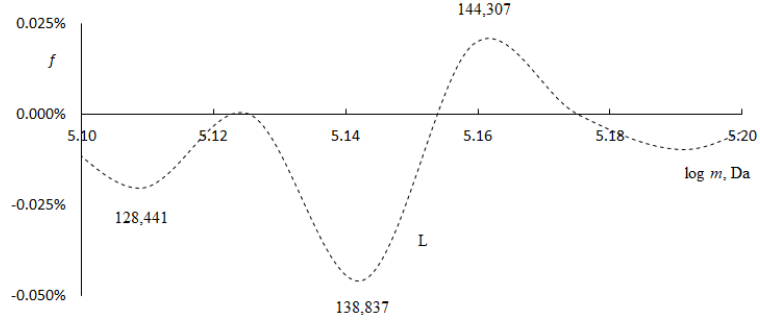

Figure 22A. GMS spectrum of the left (L) part of the brain (probant 67) in the area of HDAC6 coil oscillations (bevor multi-frequency effects on the left side of the brain, 2015).

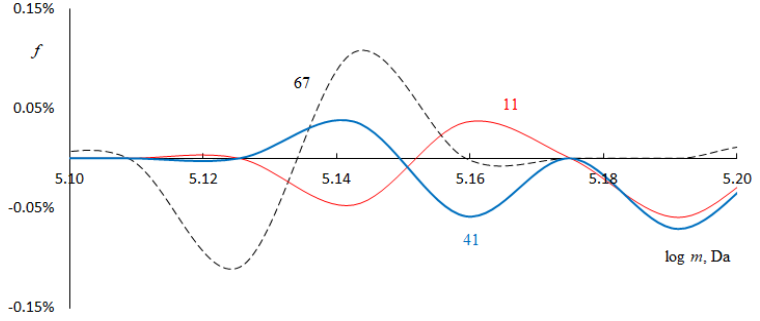

Figure 23. GMS spectra of cerebellum brain probants 67; 41 and 11 in the area of HDAC6 coil oscillations.

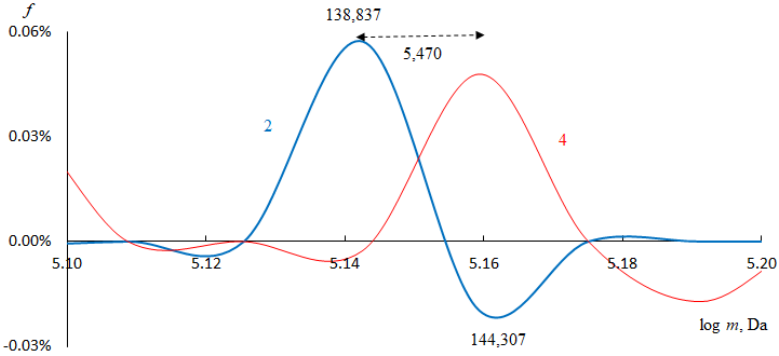

Figure 24. GMS spectra of cerebellum brain probants 2 and 4 (brother and sister) in the area of HDAC6 coil oscillations.

Of particular interest was the state of HDAC6 in the cerebellar cytoskeleton in the youngest probants, Figure 24. It was possible to notice a shift in the signals from the HDAC6 coils towards large masses for probant 4 compared to probant 2. The mass difference was 5,470 Da. It could be assumed that two types of HDAC6 with different masses worked in different parts of the neuron, in growing nanotubes of dendrites and axon terminals. Clarification of the causes of this phenomenon, whether it depends on gender or age, also requires additional research.

CONCLUSION

The GMS method allows monitoring the state of the domain structure of the brain cytoskeleton in passive mode *in vivo*, remotely, at the molecular level.

The dynamics of the formation and disappearance of atomic nuclei clusters in the human brain depends on the age and specificity of its activity.

The formation and disappearance of atomic nuclei clusters in different parts of the brain is different for each individual and reflects the dynamics of aging and professional activity of a person objectively.

There is a fundamental possibility of “repair”, the artificial reconstruction of DP in the domain structure of the brain remotely,

painlessly and not invasively, for several months by purely physical methods.

The forced change in LRO in the domain structure of the brain is based on the target effect of GN on the conformation of subdomains and even tangles of biopolymers [10].

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Chapter 2

FAST NON-INVASIVE DIAGNOSTIC OF HSV-1 ATTACK ON THE HUMAN BRAIN AT MOLECULAR DOMAIN LEVEL

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ABSTRACT

The gravitational mass spectroscopy method (GMS) was used for the fast diagnostic (10 s) of human brain states at long-range order (LRO, molecular mass range from 200 to 3E9 Daltons). Gravitational noises (GN) from the right, left and small brains of probants of 11, 41, 67 and 69 years old (grandson, son, grandfather and grandmother) were studied in the area of tubulin oscillations, cytolinkers (Gas2L1, MACF1) and herpes simplex virus type 1 (HSV-1, plasmid). A different structure of GN was found on the right and left spheres of the brain by both probants, as well as on the cerebellum. The fundamental possibility of analysis, according to the GN data, of the domain structure inside the brain cytoskeleton and the effect of surgical intervention on it and viral infections was proven. A correlation

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was found between the long-range order (LRO) at the molecular domains level and conformational changes in some protein coils/domains that bind tubulin nanotubes to actin. The mechanism of destruction of tubulin nanotubes by virus plasmid attack was discussed.

Keywords: human brain, diagnostic *in vivo*, molecular domains, tubulins, Gas2L1, MACF1, HSV-1

1. INTRODUCTION

Earlier, we showed the fundamental possibility of diagnosing the human heart muscle work *in vivo* at the level of atomic nuclei mass concentration (ANC, domains, subdomains, coils, submicelles, micelles and super micellar structures in a cytoskeleton) remotely [1]. Here the particular interest was the dynamics of tubulins activity. It allows not only to get an idea of the state of neuronal cells, but also an idea of the state of tubulin nanotubes and their interaction with actin via cytolinkers, which reflects the development of internal stresses in the brain at the level of its mechanical deformations and the dynamics of the development of paralysis in the body.

Therefore, it was of interest to test the GMS method in relation to such molecular structures in the cytoskeleton of the human brain and its further development in relation to a new stage in medicine - *in vivo* diagnostics. The aim of this work was to study the attack of the HSV-1 virus on the protein domains in the cytoskeletal structure of the human brain *in vivo* remotely.

2. MATERIAL AND METHOD

As the object of study, the cytoskeletal structures of the human brain without pathologies and a person with surgery (glioblast) were selected. The GN from the brains of 2 probants at the age of 67 (male) and 69 (female) years were investigated. The gravitational sensor was located in the ear canal of the left and right ears of probants and was applied to the occipital part in the area close to the small brain (cerebellum), Figure 1. A GMS sensor

recorded GN from ANC in the mass range from 200 Daltons to 3 billion Daltons. The GMS spectra were obtained using the first Zubow equation [2], the Zubow power constant was taken for ANC (tubulin) equal to 6.55E-15 N/m [3].

The positive values of Δf were characteristic of expanded (loose) coils, molecular clusters and domains, they reflected the energy fraction of the domain in the entire ensemble of the studied masses, negative of Δf reflected the same thing, but for collapsed (dense) ANC. The Δf value was the difference between the current value of f_t for time t and the average for the entire scan time f_{av}. Scan time 10 s. Figure 2 showed the GMS spectrum of brain GN, for understanding. The studies was focused on the areas of tubulin oscillations in nanotubes, domains Gas2L1 (growth arrest-specific 2-like, https://en.wikipedia.org/wiki/GAS2L1), MACF1 (https:// en.wikipedia.org/ wiki/ MACF1) binding nanotubes to albumin [4] and DNA rings in HSV-1 plasmid. The high activity of tubulins (signal intensity in the GMS spectra) indicated an abnormal division and cell growth, for example, in glioblastoma, and the dynamics of the conformation changes inside the cytolinker domains about the imbalance of internal stresses and pressures in the brain cytoskeleton and, as a result, the loss of electrical signal conductivity via tubulin nanotube. The latter leads to loss of sensitivity (paralysis) of organs, reduced motoric and coordination.

3. RESULTS AND DISCUSSION

Figure 3 showed the results of GN scanning from probant 69. This probant was operated on 20 years ago (glioblastoma) and received a course of treatment in 2000, the tumor growth process was stopped (indicated by an oblique arrow).

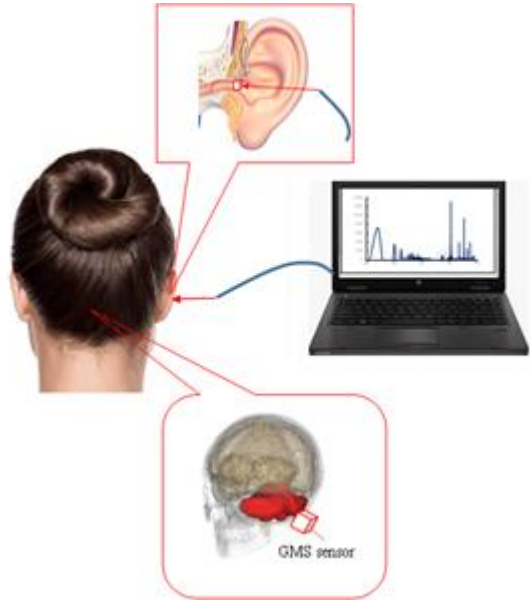

Figure 1. Schematic diagram of the GN scanning from ANC in the cytoskeletal of the human brain by the GMS method.

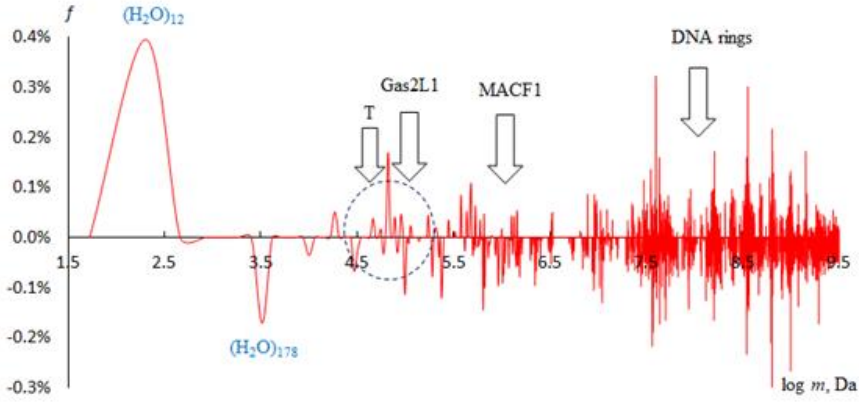

Figure 2. The GMS spectrum of GN brain (right half) from proband 67. The vibrational regions of tubulin ANC (T) and albumin binding domains Gas2L1, MACF1 and DNA rings in HSV-1 plasmid were indicated. The strong signals from the base water clusters [5] and Chaplin's water ones [6] in the brain cytoskeleton were found.

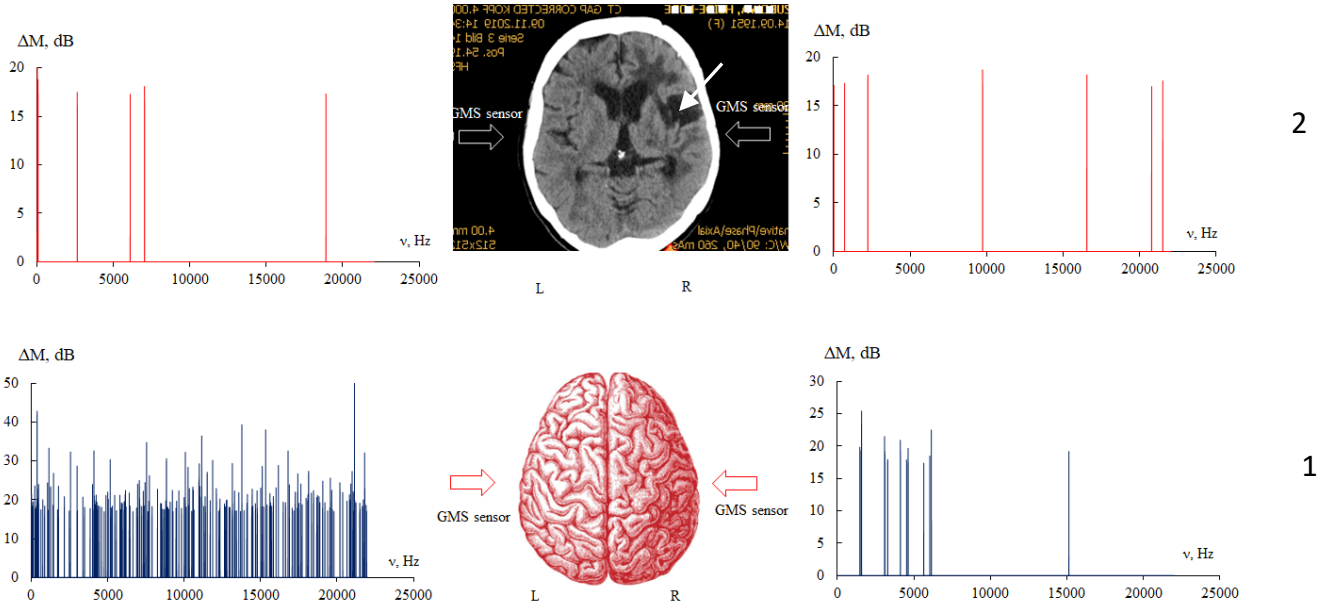

Figure 3. 1 - the structure of digitalized GN in both spheres of the brain (R-right and L - left) of probant 69 in conditions of complete rest (eyes closed), 2 - also, but with forced activation of signals using the left hand (simple raising, spectrum on the right) and the right hand - spectrum on the left. ΔM is the maximum spread in the amplitudes of GN. The photograph of GM CT/SR was taken on November 9, 2019 (the place of early postoperative treatment of glioblastoma is indicated by the oblique arrow (2 isocentric 6 MV-photon-standing fields and 2 single exposure per day from 1.6 Gy to 54.6 Gy and 4 cycles of timodal in 1999 and in 2000).

As can be seen, both parts of the brain in a quiet state of the patient had similar spectra of GN. The dispersion amplitudes of the GN (ΔM) were in the normal range for them. In December 2019, a cytological examination of cells on the right side of brain, as well as MRT and CT data, gave a negative result (cancer), but the patient clearly showed impaired motor skills and curvature of the lips on the left side of the face and paralysis of the left hand, indicating distortion of electrical signals from the right side of the brain [7]. Therefore, the analysis of GN from all ANC was carried out in their long-range order in the cytoskeleton of the small brain and the lateral external parts of brain both halves.

From Figure 3 it was seen that the structure of the GN in both parts of the brain was different and it strongly depended on the conditions of their forced generation. In quiescent conditions, GN from various ANCs were active over the entire spectrum of domains and micelles. When raising the left hand (GN spectrum on the right), ANCs were activated, which were not involved in a calm state, the spectrum was poor in signals, but their scatter values significantly increased. When raising the right hand, on the contrary, a wide range of signals with a very high dispersion in GN energy (ΔM up to 50) were activated in the left part of the brain. Recall that in the GMS method, ANCs with high dynamics of movement (rotation, movement, change in conformations, configurations, merging, etc.) are recorded. In this case, the signal intensity weakly depends on the concentration of ANC and strongly on the distance to them.

In contrast, the GN of the small brain of both probants differed greatly both in scatter intensity (ΔM) and in the number of signals, Figure 4. In the GN spectrum of probant 69 (A, not an athlete), rare signal from clusters of 69 water molecules were found, while in the GN of probant 67 (athlete, badminton), the current signal from cluster of 25 molecules was present. This means that the cytoskeleton of the small brain of Probant 69 experiences strong energy influences that destroy the basic water clusters in it. Such effects include processes with a change in pressure in hydrogels [2]. Therefore, the authors drew attention to the biochemical processes in the brain that can cause such phenomena. They include, for example, processes known in the physical chemistry of polymers as swelling processes in which

the crosslinking of macromolecules is stretched. In brain cytoskeletons, such crosslinks include the Gas2L1 and MACF1 domains [4], which bind actin chains to tubulin nanotubes.

Figures 5 and 6 showed the GMS spectra of both brain spheres of probant 67, the signal of tubulins and the Gas2L1 domains. As can be seen, in the calm state of this probant, the GN spectrum in the right side of the brain was characterized by a wider set of signals than in the left, and some stability was noticeable at the level of 16...17 ΔM for both parts of the brain.

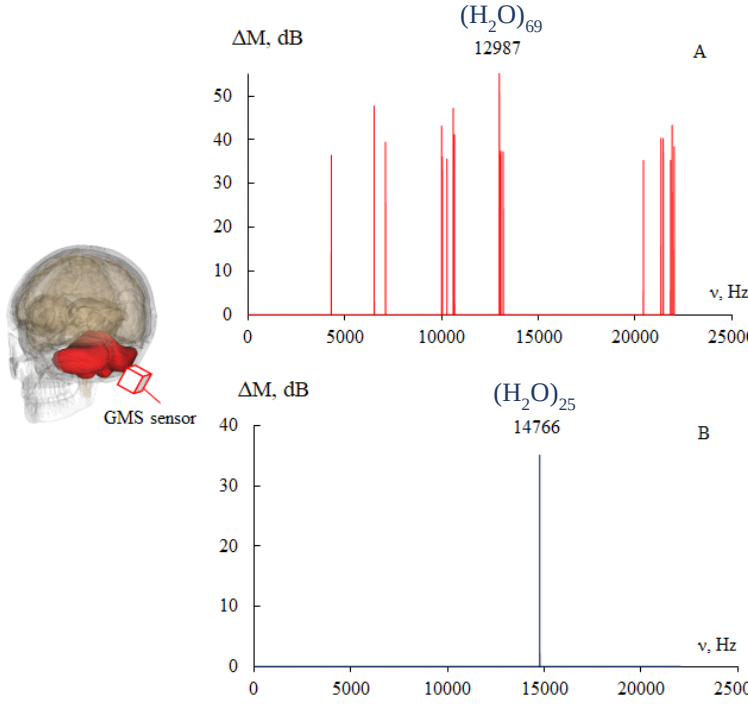

Figure 4. GN from cerebellum (*in vivo*) in the resting state of probants: A - probant 69, B-probant 67. In both cases, ΔM signals with a difference (M_{max}-M_{min}) > 35 were presented.

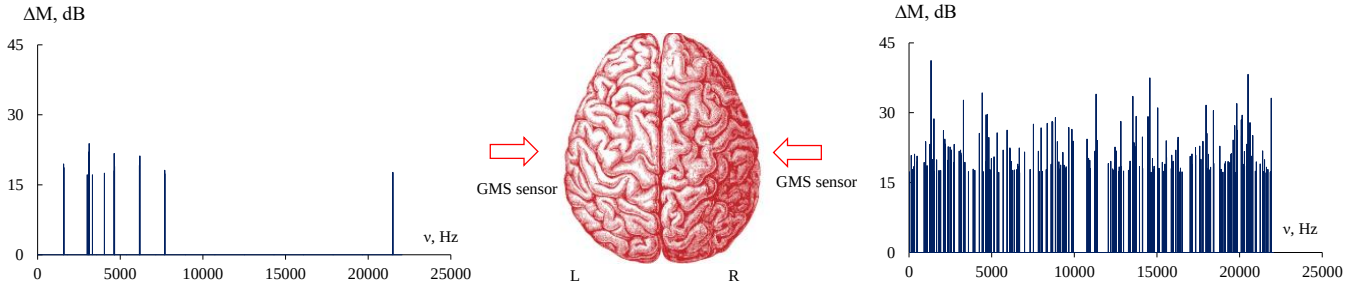

Figure 5. GN spectra of both brain spheres of probant 67 *in vivo*.

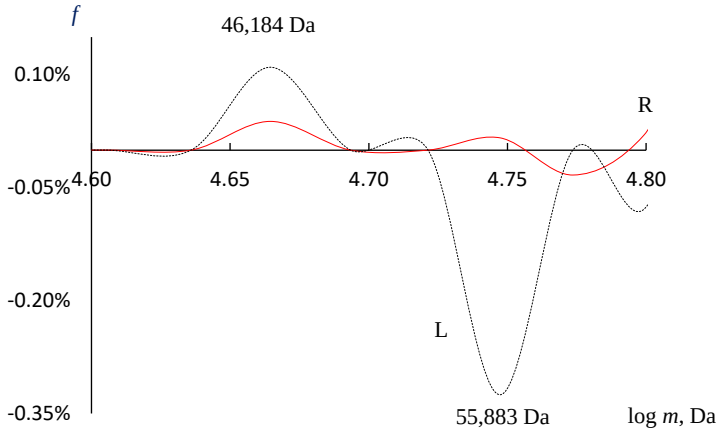

Figure 6. GMS spectra of tubulin in both hemispheres of the brain of probant 67 *in vivo.*

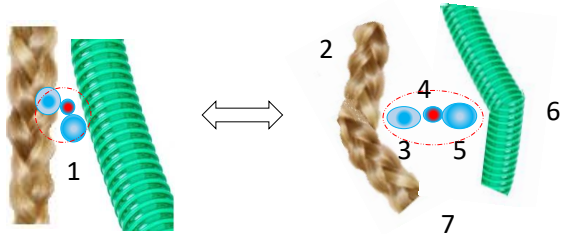

Figure 7. Model of the effect of binding actin and Gas2L1 tubulin nanotubes on the deformation properties of the cytoskeleton. 1. Gas2L1 (collapsed conformation); 2 - actin filament, 3 and 5 - CH (55.883 Da) domain; 4 - GAR (46.184 Da) domain; 6 - tubulin nanotube; 7 - expanded form of Gas2L1.

As can be seen from Figure 6, tubulin activity in both parts of the brain was relatively low. All of them were in expanded form, in the form in which the tubes "work" in the cells [3]. An exception was the signal at 55.883 Da in the left side of the brain. It was strong and indicates the collapse conformation of the domain. Nanotubes with such domains were old. However, this signal was overlapped by a stronger signal of the CH domain with a similar mass [4]. This domain, together with Gas2L1, binds nanotubes with actin. Its collapsed conformation was evidence of the stability of the ligament and the cytoskeleton as a whole, Figure 7. Deformation of a tubulin nanotube as a result of loosening of the binding domain can ultimately lead

to the loss of axon functional properties, weakening, and even finish of the electrical signal from the brain to the muscles.

Figure 8 showed the change in the state of conformations of the domain involved in the formation of the cytoskeleton (MACF1) of probe 69. In a calm state, the activity of domain oscillations in a expanded conformation was almost the same in both parts (A). When the arm was activated, two different signals appeared, from the conformations of this domain in a dense form and differing in the mass from this domain in a calm state and activation state of the right hand (B). The collapsed conformations indicated the normal construction of the cytoskeleton and its fulfillment of the basic properties of maintaining a stable connection of actin with tubulins (Figure 7). Forced activation of the left hand led to a bifurcation of the signal and the appearance of a signal of a domain with a slightly lower mass in the cytoskeleton of the right part (P). The decrease was 8.282 Da. This could be understood as the denaturation of this domain and its disappearance as a spherical oscillator in the GMS spectrum. This was possible as a result MACF1 crosslink stretching. Note that a similar situation took place in the case of another Gas2L1 cytolinker (Figure 9), and here a domain with a similar mass (8.355 Da) played a similar role - the role of a spring. Apparently, conformational changes in cytolinker between albumin and tubulin nanotubes reflect some border conditions for the deformation of the brain cytoskeleton. The appearance of new ANCs active in the GMS spectra of MACF1 coil-based oscillators made it possible to understand the entire spectrum of adhesive-cohesive interactions of the coil with its surroundings and to choose a method for controlling such interactions [8]. And the forced translation of coils as the oscillators into expanded conformations and vice versa makes it possible for an objective analysis of the boundary conditions for the stable and normal functioning of the cytoskeleton, as well as treatment by restoring the original LRO.

Figure 9 showed the state of the Gas2L1 coils in both parts of the brain. The emergence of new signals in the area of oscillations of this coil were found. They also affirmed to the restructuring of the subdomain inside Gas2L1. This could be understood from the standpoint of the fact that the actin bond with a tubulin nanotube, it was carried out not by a monomer unit

of Gas2L1, but by its dimer. At the same time, the subdomains of 4.135 Da and 8.355 Da in Gas2L1 were able to switch from one coil to another. That is, the 8.355 Da subdomain, apparently, itself consisted of 2 small subdomains with masses of 4.135 Da. Thus, these data indicated the existence of a different mechanism for the binding of nanotubes to actin, with the participation of Gas2L1 dimers, Figure 10.

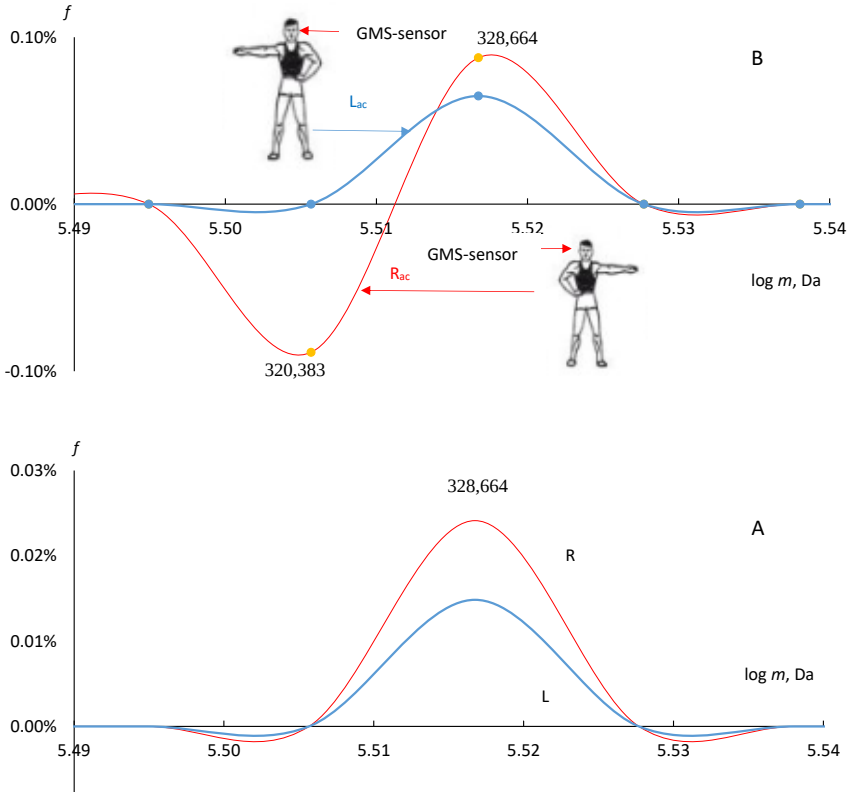

Figure 8. GMS spectra of ANC in the MACF1 mass region (probant 69) *in vivo*. A - calm state, B - hand activation (to the opposite hemisphere of the brain) and its horizontal retention for 10 s.

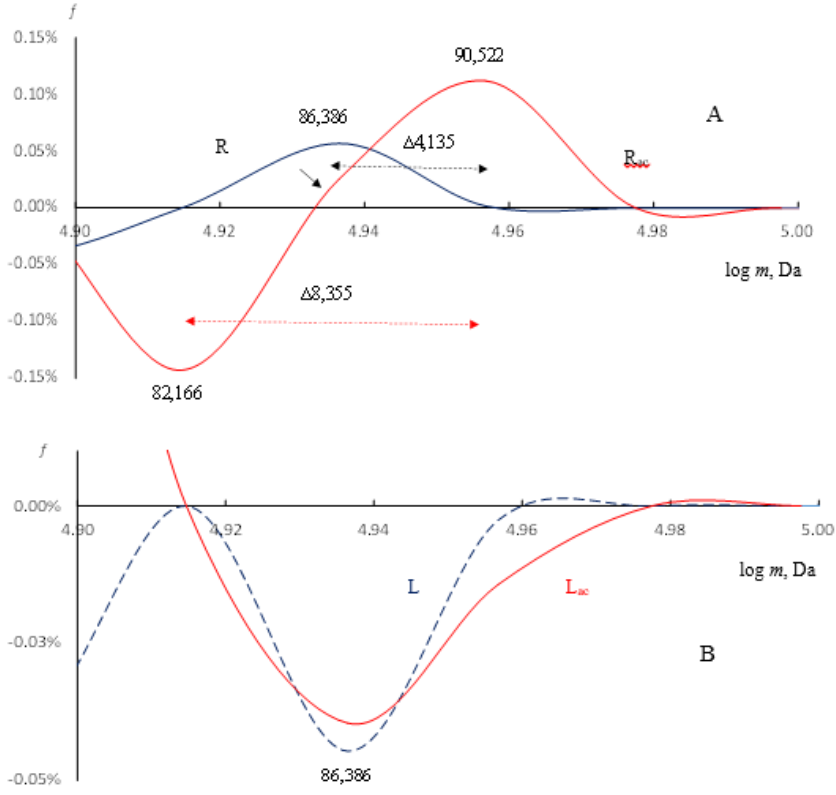

Figure 9. GMS spectra of Gas2L1 coil oscillations in both hemispheres of probant 69 brain *in vivo*. A - GMS sensor in the right ear, B - GMS sensor in the left ear. P - calm state, the hand hangs, the sensor in the right hemisphere, R_{ac} - the left hand in the horizontal position (10 s), the sensor in the right hemisphere, L - calm state, the hand hangs, the sensor in the left hemisphere, L_{ac} - the right hand in the horizontal position (10 s), sensor in the left hemisphere.

In our opinion, the binding of actin to tubulin nanotubes was predominantly carried out by Gas2L1 dimers, which provides the necessary elasticity of the cytoskeleton and a sufficient distance between actin and nanotubes. Such a constellation opened access for exposure to a bunch of dimers by other mobile tangles, for example, virus plasmids. In the case of a monomeric link, the steric accessibility of the virus plasmid to it decreases sharply and the probability of destruction of the nanotubes decreases too.

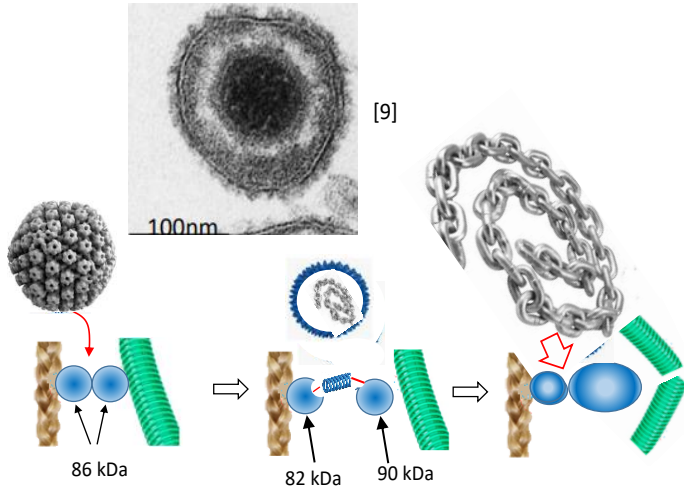

Figure 10. Model of the binding of actin and tubulin nanotubes with the Gas2L1 dimer and the destructive effect of the virus core (plasmids, ring-shaped DNA, cccDNA, https://de.wikipedia.org/wiki/CccDNA) on the dimer, compare with the model in Figure 7. Subdomain 8.255 Da is indicated by a spring. Photography was a herpes virus.

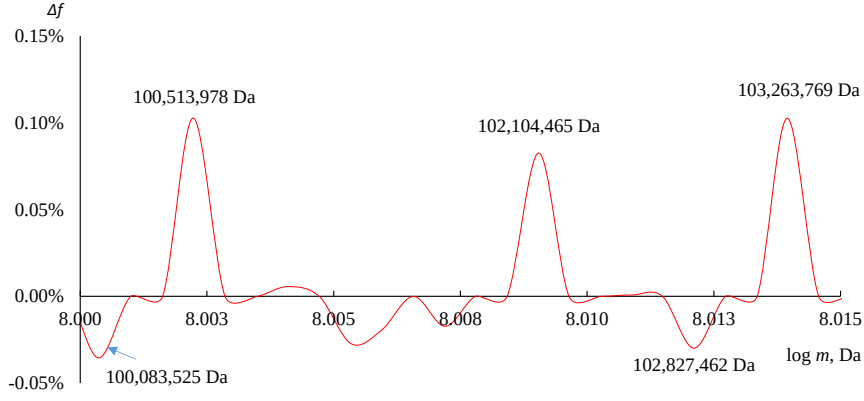

Figure 11. GMS spectra in the area of circular DNA oscillations in a virus plasmid. Here Δ*f* was the difference between the signals in the right and left parts of the brain (probant 69).

Recall that Probant 69 suffered for a long time from the herpes virus (https://de.wikipedia.org/wiki/Herpes-simplex-Viren), which apparently penetrated the brain cytoskeleton (in the form of a plasmid) during the first

operation for the removal of glioblastoma (https://edoc.ub.uni-muenchen.de/24172/2/Lindemann_Anja.pdf) [10].

In the area of oscillations of the virus plasmid (DNA double helix in the form of rings), differences in the GN of the right and left hemispheres of the brain were found, Figure 11. It can be seen from the Figure that ANCs equivalent to circular DNDs in the virus plasmids were represented by 3 expanded and 4 collapsed poor expressed ring oscillators.

The expanded structures of DNA double helices were most likely already located near the link of tubulenes with actin, as in Figure 10, and were dense (collapsed) in the viruses themselves.

This conclusion was made on the basis of the shapes and high intensity of signals of expanded conformations of rings for this area in the GMS spectrum. As can be seen from the Figure, the masses of loose ANCs were on average 433 ± 3 kDa bigger than ANCs in dense conformations. This means that ring DNAs penetrating into nerve cells cohesively attack MACF1 and 2 tubulin domains with masses of 55.883 and 46.184 Da (totaling 431 kDa) and integrate them into their oscillations, Figure 10. This confirms the mechanism of the destructive effect of the viral plasmid on tubulene nanotubes. Thus, the flow of electrical signals inside the tube is "turned off," which causes organ paralysis.

Probant 69 also experienced pain for several years in the area of the cervical muscles, typical during prolonged work on computers or when watching television programs for a long time. These pains may have led to impaired motility skills and coordination. Therefore, it was also of interest to understand the processes of change in the domain structure of the small brain responsible for motility. Figure 12 presents data on the conformations of small and very large domains LRO of the cerebellum. A small, basic water cluster quickly adapted to the thermodynamics of biopolymers and its oscillations, in principle, were synchronous with those for small domains in proteins with a similar mass. The dispersion of the amplitude of its oscillations in probant 69 was very big, which indicates the presence of more stresses in the cytoskeleton than in probant 67. But they were not of a destructive nature. In the field of micellar structures with masses of ~10 million Da, among the probants of the same family, the differences were

only in signal intensity. Apparently, they reflect differences by gender, demand of a probant in the specific development of certain coordination skills.

The data in Figure 12 were also confirmed by the low motility of probant 69 in comparison with probants 11, 41, and 67 and objectively reflect the fundamental state in the cytoskeletal at the level of its molecular domain structure. In the oscillation area of Gas2L1 and MACF1, no significant differences in the GMS spectra of the probants were detected. A more detailed explanation of the brain cytoskeleton requires further research.

CONCLUSION

The GMS method can be used for active monitoring of the brain cytoskeleton *in vivo* at the level of its domain structure.

The GMS method allows to get an idea of the course of biochemical reactions remotely.

The GMS method allows one to register the activity of conformational changes in tubulins in nanotubes and thereby gain an idea of the intensity of cell division and growth.

The domain of 8.3 kDa acts as a damper of internal stresses in the cytoskeleton. It has a spiral structure.

Influence on internal deformation stresses in the cytoskeleton of the brain is possible by non-invasively influencing the shape of the domain of 8.3 kDa (collapsed-expanded).

Conformational changes in ligaments (Gas2L1, MACF1) of albumin with tubulin nanotubes can give an idea of the mechanism of their destruction by viruses.

Conformational changes in the links of albumin with tubulin nanotubes reflect the border conditions of the deformation of the brain cytoskeleton.

The herpes virus plasmid attacks links between tubulin nanotubes and actin and thereby destroys the tubulin nanotubes, block the electrical signals, and as a result, organ paralysis.

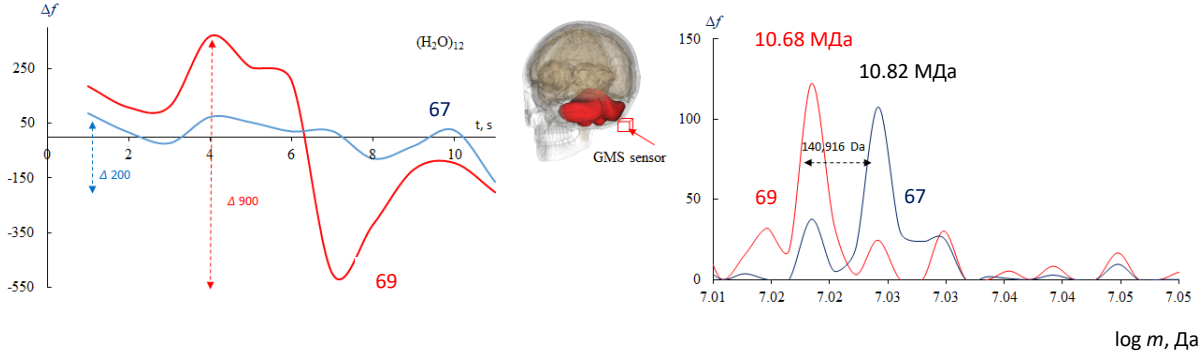

Figure 12. Dynamics of the signals from the base water cluster (left) and super micelles with masses of more than 10 million Da in the cytoskeletons of the small brain of the probants (right). 1 - probant 69, 2 - probant 67, 3 - probant 41 and 4 - probant 11.

This mechanism opens up the possibility of non-invasive “repair” of these injuries by physical methods [8].

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Chapter 3

TRAUMATIC BRAIN INJURY AND RESOURCES FOR COMMUNITY INTEGRATION POST INJURY

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ABSTRACT

In the current chapter we explore the options and resources for community integration for individuals that have acquired a traumatic brain injury (TBI). The goal of this chapter is to evaluate community integration resources and influences to highlight what is being done well and areas that need further investigation.

Traumatic brain injuries can result in lifelong difficulties in areas of mental health, cognition, physical ability, and more. The term TBI lacks specificity as the injuries are typically measured on a continuum of severity from mild, moderate, to severe. Recovery rates, similar to all other aspects of TBI, vary by degree of severity. Given the major impact of TBI, it is important to assess the opportunities available for successful community integration after injury.

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Community integration can be broken down to three main components: social integration, return to productivity, and independence. Social integration is considered to be the most important component of community integration. Despite the benefits of social support, researchers have shown that individuals with a TBI do not get adequate social support. Social support has been shown to have a significant positive impact on engaging in various health behaviors, specifically, for engaging in physical activity. Physical activity has shown to provide many benefits to this population and may provide an opportunity to encourage community engagement by the individual with a TBI and their various support systems. Informing individuals about social support resources and opportunities can help to further promote community integration following a TBI. Returning to work or school and independence following injury are also important components of community integration after injury. Researchers have suggested that an individualized approach is most effective for preparing individuals to engage in these various activities within the community.

More research is needed to determine how to effectively generate a comprehensive rehabilitation program to impact all areas of community integration. Additionally, programs are needed to continue enhancing community integration efforts after individuals have been discharged from rehabilitation programs. Individuals with TBI can live a productive and satisfying life when provided with effective programming and resources.

INTRODUCTION

Traumatic brain injury (TBI) has been gaining more attention with the rising focus on sport related concussions and wounded returning war veterans, but TBIs have been a worldwide problem for a long time. A TBI is an injury to the head that alters brain function, often resulting in immediate symptoms of confusion, altered level of consciousness, seizure, coma, among others (Bruns and Hauser, 2003). Over 10 million TBIs, serious enough to require hospitalization or death, are reported every year across the globe (Langlois, Rutland-Brown, and Wald 2006). Because many TBIs may go unreported, the actual number of individuals living with TBI-related disabilities is unknown.

As mentioned above, sport related concussions are also considered a TBI and are found to be a common cause of brain injury, but many go unreported for various reasons. The most common causes of TBI include

vehicle crashes, falls, being struck by something, or assault (Langlois et al., 2006). Additionally, there are several risk factors and demographic trends that show more TBIs compared to others. For example, males are twice as likely to experience a TBI compared to women. Young children (0 to 4 years), older adolescents (15 to 19 years) and the elderly are the most likely age groups to sustain these injuries (Bruns and Hauser, 2003). Traumatic brain injuries can result in life altering consequences regardless of any demographic characteristics.

Traumatic brain injuries are measured on a spectrum of severity, with concussions being at the least severe end, then escalating to mild, moderate, and severe (Roozenbeek, Maas, and Menon, 2013). Severity of injury can result from a variety of influences including the specific area of impact, as well as, speed and force (Maas, Stocchetti, and Bullock, 2008). The most common hospital testing protocol for diagnosis includes the use of Gloscow Comma Scale which is scored by the patient's responses of eye opening, verbal function, and motor function (Bruns and Hauser, 2003). Additionally, pre-injury functioning is used as a baseline for evaluation of deficits post-injury (MacMillan et al. 2002). These assessments and information gathering by physicians lead to a suspected severity determination. Overall prevalence of severity suggests that 80% of TBIs are mild and the other 20% of injuries is split between moderate and severe (Kraus, McArthur, Silverman, and Jayaraman, 1996). Across all severities, the Center for Disease Control and Prevention estimates that 2% of the U.S. population is living with some TBI related disability (2006).

Regardless of the severity of the TBI, any brain injury can result in lifelong difficulties in areas of mental health, cognition, physical ability, and more (Langlois et al., 2006). Symptoms often present very differently between each individual, which makes comparisons among people or groups, or mass treatment difficult to design. Similar to all other aspects of TBI, recovery rates vary by degree of severity and area of impact (Faul, Wald, Coronado, and Dellinger, 2010). Overall, around 90% of those who suffer a mild TBI make a complete recovery, while only 60% of moderate TBI and 15-20% of severe TBI survivors fully recover (Faul et al., 2010).

This is a significant number of individuals living with lifelong deficits as a result of a TBI.

Many treatment options have been considered to help with recovery following TBIs. Treatments that have been considered and utilized include pharmacological treatment, cognitive training methods for different domains, comprehensive rehabilitation, and more recently, exercise and physical activity (Cernich, Kurtz, Mordecai and Ryan, 2010). After rehabilitation programs are complete, many individuals with TBI and their caretakers are left to cope with their symptoms on their own. Given the significant impact of these deficits, it's important to better understand the support resources available in all areas of community integration and we review this literature next.

In the reminder of this chapter, we break down community integration for individuals that have acquired a TBI. We review the literature on social support and interaction, the processes of returning to productivity, and functioning independently. The overall goal for this chapter is to provide the reader with a better understanding of what resources are most successful in assisting this population, highlight resources that could be better utilized to improve community integration, and suggest future research directions to advance this knowledge.

COMMUNITY INTEGRATION

Community integration is the process of returning to full participation in society after previously being in a patient role or under care of treatment facility professionals (Bond et al., 2004). This term is commonly used for individuals with disabilities, as there are additional barriers for many areas of community engagement for these individuals.

The traditional view of community integration is often defined by three specific areas of functioning: social interaction, employment, educational, or other productive activity, and independent living (Sander, Clark, and Pappadis, 2010). Each area plays an important role for an individual working to regain independence and returning to activities of daily living (ADLs).

Though all components of community integration are important to improving quality of life post injury, it is important to be aware of the different influences the components have on the individual and how to focus on those in rehabilitation settings.

As with any multi-dimensional concept, there are many ways of measuring the various components. Ritchie and colleagues (2014) conducted a systematic review on measurement of community integration for older adults with TBI. Their review consisted of 11 studies, which included all injury severities and utilized 6 different assessment tools to measure community integration (Ritchie et al., 2014). The Community Integration Questionnaire (CIQ) was the most commonly used measure, but most researchers suggest using a battery of assessments to fully measure and predict an individual's community integration. The CIQ is considered to produce valid and reliable scores for this population (Salter et al., 2008; Willer et al., 1993). The CIQ can be used for its overall score for community integration and for the three subscales of home integration, social integration, and productivity (Willer et al., 1993). Given the multi-dimensional aspects of community integration, this measure appears to successfully examine the most influential aspects.

Community integration is an important goal after any injury requiring significant treatments. However, individuals with TBI often have increased barriers to returning to previous levels of functioning. Winkler, Unsworth, and Sloan (2006) sought to identify factors that lead to successful community integration following a severe TBI. Winkler et al. (2006) worked to move beyond the use of complete sample mean scores of community integration, which can hide the many individuals who are highly integrated and the individuals who are highly isolated. Winkler et al. (2006) separated these two groups based on the assessment of their involvement in community integration, perceptions of their own integration, and change in integration as a result of the injury. The results suggested that increased severity of injury and disability, older age of injury, and the presence of challenging behavior, referred to as "loss of emotional control," were all negatively predictive of community integration post severe TBI (Winkler, Unsworth, and Sloan, 2006). More research is needed to better understand

the impact of these factors and how to develop rehabilitation programs to maximize these factors for more successful community integration.

Many researchers believe the main goal of most rehabilitation programs should be to help the individual gain or regain the ability to participate in typical ADLs and community activities after sustaining an injury or disability (Doig, Fleming, and Tooth, 2001; McCabe et al., 2007; McColl et al., 2001). This directly applies to the rehabilitation process for individuals who have acquired a TBI, as these individuals are often found to have more difficulty with reintegration post-injury compared to the general population (Winkler, Unsworth, and Sloan, 2006). Given the importance of rehabilitation efforts for this population, it is important to evaluate characteristics and efficacy of existing efforts in rehabilitation. We next review the current literature examining the various rehabilitation programs specifically geared to enhancing overall community integration for individuals with TBI.

Kim and Colantonio (2010) conducted a systematic review of post-acute TBI rehabilitation intervention programs that include community integration as an outcome measure. Their review included a wide range of rehabilitation program types including community outreach, home-based, cognitive programs, and other multidisciplinary interventions. Given the vast differences in treatment types and outcome measures, generalizable conclusions are unavailable. However, a community-based outreach program and multidisciplinary program showed to be more effective than their control group comparisons (Kim and Colantonio 2010). Specifically, a well-structured, intensive outreach program was more effective for increasing community integration compared to a less structured control. Additionally, multidisciplinary programs that include team members of varying specialties greatly increased social integration and productivity for participants (Kim and Colantonio 2010). These findings are important to advancing the knowledge of community integration research for individuals with TBI, as they provide some insight on the structure and components needed for successful programming. It is important to consider the various potential methods of rehabilitation and the implementation of different

treatment types. We continue by looking further into individual studies to assess the specific impact of these varying rehabilitation methods.

Kanchan and colleagues (2018) examined the impact of a neuropsychological rehabilitation program on ADLs and community integration. This study evaluated community integration skills before and after implementation of the Brainwave-R program of rehabilitation over a 6th month period of time. This program focuses on cognitive strategies and techniques specifically for brain injury rehabilitation (Malia, Bewick, Raymond, and Bennet, 2002). Kanchan et al. (2018) found that engagement in the neurorehabilitation program significantly improved community integration and all three sub-components for individuals with TBI (Kanchan et al., 2018). These findings are important, because it is clear that specific cognitive focus is needed in rehabilitation efforts. However, more research is needed to better understand how cognitive rehabilitation methods can be used for improving community integration overall.

A study by Cicerone and colleagues (2004) examined the effectiveness of an intensive cognitive rehabilitation program for individuals with TBI to impact overall community integration in comparison to a standard neurorehabilitation program. Both programs lasted around 4 months. The standard program consisted of physical, occupational, speech, and neuropsychological therapy. Additionally, this program included recreational therapy, vocational or educational interventions, and psychological counseling. Each specific treatment protocol was determined for the individual's needs. This treatment program was in the same facility as the cognitive program but was less intensive and less structured. The intensive cognitive program included individual and group cognitive remediation, small-group treatment for communication skills, psychotherapy, family support, and therapeutic work trials to facilitate educational or vocational readiness. Outcome variables examined in this study included community integration, satisfaction with functioning, and neuropsychological functioning.

Both groups showed improvements following treatment, but the intensive cognitive program showed significantly greater improvement in community integration and neuropsychological functioning (Cicerone et al.,

2004). This is important information, because it demonstrates that a more wholistic, intensive approach of rehabilitation can lead to better community integration after injury. More research is needed to continue the investigation of rehabilitation methods that allow individuals with TBI to best prepare for community integration post injury.

The studies highlighted here provide an introduction into the various rehabilitation options available for individuals with TBI and how they can directly impact community integration overall. As mentioned above, community integration can be broken down into several different components including social integration, return to productivity, and independence. Moving forward in this chapter, we next discuss the importance of these individual components, the rehabilitation efforts that have focused on improving these areas, and the available resources for individuals with TBI.

Social Support

The first individual component of community integration we review is social integration, as some experts consider this the most important component. A review by Ritchie and colleagues (2014) suggested that when individuals were asked post-TBI what community integration means to them, the most prominent theme was social connection (Ritchie et al. 2014). In this section, we will review the various influences of social interaction after TBI, how interaction impacts the individual, and rehabilitation strategies that have been done to encourage more social integration and connection.

The importance of social integration as part of community integration was demonstrated in a qualitative study conducted by McColl and colleagues that examined how individuals with moderate to severe TBI defined community integration (2009). The researchers tracked participants over the course of a year to assess their integration over time. They found that a positive evaluation over time was frequently related to meeting new people and increased social interaction (McColl et al., 2009). Though this

knowledge is promising, the act of meeting new people isn't that easy. There are many barriers to social interaction for individuals with a TBI.

One study investigating the relationship between community integration and life satisfaction for individuals with TBI found that the only significant relationship with life satisfaction was the social integration component and overall community integration was not significant (Burleigh, Farber, and Gillard 1998). For individuals with TBI, social support and social integration are critical for overall well-being post injury. This finding further highlights the importance of breaking down community integration into its various individual components and specifically the value of social integration after injury. Additionally, the study revealed that individuals who had longer time since injury had significantly lower community integration scores, including lower social integration (Burleigh et al., 1998). This finding has been supported throughout the literature, demonstrating that social support continues to decrease over time following a TBI.

Despite being a beneficial resource to individuals with TBI, social interaction and engagement can be difficult for many reasons. Brown, Gordon and Spielman (2003) examined the social and recreational community involvement of individuals with TBI compared to individuals with no disabilities. Social-recreational life was described as out-of-home recreational activity and pure social activities, including socializing and opportunities to meet new people. As expected, individuals with TBI were significantly less active compared to individuals with no disabilities. In both groups, individuals who were single and more financially secure were more socially active. In the TBI group, depression and fatigue were significant negative predictors of social interaction, while vocational involvement and more time since injury were positive predictors. Individuals with greater vocational engagement and more time since injury reported greater social interaction compared to those with less vocational engagement and less time since injury. These findings suggest that overtime, employment opportunities may help increase social engagement, further supporting the overall community integration construct. Other factors that limited social interaction for the individuals with TBI include physical limitations, cognitive and emotional symptoms, as well as, environmental barriers, such

as a lack of transportation. Interestingly, despite the differences in external social activities between groups, both groups in this study were found to be equal in participation of household activities and quiet recreation (Brown, Gordon, and Spielman 2003). This potentially indicates that injury has a much greater impact on abilities in the community, versus the ADL needed inside the home.

Additionally, a study by Farmer, Clark, and Sherman (2003) found that negative attitudes and beliefs about seeking social support were significantly related to lower levels of social support, quality of life, and living in an urban area. For example, participants with negative beliefs about seeking social support reported concerns about being a burden and having to repay others. Additionally, previous relationship history can impact an individuals' perception on seeking social support. If someone has encountered numerous failed relationships in the past, they will be less likely to actively search for social support. In contrast, the study also found that living in a rural area, ability to engage in productive activity, and positive appraisals of seeking social support significantly predicted higher quality of life (Farmer, Clark, and Sherman, 2003). The study by Farmer and colleagues (2003) evaluated different demographic factors that are not addressed in many studies, including living in a rural or urban area and preconceived feelings about seeking social support. It is impossible to know what previous experiences an individual has prior to their TBI and how this may impact their desire to seek social support but is very important to keep in mind when intervening post-injury. These findings provide some insight as to what causes decreased social interaction, as well as, shine light on areas that can be included in future intervention to increase social interaction.

In addition to the importance of engaging in various social interactions, a general network of social support has been shown to be tremendously important for individuals with TBI as it has been shown to increase the number of resources and supports successful efforts in stressful situations (i.e., rehabilitation) (Driver 2005). Given this information, it is important to understand the multi-dimensional nature of social support and how the various dimensions positively influence individuals with TBI.

Social support is defined as an exchange of support between individuals, this support exchange can appear different in each relationship. Primary sources of social support typically include family, friends, and health care professionals (Chogahara, 1999; Zimet et al., 1988). For the individual with TBI, family and health care professionals will be the most involved with their rehabilitation efforts and working toward community integration. These various sources of social support have demonstrated varying levels of positive and negative support for many activities, including rehabilitation, social interaction, and community integration (Chogahara, 1999; Ruehlman and Karoly, 1991). It is important to consider the influence of each different source on various activities, as some support sources may be more engaged in specific rehabilitation efforts, while others are more involved in community integration. Each situation is different based on relationship dynamics, injury severity, and resources available.

Depending on the severity of the individual's TBI, one family member (or more) may automatically fall into a role of primary care giver to their loved one who was injured. This can mean the new caregiver is helping with physiological, psychological, neurobehavioral consequences and more, causing an additional significant impact on their life, as well as the individuals they are caring for (Broodryk and Pretorius, 2015). Researchers have shown that caregivers of individuals with disabilities are at increased risk for negative physical, emotional, and social outcomes themselves (Fengler and Goodrich 1979). Additionally, researchers have demonstrated that the family of an individual who acquired a TBI often have many unmet needs in regards to support and information resulting in their own decreased quality of life (Kolakowsky-Hayner, Miner, and Kreutzer, 2001). As the individual with TBI needs, and often depends on, social support, understanding negative stressors placed on these social support sources is important.

Potentially due to this added stress and reduced quality of life for the caregivers and sources of support, research has shown that individuals with a TBI do not get adequate support. That support continuously decreases with increased age and time post-injury (Finset, Dyrnes, Krogstad and Berstad, 1995). Koskinen (1998) conducted a 10-year follow-up for individuals with

severe TBIs and found that 80% reported losing friends and deteriorated quality of friendships since their injury. Though this decrease in friendships and deterioration in relationships is consistently shown throughout the literature, there is little research examining why this occurs. One reason that this decrease happens may be because of the change of roles a person encounters after having a TBI. Davies and colleagues (1992) evaluated the change in adult roles an individual faces following a severe TBI. Roles evaluated included worker, hobbyist, friend, family member, volunteer, and several more. Almost 40% of participants reported a loss in the friend role category and associated this loss with feelings like lonely, angry, confused, defensive, and embarrassed. Additionally, reasons participants cited for change in this role included lack of desire to go out with old friends, not participating in the same activities as before, and old friends having a negative perception of the individual's behavior post-injury, for example, increased fatigue and quick to become angry (Hallett et al., 1992). Though these are not the only reasons for decreased social support after TBI, the change in life roles functions as a good starting point for understanding this dynamic.

There may be a lack of understanding or awareness of post-injury ability by friends or individuals outside of the immediate family and primary caregivers. Additionally, old friends may have difficulty adjusting to the changes an individual faces post injury, as demonstrated by the perceptions of participants in the study by Hallett and colleagues (1992). Despite this, Bogart and colleagues (2012) evaluated ability to engage in a casual conversation between individuals with severe TBI and their friends in comparison to matched controls without TBI. The study found that there was no difference in the ability of the individuals with severe TBI to engage in typical information giving and requesting roles in a casual conversation with friends compared to the matched controls (Bogart et al., 2012). Basic conversation ability appears not to be majorly disrupted after injury, therefore, should not serve as a major hindrance for social interactions with old or new friends. More research is needed to better understand the factors that directly impact the decrease in social support overtime for individuals with TBI.

Regardless of the reason for the decrease, the lack of social support experienced can have many negative consequences following TBI. These consequences can include reduced likeliness for returning to work (Kaplan, 1990), decreased rehabilitation outcomes (Marsh et al., 2013), and overall reduced quality of life (Finset et al., 1995). This decrease in social support and a decrease in opportunities for social interaction continues as a negative cycle and continues to decline as more time passes after injury.

Given the value of important social interactions, what social support looks like, and how decreased social support can negatively impact an individual with TBI, we next review the literature on resources of social interaction and social support for this population. Given the negative impact of the TBI for everyone involved, researchers and health care professionals must best support the individual with TBI, along with their caregiver and family members.

Peer mentorship or peer support programs have been implemented for individuals with TBI and their families in order to provide support that is more individualized to a support group. A study by Hibbard and colleagues (2002) investigated the initial findings of implementation of the TBI Mentorship Partnership Program (TBI-MPP). This program was modeled after a parent peer program specifically for parents of children with developmental disabilities. The TBI-MPP was modified to also include the individual with the TBI, along with their families. The program paired TBI "veterans" with individuals with TBI or their family members to provide support, knowledge, and advocacy skills (Hibbard et al., 2002). Mentors were recruited from various TBI resources, screened for willingness to help and personal adjustment to living with a TBI, and trained on many different resources for overcoming the challenges of living with TBI.

Partners were recruited and screened for the support needed and suitability for the program. The research team matched the peer pairs based on how the partner's needs could be best met. After one year, if still on going, the partnerships were "terminated" for evaluation purposes. Overall, individuals with TBI and family members reported that participating in the program had a positive impact on their life including enhanced ability to cope, improved quality of life, and improved general outlook. Though the

partnerships were supportive, both individuals with TBI and family members reported that the program had little benefit to improving social support from family, friends, or the community (Hibbard et al., 2002). This study provides a very interesting approach to improving social support for individuals with TBI and their family members. The TBI-MPP provides individualized support for the individual with TBI directly from another individual with TBI, creating an environment of acceptance and understanding. Though personal benefits were generated from the program, the impact of social support did not continue outside of the program or with other relationships. More research is needed to better understand if peer mentorship is a beneficial way to improve social support and how this can be continued over time.

Struchen and colleagues (2011) conducted a study to evaluate the use of peer mentorship programs in creating more social integration for individuals with TBI. In this program, social peer mentors consisted of individuals who had suffered a TBI and successfully developed and maintained social networks after injury. Social mentors were screened for their social integration and willingness to help, followed by extensive training on mentorship and skill-building. The research team matched the mentorship pairs based on various demographic characteristics and interests. The mentorship pairs lasted for three months. At the conclusion of the program, 67% of the partners felt that the program helped to increase their social activities and decrease loneliness. Some challenges to social integration included scheduling concerns and budget or transportation issues (Struchen et al., 2010). These findings further demonstrate the value of peer mentoring programs for individuals with TBI. More longitudinal research is needed to better understand the long-term value of a TBI peer program.

Different community-based activities have been created to cater to the specific needs of individuals with TBI. A systematic review by Tate, Wakim, and Genders (2014) examined community-based leisure or social activity program for individuals with TBI. These researchers identified various programs of physical activity, education, kayaking, outdoor camping adventures and social skills groups (Tate, Wakim, and Genders 2014). Overall results concluded that most programs had benefits for

psychological well-being and improved quality of life. However, there was not enough research on the social or long-term impact these programs had on the individuals' life. More research is needed to evaluate the impact community-based programs have on social integration for individuals with TBI.

Engagement in various health behaviors, including physical activity (PA), is heavily influenced by sources of social support (Duncan and McAuley, 1993). PA has shown to provide many benefits for individuals with TBI and may provide an opportunity to encourage engagement by the individual with a TBI and their various support systems (Lorenz et al., 2018). Driver (2007) investigated the types and sources of social influences that impacted PA participation for individuals with TBI. Participants were assessed on the positive and negative social influences of family, friends, and caregivers. Driver (2007) found that the greatest positive influence came from family members, then caregivers, and then friends, while more negative influences, such as criticism, came from family, then friends, and then caregivers (Driver, 2007). These findings were supported in a qualitative study by self and colleagues (2013). Individuals with TBI in a comprehensive outpatient program were assessed on knowledge regarding PA experiences and expectations post injury. Participants suggested many forms of support, including friends, significant others, parents, coworkers and peers. Specifically, participants reported understanding that social support plays a large role in being physically active and being motivated. Additionally, some participants identified negative sources of social influences, suggesting that their family was inactive and that's how they learned what not to do (Self et al., 2013). These findings are interesting when considering how much support individuals receive from each source and further considering what influence is positive and negative.

PA can be a very broad umbrella that encompasses many different forms of exercise, sport, and other recreational activities. Many different forms of PA programs have been evaluated within the TBI population, including aerobic exercise (Wise et al., 2012), anaerobic exercise (Morris et al., 2009), combination of both (Hassett et al., 2009), circuit training (Hassett et al., 2012) and other alternative exercise forms, such as Tai Chi (Blake and

Batson, 2009), yoga (Schmid et al., 2015), and virtual reality (Thornton et al., 2005). Most types of PA have been shown to result in benefits of some form, whether it is physical, cognitive, or psychological, but not enough studies have examined the social interaction benefits associated with PA

Though evidence is limited, it is promising. One study of a home-based PA program for adults with TBI found improved social support scores post-intervention, but the changes were not significant (Clanchy, Tweedy, and Trost, 2016). Two studies evaluating the impact of a Tai Chi program for individuals with TBI found that social support or interaction was not significantly impacted through the programs, despite having multiple positive physical and psychological effects (Blake and Batson, 2009; Reavenall and Blake, 2010). Though not a primary outcome measure in either study, two yoga-based studies found participants socially benefited from participation in the program. A breath-focused yoga program for individuals with severe TBI found self-reported improvements in social function, while an adapted yoga program for individuals receiving inpatient rehabilitation reported enjoying the social interaction of the program (Schmid et al., 2015; Silverthorne et al., 2012). There is a positive association between social support and PA, but more research is needed to evaluate this relationship.

Given the benefits associated with engaging in PA for individuals with TBI and the important influence of social support for consistent participation, more research is needed to determine how to encourage the individual with TBI and their support system to participate in PA programs together.

Social integration is a complex and multi-dimensional aspect of overall community integration after a TBI. Despite the difficulty that may be associated with social engagement and trends of isolation that make it difficult to resume normal activities, there are many opportunities available for individuals with TBI to engage in various forms of social integration. More research is needed to evaluate the long-term impact of social programs, as well as, evaluate the involvement of the primary social support network into the social programs.

Return to Productivity

Another large component of successful community integration after injury is returning to work, school, or other productive activity. There is variability in the way return to work is defined in the current research. Some researchers broadly define the category as returning to productive activity, which can include paid work, school, volunteer or internship positions (Wagner et al., 2000). Other researchers more specifically divide returning to pre-injury work or returning to modified work (Ruffolo et al., 1999). Employment and productive activity after TBI is often found to be positively related to improved quality of life, while unemployment is found to be related to more negative psychosocial factors and less social integration (Kreutzer et al., 2003; Ruffolo et al., 1999; Webb et al., 1995). Given the variability in injury and symptoms, it is difficult to directly predict success in this area, so in this section, we review the literature evaluating the factors associated with returning to productivity.

First, it is important to understand how likely individuals with TBI are to return to work or other productive activities. As one might expect, individuals who have experienced a TBI report lower rates of returning to productivity (i.e., work or education) after injury compared to individuals who have not experienced a TBI (Stalnacke., 2007). With the varying and potentially life altering consequences associated with a TBI, this is a much different injury to recover from than many other types of injuries (e.g., a broken finger). Falling under the community integration umbrella, participating in more social integration and activities may lead to higher rates of returning to productivity. For example, individuals with TBI who engage in PA were shown to be more productive compared to individuals with TBI who did not exercise (Gordon et al., 1998). This relationship could work both ways, as participation in exercise may influence productivity, while being more productive may also lead to higher engagement in exercise.

A review by Cancelliere and colleagues (2014) found that there is agreement among the results of various studies where researchers examined return to work rate for individuals that suffered a mild TBI. In the 4 studies

that were included, the results suggest that most individuals who suffer a mild TBI returned to work, ultimately suggesting that mild TBI is not a significant risk factor for long-term disability (Cancelliere et al., 2014). However, these researchers suggested that longitudinal research is needed to better understand the long-term impact of returning to work through a complicated multi-layered system. Many stakeholders are involved in the process of returning to work for individuals with a TBI including the individual, health care providers, coworkers, supervisors, employers, unions, insurers, government, and society in general (Cancelliere et al., 2014). This indicates that more than just the individual's job role is impacted by potential deficits they encounter after injury. Following these individuals over a longer period of time may provide more information on the overall impact. In addition to longitudinal research after mild TBI, more research is needed to compare the return to work potential for moderate and severe TBIs.

The study by Ruffolo and colleagues (1999), reviewed earlier was included in Cancelliere's review. These researchers examined the return to work rate for individuals with mild TBI following a motor vehicle accident. Participants (N=63) were initially assessed one month after injury, then follow-up assessments were done 6 to 9 months post injury. At follow up, 12% returned to pre-injury employment, 30% found modified employment, and 58% had not returned to work. The group who had returned to work reported significantly more social interaction than those who had not. There were no significant differences between injury severity or demographic characteristics between those who returned to work and those who hadn't. However, individuals with higher education were more prominent in the return to work group (Ruffolo et al., 1999). These findings are interesting, because they demonstrate the variability between individuals' ability to return to work within the same injury severity diagnosis. More research is needed to better understand what other factors are involved in returning to work following TBI.

A study by Cifu and colleagues (1997) evaluated individuals at four TBI treatment centers. The individuals were admitted to acute care within 8 hours of injury and then assessed at one-year follow ups for employment status.

Individuals who were unemployed at follow-up were found to have significantly longer hospitalizations, higher Gloscow Coma Scores at admission, and significantly longer posttraumatic amnesia. Additionally, individuals who were unemployed at follow-up had lower physical functioning levels at entrance to rehabilitation, more challenging behavior, and substantially lower cognitive scores (Cifu et al., 1997). These findings provide a significant amount of information regarding someone's TBI deficits before and after rehabilitation and how that relates to their employment status at a one-year follow up. Individuals who have a more severe injury and are at a lower rate of functioning on various levels before and after rehabilitation are less likely to be employed. More research is needed to understand the other outside factors that can play a role in returning to employment following TBI.

Similarly, Benedictus, Spikman, and van der Naalt (2010) investigated the relationship between cognitive and behavioral impairment and return to work for individuals with TBI of all severity levels. Outcome measures, including a return to productivity measure, were assessed at 6-months for mild and moderate TBI and at one-year for severe TBI. Half of the participants in the study (N=434) were able to return to their previous productive activities completely. Twenty-five percent of participants resumed work at a lower level, leaving 25% who had not returned to productivity at all. As expected, individuals with injuries of lower severity had a higher return to productivity rate. Physical, cognitive, behavioral, and social functioning were all assessed separately and significantly predictive of returning to work (Benedictus, Spikman, and van der Naalt, 2010). Individuals who had a higher level of functioning in all areas were more likely to return to work, with individuals who had less severe injuries returning at the highest rate. More intervention research is needed to evaluate the impact of programs that focus on returning to productivity after injury.

Given the amount of research available on follow up for returning to productivity after a TBI, it is clear that there are potential deficits, but many individuals do manage to either return to pre-injury activities or engage in lower level activities. Individuals who do not return to work or have more

difficulty finding a new vocational option compatible with their post-injury abilities are important to consider. Fortunately, programs have been developed to aid in relearning or developing skills for individuals after a TBI.

Fadyl and McPherson (2009) conducted a review on vocational rehabilitation efforts for individuals with TBI. This review evaluated studies that examined "vocational rehabilitation," which included programs for individuals with TBI with the main goal of achieving a vocational outcome. The researchers identified three categories of programs: program-based vocational rehabilitation, supported employment, and case coordination. The program-based vocational rehabilitation consists of intensive individualized work skills, guided work trials, and assisted placement with transitional job support. Supported employment consists of job placement, on-the-job training, and long-term support. Case coordination is a holistic approach, individualized to meet the individual's needs. The studies included in this review under each of the three categories varied differently in approach, injury severity addressed, and outcomes measured, so it is difficult to come to a general conclusion (Fadyl and McPherson, 2009). However, it is clear that vocational rehabilitation is very important for this population. More research is needed to better under how to improve the quality of various vocational rehabilitation programs to better meet the needs of individuals with TBI.

Though returning to productive activity is an important part of community integration post injury and the role of most rehabilitation programs is to encourage community integration, more research is needed to best determine how to increase the return to productivity rate for individuals with more severe TBIs. There is a vast amount of research evaluating the return to work rate, but not enough interventions focused on vocational rehabilitation programs to increase the opportunities for this population to return to work.

Independence

The third major component of community integration following TBI is independence. As discussed in the previous section, returning to work or school can provide some independence. Individuals who do not return to productive activity may feel less independence or sense of belonging without it (Rapport, Hanks, and Bryer, 2006). However, it is important that these steps are taken at the appropriate time for the individual with TBI. Sanders and colleagues (1997) assessed the individual with TBI and family members on the individual's post-injury community integration. Interestingly, they found that individuals with TBI reported their productivity levels and home integration levels higher than their family members in all areas except for daily travel. With this difference in perceptions, it is important to understand independence predictors and potential outcomes.

Independence is more than just living independently or what is done within the home. It can include personal care, such as feeding or grooming oneself, more domestic activities, such as laundry or cleaning, and more community integrated tasks, such as the ability to use public transportation, drive, or grocery shop. These abilities of independence significantly impact overall community integration and quality of life for individuals with TBI.

Hoofien and colleagues (2002) assessed various socio-economic variables and injury severity for predicting long-term outcomes following TBI, including daily functioning. They found that severity of injury, length of hospitalization, and time in rehabilitation predicted ability to complete ADLs (Hoofien et al., 2002). This is to be expected as more severe injuries result in more significant deficits in various areas that impact daily functioning.

Olver, Ponsford, and Curran (1996) evaluated individuals with TBI 2- and 5-years post injury to assess their levels of functioning overtime. For independence functioning, a significant number of individuals improved their ability to do ADLs improved between year 2 and 5. Increased independence was shown in personal tasks (i.e., feeding and grooming), as well as, larger tasks (i.e., laundry and gardening) (Olver, Ponsford, and

Curran, 1996). Additionally, some participants were able to do more community tasks independently and even driving. Another follow-up was done at 10 years post injury for this cohort, to find there was a small decline in independence in use of public transportation and driving. Additionally, there was some decline in leisure activities at the 10 year follow up for individuals with moderate to very severe injuries (Ponsford et al., 2014). These findings demonstrate the importance of longitudinal research for individuals with TBI, as many participants in this study continued to make significant progress in daily tasks several years after injury and with minimal decline in independence.

As noted in the longitudinal studies above, return to driving is a major part of regaining independence following TBI. A study by Rapport and colleagues (2006) found that individuals who had returned to driving after a TBI reported a sense of belonging, social mobility, and occupational integration (Rapport, Hanks, and Bryer, 2006). Another study by Rapport and colleagues (2008) examined the existing barriers individuals with TBI face when attempting to return to driving. A majority of the sample (76%) reported diagnosis of a moderate to severe TBI. Nearly half of the participants reported returning to driving, with most of those who had not returned to driving being individuals with more severe injuries. Individuals who had not returned to driving, but wanted to, reported social and resource related barriers such as the primary caregiver not wanting the individual to drive or lack of access to a vehicle. Additionally, the researchers examined how independent driving can impact community integration post-injury. Individuals who had not resumed driving reported lower scores of community integration compared to those who had resumed driving. The largest negative impacts on community integration were related to social integration and productivity opportunities (Rapport, Bryer, and Hanks, 2008). These findings bring us full circle to the overall concept of community integration. Through this chapter we have explained the components separately but each component influences other components in various ways.

Regaining independence after TBI can be a long term, multi-layer process. The research reviewed in this section demonstrates that recovery

can continue for several years after injury. Additionally, we know that severity of injury significantly impacts the individual's ability and independence. Future research is needed to determine how various aspects of independence can be improved after rehabilitation programs have concluded.

CONCLUSION

Traumatic brain injuries impact millions of individuals around the world every year. The variety of chronic deficits individuals face after a TBI can include physical, psychological, and behavioral areas. These deficits can make integration back into the community difficult post injury. Though injury and recovery is different for each person, there are many systems in place to support recovery.

Many rehabilitation programs have been developed with the primary goal of helping the individual integrate back into the community. Community integration is a multidimensional concept that can be broken down and evaluated as three main components, including social integration, return to productivity, and independence. Rehabilitation programs have been created to focus and successfully improve each of these components, as the most effective programs tend to consist of multidimensional programs that address the multitude of deficits. These components can be individually influenced, but also have been shown to influence each other. Social integration is potentially the most important component of community integration, as it has such a large impact on success in rehabilitation efforts, quality of life post injury, and opportunities for returning to productivity. More research is needed to better understand the dynamic of social support for individuals with TBI and why there is a decrease overtime post injury.

Additionally, more individualized programs are needed to better actively prepare individuals for return to productivity. Regaining independence after injury is another multilayered aspect that also requires individualized attention to improve on the needs of the individual. Future research should focus on how the components of community integration can

be addressed and integrated into a comprehensive program for individuals with TBI. More programs are needed to provide assistance after individuals are discharged from rehabilitation programs. With the right programming and resources, individuals with TBI can regain community integration and live a satisfying life post injury.

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Chapter 4

MANAGEMENT OF ACUTE ISCHAEMIC STROKE

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ABSTRACT

In this chapter, the various management of ischaemic stroke will be discussed.

The management of ischaemic stroke can be divided into hyper acute management, acute management and long term management of stroke. In addition, the updates of hyperacute management of acute ischaemic stroke such as thrombolysis with intravenous alteplase and mechanical thrombectomy will be discussed.

The acute management in stroke unit is also very important. The control of blood pressure is essential. A multidisciplinary team consisting stroke neurologists, rehabilitation doctors, physiotherapists, occupational therapists, speech therapists, dietitians and staff nurses, is essential in the management of stroke. Moreover, the long term management which includes rehabilitation and follow-up in clinics will be discussed. The

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identification and optimization of vascular risk factors, such as atrial fibrillation, diabetes mellitus, hypertension and hyperlipidaemia, need to be emphasized.

INTRODUCTION

Intravenous thrombolysis with Recombinant Tissue-type Plasminogen Activator (rt-PA) is the only effective treatment for acute ischaemic stroke (AIS) [1, 2]. In patients who have AIS and large vessel occlusion (LVO), intravenous thrombolysis and endovascular therapy are standard of care [3]. Nevertheless, the effects of endovascular therapy (EVT) is superior to intravenous thrombolysis [3].

Neuroimaging in stroke patients, especially in the patients with AIS, plays a crucial role [4]. Brain imaging assists in distinguishing other causes of stroke such as seizures, tumours and migraine [4]. Plain computed tomography (CT) scan of the brain differentiates ischaemic stroke from hemorrhagic stroke [4]. CT angiography (CTA) of the brain helps in providing treatment planning for intravenous thrombolysis and EVT [4]. CT perfusion demonstrates the penumbra and helps in the identification of salvageable tissue from irreversible infarcted tissue [4].

HYPERACUTE MANAGEMENT: THROMBOLYSIS WITH INTRAVENOUS ALTEPLASE

Clinical Outcome

Early initiation of stroke thrombolysis and shorter door to needle time (DNT) are associated with good functional outcome [5, 6]. The administration of IV alteplase was associated with a reduction in oedema-corrected tissue infarct volume, which may help improve clinical outcome [7, 8]. The NIHSS score pre-thrombolysis was an independent factor for the functional outcome of the thrombolsyed patients [9].

In addition, fasting blood glucose and SBP on admission were independently associated with poor outcome in the AIS patients who were thrombolysed [8]. SBP on admission and mean arterial pressure (MAP) during thrombolysis were independently associated with outcome of these patients [9]. The glycated hemoglobin index of the patients with diabetes mellitus (DM) and the accumulated amount of cigarette consumption was negatively correlated with the functional outcome after stroke thrombolysis [9].

In a previous study, ADAMTS13 activity was associated with early neurological improvement in the AIS patients treated with alteplase [10]. Furthermore, higher levels of serum cystatin C in the patients with AIS after administration of iv alteplase were independently associated with poorer clinical outcomes [11]. Serum cystatin C reflects chronic kidney disease.

Circulating microRNAs consisting of miR-124-3p, miR-125b-5p and miR-192-5p were associated with poor clinical outcome at 3 months in the patients with AIS who were administered alteplase [12]. Subclinical hyperthyroidism was associated with higher risk of early neurological deterioration, poor functional outcome and death at 3 months in thrombolysed AIS patients [13].

Haematological parameters also determine the functional outcome of the patients. An increase in the baseline absolute neutrophil counts and neutrophil ratio were associated with higher risk of disability and mortality at 3 months in the patients with minor stroke who received intravenous alteplase [14]. Peripheral monocyte count $\geq 0.53 \times 10^9$/L is also an independent prognostic marker in the thrombolysed patients at 3 months [8].

In summary, the factors which determine clinical outcome in the thrombolysed stroke patients are shorter door to needle time (DNT), reduction in infarct volume, fasting blood glucose on admission, SBP on admission, MAP during thrombolysis glycated hemoglobin index, accumulated amount of cigarette consumption, serum cystatin C, microRNAs, subclinical hyperthyroidism, neutrophil count and monocyte count.

Complications of Intravenous Alteplase

Symptomatic intracranial haemorrhage (SICH) is a complication of intravenous alteplase [34]. The predictors of SICH are renal dysfunction, MAP on presentation to emergency, presence of early infarct signs on CT scan of the brain and blood glucose ≥ 185 mg/dL (10.3 mmol/L) on presentation [15, 16]. Renal function is independently associated with SICH after intravenous thrombolysis [15]. Renal dysfunction is an independent predictor for both $SICH_{NINDS}$ and $SICH_{ECASS\ II}$ [15].

Intravenous alteplase increases the biomarkers of blood brain barrier breakdown [7]. Alteplase is associated with haemorrhagic transformation of the infarct [7]. The predictors of haemorrhagic transformation are infarct volume and atrial fibrillation (AF) [17, 18]. In a previous study, infarct volume observed on the diffusion weighted image (DWI) sequence of the Magnetic resonance imaging (MRI) of brain was the only MRI brain parameter that gave additional clinical and biological value for predicting haemorrhagic transformation [17]. In addition, AF was independently associated with the presence of haemorrhagic transformation [18].

Ischaemia/reperfusion injury is a complication of alteplase [19]. Oxidative stress plays an essential role in the pathogenesis of ischaemia/reperfusion injury [19]. Hypoxia and reoxygenation induced expression of oxidative stress-responsive apoptosis inducing protein (ORAIP) in the neurons of cultured rats, lead to extensive apoptosis of these cells [19]. The apoptosis was predominantly inhibited by neutralizing anti-ORAIP monoclonal antibody in vitro. The brain ischaemia/reperfusion significantly increased ORAIP levels in cerebrospinal fluid. ORAIP may play an important role in the cerebral ischaemia/reperfusion injury induced by thrombolysis and thrombectomy [19].

In addition to bleeding, anaphylaxis is another complication of alteplase [20]. In a recent study, anaphylaxis occurred in 0.54% of the patients who received intravenous alteplase compared to 0.07% who did not receive alteplase [20].

Histopathology of Thrombus in AIS

The thrombi found in the arteries of the patients with AIS had highly heterogeneous composition and organization [21]. Despite so, the similarity between all the thrombi was the outer shell comprising of fibrin, von Willebrand factor and aggregated platelets [21]. In the thrombi in patients and in vivo, the outer shell demonstrated showed a reduced tendency to lysis by alteplase compared to the inner core [21].

Statin Therapy

Statin is an important medication in AIS. Statin reduces the serum lipid levels, acts on the inflammatory response and is involved in cell apoptosis. [22]. In a large meta-analysis, treatment with statin at stroke onset was associated with good functional outcome at three months [23]. In a previous study, high-intensity statin with good adherence after AIS was significantly associated with a lower risk of recurrent strokes, acute myocardial infarction and all-cause mortality [24] Improved adherence to statin therapy was associated with a lower risk of stroke, especially ischaemic stroke [25]. In addition, good adherence to statin or high dose statin was not associated with an increased risk of hemorrhagic stroke [24].

Thrombolysis in the Patients with Minor Stroke

In a recent study, thrombolysis with alteplase was reported to be safe in the patients with AIS presenting with with minor deficits (initial NIHSS score ≤ 5) and were initially assessed by MRI of the brain [26]. In these patients, the frequency of haemorrhagic transformation was 13% [26]. Whereas, the frequency of SICH was only less than one percent [26]. 74% of the study patients had good outcome at 3 months [26]. Although administration of alteplase may increase the risk of SICH based on existing studies, the patients with minor AIS benefitted from alteplase at 3 months [27].

In another recent study, mild ischaemic stroke patients with (LVO) and did not have rapidly improving symptoms had good outcome at 3 months [28]. However, recent Potential of rtPA for Ischemic Strokes with Mild Symptoms (PRISMS) trial, which randomized patients to thrombolysis vs aspirin, did not show benefit to the patients with mild ischæmic stroke [26, 29]. However, the very early study termination precludes any definitive conclusions [29].

Aphasia

In a previous study, the percentage of patients with resolved aphasia was significantly higher in the patients with alteplase compared to the non-treated patients [30]. In addition, the non-treated patients had a higher percentage of global aphasia [30]. Evaluation of the subtypes of aphasia, whether receptive aphasia or expressive aphasia after stroke thrombolysis could be performed even though the cerebral regions had been reperfused [30]. Reperfusion treatment with alteplase, NIHSS on arrival to emergency and lacunar stroke were the major predictors of aphasia recovery [30].

Carotid Endarterectomy after Stroke Thrombolysis

The timing of carotid endarterectomy (CEA) after intravenous thrombolysis is still not known. In a previous study, CEA performed early after intravenous thrombolysis for AIS (within first 24 hours to 13 days) was reported to reduce the risk of stroke recurrence but also achieve neurological improvement by reperfusion of the ischaemic penumbra [31]. This may be safe and can lead to good clinical outcome [31].

In another study, CEA post-thrombolysis had a low incidence of mortality [32]. However, in another study, the clinical outcome of CEA after administration of alteplase was similar to the outcome of CEA in the general stroke population [32].

HYPERACUTE MANAGEMENT WITH THROMBECTOMY

Endovascular therapy (EVT) for ischaemic stroke due to LVO was widely accepted especially in the year 2015 onwards [33, 34]. EVT is the standard of care for anterior circulation ischaemic strokes due to LVO in the patients who are eligible for this management [35, 36]. Appropriate patient selection is important so that timely reperfusion can be achieved [36]. Recommendation of EVT and best medical management, including intravenous thrombolysis is based on high quality in improving the functional outcome in the patients with AIS due to LVO within 6 hours after stroke onset [36]. In addition, recommendation of EVT and best medical management in the time window of 6 to 24 hours, is based on moderate quality of evidence [36]. In the patients with AIS due to LVO in the proximal anterior intracranial circulation, less than 40% had functional independence when administered alteplase [37]. EVT with stent retriever, in addition to intravenous alteplase, increases reperfusion rates and may improve long-term clinical outcome [37].

Landmark Studies

There were several landmark studies which reported on the benefits of EVT [38-40]. The landmark studies published were Diffusion-weighted imaging (DWI) or computerized tomography perfusion assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) and Endovascular Therapy Following Imaging Evaluation for Ischaemic Stroke 3 (DEFUSE 3) [38-40]. The studies demonstrated the benefits of EVT in the patients with target mismatch [38, 41-42]. The penumbra was evaluated by clinical-core mismatch or perfusion-core mismatch in the extended time period up to 16 hours in DEFUSE 3 clinical trial after last known normal time (LNT) [38, 41-41]. In the DAWN trial, the target mismatch was measured 24 hours LNT [38, 41-42]. In the patients with wake-up stroke, the LNT was presumed to be the onset time of the stroke [43].

In the DAWN study, the patients with LVO in the anterior circulation were randomized between 6 and 24 hours from LNT [41]. These patients were subsequently assessed for target mismatch between clinical deficit and ischaemic core [41]. Most of the patients (78%) had occlusion in the first segment of the middle cerebral artery (MCA), followed by the intracranial internal carotid artery (19.9%) and the second segment of MCA (2.4%) [41]. The percentage of the patients with good outcome (MRS 0-2) at 3 months was significantly higher in the EVT group (49%) compared to the control group (13%) [41]. For every two patients managed with EVT, one additional patient had a clinical improvement in three months [41]. For every 2.8 patients who underwent EVT, one additional patient had good outcome (MRS 0-2) at 3 months [41].

The clinical benefit observed in DAWN was demonstrated by successful reperfusion with EVT [41]. In the EVT group of patients, 84% of the patients had successful recanalisation (grade 2b or 3 on modified Thrombolysis in Cerebral Infarction, mTICI scale [41]. There canalization was achieved at a median interval period of 13.6 hours from LNT to reperfusion [41]. In the EVT group of patients, they had significantly higher rates of early response [41]. Early response is defined by a reduction in the NIHSS score by at least 10 points or NIHSS score 0–1 within 7 days or at discharge in comparison to the control group [41]. In addition, the EVT group had significantly higher rates of early recanalisation at 24 hours from stroke onset [41]. The EVT patients also had significantly lower infarct volume and infarct progression at 24 hours [41].

In the DEFUSE 3 study, the patients with large vessel occlusion (LVO) in the anterior circulation had EVT in 6 to 16 hours from LNT [42]. They were also evaluated for target mismatch by ischaemic core and penumbral regions with then CT perfusion as well as MRI diffusion and perfusion images [42]. The most common location of occlusion was the MCA (114 patients, 63%) [42]. 113 patients had LVO at first segment of MCA (M1 segment) and one patient had occlusion in the second segment of MCA (M2 segment) [42]. The next common site of occlusion was the intracranial internal carotid artery (ICA) (37%) [42]. The MRS at 3 months was better in the EVT group compared to the control group [42]. The percentage of the

patients with good functional outcome (MRS 0-2) at 3 months was much higher in the EVT group of patients compared to the control group (45% vs. 17%) [42].

In the patients who underwent EVT, 76% of them had successful recanalisation at median interval of 11.5 hours from LNT [42]. At 24 hours, infarct volume was lower in the EVT group than in the control group (35 mL vs. 41 mL) [42]. In addition, infarct growth was lower in the EVT group than in the control group (23 mL vs. 33 mL) [42]. Complete recanalisation at 24 hours was more than four times higher in the EVT group compared to the control group [42]. Reperfusion of more than 90% was increased more than four-fold in the EVT group [42].

However, there was not much difference in the percentages of SICH between the EVT group and the control group (7% vs. 4%) [42]. The mortality rate at 3 months was slightly lower in the EVT group than in the control group (14% vs. 26%, P=0.05) [42].

CT Perfusion Imaging and Other Neuroimaging

Many guidelines recommend CT perfusion as an essential investigation before EVT is performed [43]. The main role of CT perfusion in AIS is to assess whether there is a large area of cerebral tissue which can be salvaged and saved (penumbra) with timely reperfusion [44, 45]. CT perfusion enables the distinction between penumbra from infarcted and unsalvageable areas of brain (ischaemic core) from areas of potentially salvageable (penumbra) tissue [43, 45]. The penumbra is the target for reperfusion therapy [45]. In AIS, a critical reduction in blood flow results in the ischaemic core [46]. The penumbra can remain salvageable for a few hours [46]. Therefore, urgent restoration of blood flow is very important [46]. CT perfusion images can be rapidly and easily obtained on all the CT scan machines and easily incorporated into an AIS neuroimaging protocol [45].

AIS patient selection for EVT using advanced neuroimaging (perfusion scans) is associated with improved clinical outcomes [47]. Studies using advanced neuroimaging showed higher treatment effects of EVT on 3-month

functional independence, favourable functional outcome and functional improvement compared with studies using conventional neuroimaging [47]. The pooled rate of successful reperfusion after EVT was higher in studies with advanced neuroimaging [47].

CT perfusion is a one-min dynamic acquisition of contrast bolus passing through the brain [44]. This is selected on CT perfusion maps which demonstrate various features, such as, cerebral blood flow (CBF), cerebral blood volume (CBV), and the timing of the bolus contrast arrival and passage (time to maximum and mean transit time) [44].

The time to maximum (Tmax) is defined as the time from the start of the CT perfusion scan until the maximum intensity of contrast material arrives at each voxel [45]. CBV represents the total volume of flowing blood in a given volume in the brain [45]. CBF is a measure of rate, and is defined as the volume of blood flowing through a given volume of brain per unit time [45]. The mean transit time (MTT) is the average time taken for the contrast to flow through a region in the brain [45].

The time to peak (TTP) is the time from the start of injection until the maximum peak of contrast enhancement [45]. The time to drain (TTD) is the time from maximum enhancement to a defined low cut-off [45].

The ischaemic core which is the infarcted area, has severe reduction of CBF and also decreased CBV [45]. The values of MTT and TTP are prolonged [46]. The ischaemic penumbra has increased MTT and Tmax [45]. The penumbra has moderately reduced CBF [45]. In addition, the penumbra has near normal or even increased cerebral blood volume because of autoregulatory vasodilatation [45]. The cerebral metabolism is usually reduced despite the relative hyperaemia [45]. Therefore this is called luxury perfusion [45].

The patients transferred from other hospitals (under “mothership” or drip and ship” models) are seen in the emergency department by the local stroke team and transferred to the neuroradiology suite [46]. The neuroradiologist, will decide on the need for CT perfusion to assess for eligibility for EVT [46].

In a recent study, use of CT perfusion instead of MRI of the brain (stroke protocol without perfusion) in the hyperacute stroke protocol may expedite

intra-arterial intervention [44, 48]. In this study, stroke imaging time was reduced from an average of 158 minutes to 81 minutes (49%) by substituting CT perfusion for MRI brain [48]. Other reasons for the utilisation of CT perfusion rather than MRI are cost factors and workflow reasons [44].

Besides evaluating for penumbra and infarct area, CT perfusion can assist in ruling out cerebral ischaemia when the clinical diagnosis is not certain [44]. In addition, CT perfusion can help clarify and confirm if there is LVO when the CT angiography (CTA) results are equivocal [44].

Recently, susceptibility vessel sign has been reported to be a reliable predictor of recanalization success and early clinical improvement after EVT [43]. Bourcier et al. reported that susceptibility vessel sign on MR imaging before treatment is predictive of favorable clinical outcome for patients presenting with anterior circulation acute stroke and treated with mechanical thrombectomy [36].

Stent Retriever and Catheter

The two most common methods for EVT of LVO are direct aspiration and primary stent retriever [49]. In a recent study, both aspiration-first (including the subsequent use of stent retriever) and primary stent retriever EVT approaches are equally effective in achieving good functional outcomes [49]. This study suggested that direct aspiration with or without subsequent use of stent retriever was a safe and effective alternative to primary stent retriever in AIS [49].

There were several developments regarding catheters and stent retrievers in EVT. In a recent study, the use of a balloon guide catheter was associated with higher reperfusion grade and early improvement of neurological deficits [50]. However, the use of balloon guide catheter did not lead to any benefit on long-term clinical outcome [50].

In another study, stent retriever device may be more likely to retrieve high-density thrombi [51]. Whereas contact aspiration is more likely to retrieve low-density thrombi [51]. The CATCH+ stent retriever device was reported to be a safe and effective device for EVT [52]. In addition, the use

of argatroban after EVT prevents reocclusion of the stenosed artery [53]. Argatroban, is an anticoagulant that is a small molecule direct thrombin inhibitor. The bleeding complications with argatroban is minimal [53].

Low NIHSS and Large Vessel Occlusion

The guidelines recommended EVT for NIHSS ≥6 [54]. In the study by Sarraj et al. there was no improvement in excellent and independent functional outcomes in mild strokes (NIHSS <6) receiving thrombectomy irrespective of thrombus location, with increased SICH rates [54]. However, in another study by Toth et al. EVT has been reported to be safe and feasible in the patients with low NIHSS (NIHSS < 6) and LVO [55].

In the study by Pfaff et al. the clinical outcome of patients undergoing EVT for mild AIS with (NIHSS ≤ 8) due to LVO seems to be mainly favourable, even in a prolonged time window [56]. Nagel et al. reported that EVT in LVO patients with low NIHSS (NIHSS ≤ 5) on presentation may be safe and had the potential to lead to improved clinical outcomes [57].

Anaesthesia

The more common types of anaesthesia used in EVT are conscious sedation (CS) or general anaesthesia (GA). Anaesthesia will be more comfortable for the patients undergoing EVT [35, 46]. Conscious sedation (CS) or general anaesthesia (GA) will reduce movement and restlessness during EVT [35].

There were three recent prospective randomised controlled studies of CS vs GA for EVT which were published [46]. The Sedation vs Intubation for Endovascular Stroke Treatment (SIESTA) trial did not show an advantage of CS over GA [46, 47]. In this trial, the percentage of the patients with MRS of less than two at 3 months was significantly higher in the GA group [46, 47]. In addition, in the Anesthesia during Stroke (AnStroke) trial, the patients were randomised patients to GA (propofol/remifentanil for

induction with sevoflurane/remifentanil maintenance) or CS (remifentanil infusion) [46, 58]. There were no differences in early neurological recovery, infarct volume, anaesthetic complication and neurointerventional complication [46, 58].

In the General or Local Anaesthesia in IntraArterial Therapy (GOLIATH) clincal trial, the patients were randomized to CS (fentanyl and propofol) or GA (propofol and remifentanil for maintenance of anaesthesia) [46, 59]. There was a trend towards better clinical outcomes in the GA group with lower MRS scores [46, 59]. However, similar to the AnSTROKE study, there was no difference in the infarct volume [46, 59].

In the HERMES collaboration on the role of GA in a meta-analysis, the patients who had GA had worse outcome after adjusting for baseline characteristics [46, 60]. The conclusion from this meta-analysis was that GA should be avoided whenever possible [46, 60].

For every 100 patients who either had treated GA vs non-GA, 18 patients had worse clinical outcome. Out of these 18 patients, 10 did not achieve independence [46, 60].

STROKE UNIT

The stroke patients who receive treatment in stroke unit in the hospital wards have reduced morbidity and mortality [61, 61]. They have better functional outcome because of the specialist multidisciplinary care available in the stroke units [61, 61]. The patients managed in stroke units are also more likely to be independent and living at home one year after the stroke [61].

Specialist multidisciplinary care in stroke units allow for early diagnosis of complications of stroke such as haemorrhagic transformation of infarcts [62]. Availability of stroke unit also enables prevention of complications such as aspiration pneumonia, deep venous thrombosis and urinary tract infection [62]. Secondary prevention of strokes can be achieved when there are stroke units [62].

A standard patient pathway for stroke management includes an assessment of neurological deficit, speech impairment, dysphagia, nasogastric tube feeding and fluid balance [31]. The other management plans are evaluation of ADLs, rehabilitation plans, continence, depression and cognitive function [31]. It is crucial that good communication and shared decision making with the stroke patients and their families are present [31].

BLOOD PRESSURE CONTROL DURING ACUTE STROKE

Systolic blood pressure (SBP) needs to be managed adequately (towards normal values) after thrombolysis for AIS [63]. Proper treatment of SBP is associated with an increase in early neurological improvement [63]. This is demonstrated in terms of improvement of NIH stroke scale (NIHSS) [63]. A reduction of 10 mmHg in SBP after 24 hours is associated with a 0.51 point reduction in the NIHSS score [63].

Blood pressure treatment after stroke thrombolysis with the aim of SBP < 180 mm Hg is consistent with guidelines and is recommended [64, 65]. In a study on the patients who had thrombectomy for AIS, the percentage of patients with good outcome (MRS 0-2) at 3 months was significantly lower in the patients who had mean SBP >130 mm Hg over the 24 hours after EVT (40.5% vs. 66.7%,) [66]. In EVT, arterial BP should be maintained within the patient's physiological range (within 10% of the baseline values) [31].

MULTIDISCIPLINARY TEAM APPROACH AND REHABILITATION

Rehabilitation which includes optimal positioning and early mobilisation for the patients with acute *stroke is encouraged* [67]. Moreover, a co-ordinated multidisciplinary team at work has made a significant contribution to improvement in the quality of care in the stroke services rendered to the patients [68]. In addition to impairment of upper and lower limb function as well as mobility, the other consequences of stroke include

cognitive, speech, communication and visual field disturbances [68]. The impact of stroke also includes relationship changes, psychological problems and the challenges of coping with long-term disability [68]. As a result, multidisciplinary approach is important.

Multidisciplinary team approach in stroke is fundamental to delivering effective rehabilitation for the stroke patients [68]. Rehabilitation should commence as early as possible after stroke [68, 69]. Repetitive task-oriented training targeted at goals or activities relevant to the needs of patients can contribute to functional recovery, especially where the training is conducted in the patient's own environment [68, 70-72]. An increase in intensity of training is beneficial [68, 72].

The stroke team consist of stroke physicians, occupational therapists, physiotherapists, speech therapists, stroke nurses, rehabilitation specialists and stroke psychologists [68]. Stroke nurses can talk to the patients and relatives, and educate them on secondary stroke prevention [68].

Reported benefits of effective multidisciplinary team working include more patient-centred decision making, a reduction in the fragmentation of care and increased staff satisfaction, as well as more efficient and effective use of resources [68, 73-80]. A multidisciplinary team approach is the most effective way of providing high-quality stroke services [61, 68, 81].

EARLY SUPPORTED DISCHARGE

Early supported discharge (ESD) is important because ESD leads to earlier discharge to the home and increase the likelihood that the patients will regain independence in the activities of daily living (ADL) [68, 81-83]. This will result in fewer patients requiring long-term institutional care [68, 81-83]. The stable stroke patients with mild or moderate disability can continue rehabilitation at home with ESD teams rather than needing a prolonged stay in hospital [31].

The ESD team provides for continuity in rehabilitation, initially with the stroke unit multidisciplinary team and then after several weeks, there will be the involvement of the wider community rehabilitation team [68]. A

decrease in the length of stay in hospital of up to ten days can be achieved for those who are suitable for the ESD [68, 88]. ESD has resulted in significant potential saving of cost and money [68, 88].

PSYCHOLOGICAL CARE OF STROKE PATIENTS

Management of psychological care after stroke is important because up to 31 percent of the patients will have depression [68, 85, 86]. Approximately 20 percent of the stroke patients will experience anxiety [68, 85, 86]. In addition, 35 to 60 percent of them will have cognitive impairment of varying degrees [68, 85, 86].

There were several reasons for depression post-stroke. Physical disability is the main reason for depression after stroke. Approximately 15-40% of the stroke patients have loss of function of the upper limbs one year after the stroke onset [86, 87]. Furthermore, about 40% of the patients with stroke have problems with swallowing and may require nasogastric tube or percutaneous endoscopic gastrostomy (PEG) [86, 87]. Approximately 33% of the stroke patients had speech difficulties, including expressive dysphasia and receptive dysphasia [86, 87]. Some of the patients need help for their ADLs [86, 88].

LONG TERM MANAGEMENT

Follow-up in Stroke and Neurology Clinics

It is important to refer to stroke clinic when the stroke patients are discharged. This is because in a previous study, stroke clinic referral was associated with a lower risk of one-year mortality compared to the patients who were discharged without follow-up [89].

In a previous study, the factors associated with successful follow-up in stroke clinic were hospitalization to the neurology ward ($p=0.015$) and use of templated stroke-specific discharge instructions ($p=0.007$) [90]. The

presence of written date and time for follow-up on the instructions ($p<0.001$) was also associated with follow-up in stroke clinic [90].

In the study, the patients with milder strokes (NIHSS < 5 on admission and discharge were more likely to have follow-up in stroke clinic ($p=0.003$ and $p=0.006$ respectively) [90]. However, there was only borderline statistical significance for successful follow-up in stroke clinic among the patients discharged home in comparison to rehabilitation centre or nursing home ($p=0.05$) [90].

In another study, only health insurance status was associated with neurology clinic follow-up after acute stroke admission (51% without insurance vs. 59% with insurance attended follow-up, $p=0.02$) [91]. In another study, the association of 90-day follow-up visit in clinic at 3 months with patient demographics, clinical factors and discharge variables were analysed [92]. Differences were significant for insurance carrier [commercial (55%) vs Medicare (28%) and Medicaid (31%); $p<0.001$)], appointment scheduled at discharge (54% vs 32%, $p<0.001$), primary service [neurology (49%) vs medicine (13%); $p<0.001$)], mRS [less than 4 (52–58%) vs 4 (34%) vs 5 (0%); $p=0.01$], ambulatory status [independent (52%) vs assistance (44%) vs non-ambulatory; $p=0.003$], transition of care call [called-confirmed (79%) vs called-unreachable vs no documented call (41%)] and discharge disposition [Home (52%) vs acute care facility (38%) vs other (35%); $p=0.006$]. Insurance carrier, ambulation, transition of care call and appointment at discharge statuses remained significant in the multivariate analysis [92].

In the study by Temple et al. the patients were more likely to arrive for their appointment if they lived closer to the clinic (although rural/urban residence did not differ) had shorter length of stay, lower admission NIHSS and lower discharge MRS [93]. When controlling for distance to clinic, smokers were at a higher odds of being a no show or cancelling their appointment [93].

Optimisation of Vascular Risk Factors

It is important to optimize vascular risk factors for secondary prevention of stroke [94]. The modifiable risk factors are include hypertension, diabetes mellitus, hyperlipidaemia, smoking, atrial fibrillation, ischaemic heart disease, carotid artery stenosis, obesity and postmenopausal hormonal therapy [95]. Nonmodifiable risk factors are increasing age, gender and ethnicity [95]. Less well-documented or potentially modifiable risk factors include metabolic syndrome, alcohol abuse, drug abuse, oral contraceptive pill (OCP) use, sleep-disordered breathing, migraine and raised serum homocysteine [95].

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Chapter 5

NEWER APPROACHES TO NEUROSURGERY

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ABSTRACT

As the scientists continue to make new innovations with each passing day,wider coverage of information technology, better imaging techniques, use of neuro-navigation and more refined surgical instruments now allow the operating surgeons to attempt surgeries and approaches which were not possible earlier.

In this article, we attempt to review the newer technologies and approaches being applied in the field of neurosurgery and which have the potential to cause major changes in the treatment of neurosurgical illnesses.

INTRODUCTION

In last few years, the field of neurosurgery has witnessed epic progress. And the scientists continue to make new innovations each passing day. Wider coverage of information technology, better imaging techniques, use of neuronavigation and more refined surgical instruments now allow the operating surgeons to attempt surgeries and approaches which were not possible earlier. While some of these newer approaches have established themselves as treatment modalities of choice, others need to be further understood to realize their full potential.

In this chapter we attempt to review the newer technologies and approaches being applied in the field of neurosurgery and which have the potential to cause major changes in the treatment of neurosurgical illnesses. We discuss the following newer approaches in the chapter

1. Magnetic Resonance Focused Ultrasound (MRFS)
2. Tubular Retractors
3. Tumor Treating Fields (TTF)
4. Minimally Invasive Pediatric Neurosurgery
5. Genetic Strategies
6. Gamma Knife Surgery
7. Laser Interstitial Thermal Therapy (LITT)
8. Robotic Neurosurgery

Magnetic Resonance Focused Ultrasound (MRFS)

MRFS has been touted to be a potentially game changing technology that has the potential to replace the presently popular techniques and technologies. MRI-guided high-intensity focused ultrasound (MRFS) is a novel technique which allows for precise targeting of intracranial lesions using the help of MRI. An ultrasonic beam is then delivered to the target. This ultrasonic beam destroys the lesion selectively using ultrasound-induced thermocoagulation. The ultrasound waves traverse intervening

tissues and generate heat at the point of focus. The ultrasound waves cause vibrations of molecules, which in turn generates frictional heat. Protein denaturation or coagulative necrosis occurs in the cells at a temperature of 56□C for 1 second [1].

It has been shown that MRFS acts in cancer cases by disrupting the tumour microenvironment and triggering an immune response and it also increases the effectiveness of immunotherapy [2]. MRFS has been employed in management of deep inaccessible brain tumors, like recurrent glioblastoma multiforme etc.

The procedure of MRFS takes place inside MR suite. The patient's scalp is completely shaved prior to procedure (to prevent burning of scalp by absorbed high energy from the ultrasound). General anesthesia is usually not needed though sedation may be employed. Under local anesthesia, a stereotactic frame (Cosman−Roberts−Wells stereotactic frame) is fixed on the head of the patient.

Many MRFS systems have been developed, of which ExAblate 2000 system is a popular MRFS system. In the ExAblate 2000 system, the focused ultrasound device (used for targeting region of interest) is embedded within the MRI table on which the patient lies. There is a sealed water bath inside the MRI table. The water bath also has an ultrasonic transducer. The patient is positioned with the craniotomy on top of this sealed water bath. The procedure of MRFS begins with the operating doctor employing the conventional MRI scans which are displayed on the ExAblate computer, in order to find out the target volume. The input from the physician is then used by the ExAblate computer to decide upon the optimal area to be covered by the ultrasound waves. Release of each sonication volume occurs only after image registration and confirmation of system parameters by the physician, hence the procedure minimises the chances of treatment failure as well as destruction of 'normal' areas. The physician has to make sure that the beam passes through the site of craniotomy. In this way, the whole of target volume is irradiated by the sonication volumes sequentially.

During the period of MRFS treatment, the temperature of tissue of interest rises in the range of 65 and 85°C. A set of MRI scans are acquired continuously throughout the procedure. These are called 'thermal maps' and

these are characterised by the reflection of contrast changing with change in temperature as compared to the initially acquired image. The thermal maps are used to find out thermal dose maps. These are representations which calculate the energy deposited in the area of interest from the temperature changes and their duration (in the target region). These thermal dose maps are images in which the pixels reaching predefined thresholds are displayed in different colours according to the dose received in that particular area.

Hence, these maps provide the treatment volume to confirm the therapeutic effect. Post the procedure, on table assessment of the effect of treatment can be done using MRI. The total treatment time spent during a standard MRFS procedure (including positioning, imaging, planning, and sonications) is around three hours.

MRFS has been used in patients of Parkinsonism and was found to be effective, provided immediate results and was without adverse effects [3]. It's advantages over Deep Brain Stimulator include non-invasiveness, no requirement of anesthesia or a sterile OT and no need for hardware adjustment.

Brief Clinical Review of MRFS in Neurosurgery

MRFS has been used for essential tremors, trigeminal neuralgia (refractory to medical treatment), chronic pain, brain tumors, ischaemic stroke (sonothrombolysis) and epilepsy [4-8]. MRFS has been used as a noninvasive treatment option in intracranial hemorrhage patients. MRFS is said to break down the ICH clot using both inertial cavitation and mechanical forces.

Zvi et al. demonstrated for the first time the efficacy of MRFS in destroying intracranial tumors [9]. They employed the technique on 3 patients and thermocoagulation was evident in all three patients. However, one patient developed neurodeficit due to heating of brain tissue in the sonication path.

This was followed by a report of successful ablation of an anaplastic astrocytoma transcranially ina 17-year-old female patient by Park et al. [10]. It has been suggested that MGFS is best suited for well-circumscribed

lesions such as metastases and benign tumors in locations that are difficult to access surgically. Other notable research involving MRFS included

a) Chauvet et al. in 2013 evaluated the accuracy of MRFS brain therapy using human cadavers. They demonstrated that MRFS had millimetre accuracy in brain procedures [11].
b) 30 patients with severe medication-resistant tremor underwent unilateral VIM thalamotomy using MRFS. It was found that MRFS guided VIM thalamotomy was safe and effective in patients with essential tremors and parkinson's disease. In fact, tremor reduction was comparable to that achieved after deep brain stimulation procedure [3].
c) Elias et al. in 2016 conducted a study involving 76 patients with moderate-to-severe essential tremor unresponsive to at least two trials of medical therapy. Focused ultrasound thalamotomy was performed in 56 patients while 20 patients underwent a sham procedure. They demonstrated reduced hand tremor and better quality of life in the intervention group [12].

Previously MRFS required presence of a previous craniotomy. Improvements in technique have now made possible administration of MRFS without the need of a previous craniotomy. Advantages of MRFS over traditional therapic modalities include absence of any incisions (unlike surgery), radiation necrosis and tumors (unlike radiosurgery).

However, MRFS has its share of shortcomings as well. It is not very effective for larger lesions. In addition, there is loss of energy while the ultrasonic waves travel inside the brain. Many authors have described failure of the procedure due to insufficient energy transfer to the area of interest [12, 13].

Another problem with the procedure is that the high frequency waves (which can be accurately focused and hence more safe) are more easily attenuated during their travel through the skull and hence one has to use lower frequency waves, which have less focussing abilities and can destroy the nearby 'normal' areas.

Tubular Retractors

This is a new microinvasive technique which allows management of cerebral aneurysms, cerebral tumors, intracerebral bleed, spinal surgeries etc. Tubular retractors provide a surgical corridor to treat these lesions and minimize the extent of retraction on the brain. The advantages of Tubular retractors over traditional systems include the ability to directly visualize the operative field, reduced trauma to tissues and anatomical familiarity to spine surgeons.

Using the modern systems, one can cause progressive dilatation and thus minimize the injury caused due to transection of white matter tracts. Tubular retractors have an inner obturator and a clear outer canniula. The outer cannula is fixed to a retractor system while the inner obturator separates the white matter tracts bluntly without cutting them. The path of tubular retractors is commonly planned preoperatively with or without the help of MRI such that there is minimimum transgression of eloquent brain. An approximately 3cm craniotomy is created using neuronavigation, centered on the entry point of the trajectory. Whenever possible, sulci are dissected toso that the tube can be advanced through the sulcus. Recently, intraoperative ultrasound has been used to supplement the use of tubular retractors. BrainPath and ViewSite Brain Access System are the one of most commonly used tubular retractor systems.

In spinal surgeries, tubular retractors have been used for management of lumbar instability, spine trauma, herniated intervertebral discs, synovial cysts, lumbar and cervical stenosi and even some intraspinal tumors. The first commercially available product as a tubular retractor system was METRx system (Medtronic Sofamor Danek, Memphis, TN). Since it splits the muscles rather than cutting it, it reduces muscle damage and hence post-operative back pain. For lumbar discectomies, 4 - 5cm long and 20mm cylindrical tubes are usually used (figure 1). Exact location of operation site is determined using a C-arm and a Steinmann pin. Then the spinal posterior arch muscles and the ligamentum flavum are dissected. Drills are used for laminectomy and then the disc is removed as in conventional surgery.

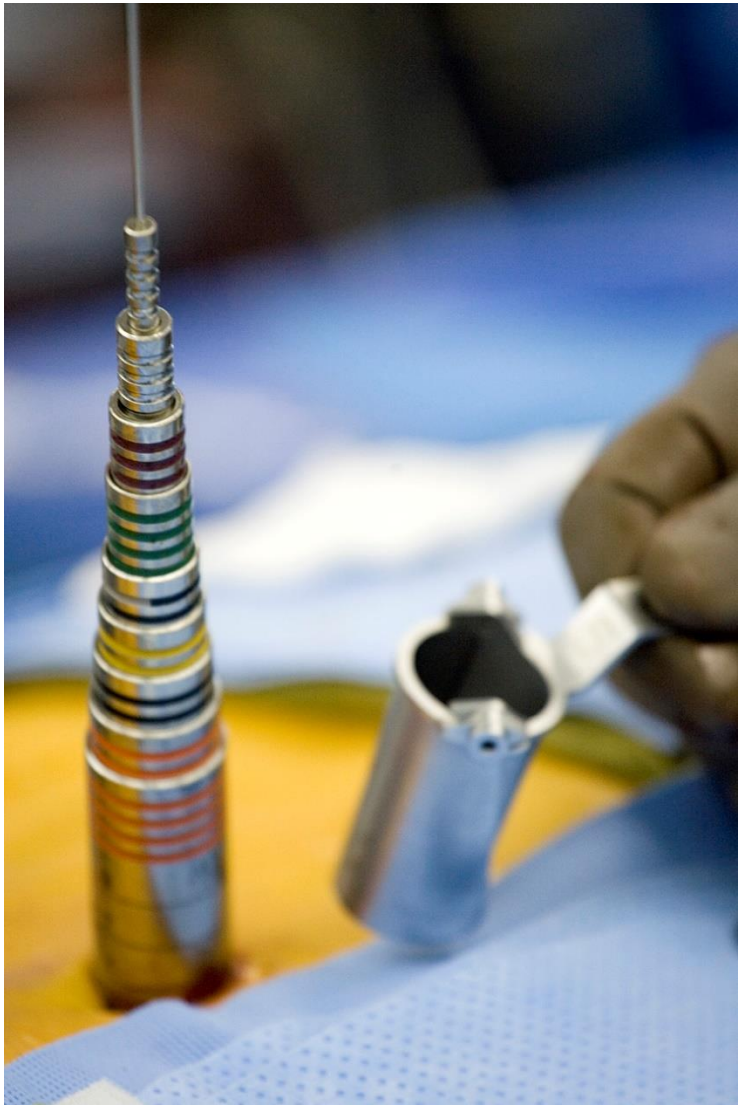

Figure 1. Tubular dilators for lumbar discectomies.

Figure 2. Tubular retractors.

One must be sure of not having even minimal bleeding. Similarly, tubular retractors have been used for decompression of lumbar spine (figure 2), thoracic discectomy, instrumentation of the cervical spine, spinal tumor surgery, instrumentation of the cervical spine and cervical spine decompression and/or discectomy.

Disadvantages of the use of tubular retractors in spine surgeries include availability of a limited space for working which can cause difficulty in interpreting the anatomical structures and learning curve to achieve appropriate surgical tools and manual skills for using tubular dilators.

There have been continuous attempts to improve tubular retractors for intracranial surgeries [14, 15]. Tubular retractors have been utilized for resection of colloid cysts and other deep seated brain lesions [16, 17]. The critics of the use of tubular retractors claim that during use of tubular retractors, the surrounding brain remains under continuous retraction throughout the procedure in all the directions and hence they may not be better than traditional retractors for brain surgery. Also, as in spine surgeries, the space for working for surgeon remains limited.

Brief Clinical Review of Tubular Retractors in Spine Procedures

- Microendoscopic discectomy using tubular retractors was first described by Foley et al. in 1997 [18].
- Huang et al. demonstrated Less systemic cytokine response in patients following microendoscopic versus open lumbar discectomy in their study involving 22 patients [19].
- Righesso O. et al. in 2007 compared open discectomy with microendoscopic discectomy in 40 patients having lumbar disc herniations.

  They suggested similar clinical and neurological outcome in both the groups, although the size of the incision, length of hospital stay, and operative time were smaller in patients operated with microendoscopic discectomy [20].
- German H. et al. in 2008 provided a retrospective chart review of 172 patients who had undergone a first-time, single-level lumbar discectomy at either L3-4, L4-5, or L5-S1 and compared minimally invasive discectomy with standard open microsurgical discectomy. Both the groups had similar perioperative results [21].
- Arts et al. (2011) compared tubular discectomy with conventional microdiscectomy in 216 patients. They evaluated creatine phosphokinase (CPK) in serum and the cross-sectional area (CSA) of the multifidus muscle on magnetic resonance imaging as indicators of muscle injury. Their results suggested that tubular discectomy compared with conventional microdiscectomy did not result in reduced muscle injury. Postoperative evaluation of CPK and the multifidus muscle showed similar results in both groups, although patients who underwent tubular discectomy reported more low-back pain during the first year after surgery. However, in this trial, a relatively large midline incision was made for the tubular group, which deviates from the original description of the tubular procedure [22].
- Cahill et al. in a retrospective review suggested that there was decreased use of postoperative resources in the patients undergoing

tubular microdiskectomy leading to lesser hospital charges than those undergoing open microdiskectomy [23].

Brief Clinical Review of Tubular Retractors in Spine Procedures

- Cabbell et al. in 1996 described the use of cylindrical retractors in resection of colloid cysts. They suggested shortening of operative time, compared with conventional craniotomy, and definitive treatment of the lesion.udinf retractors [24].
- Harris et al. on the basis of a small study, in 2005, concluded that the combination of intraoperative computed tomography-guided stereotactic technique and rigid endoscopy facilitated an accurate, minimally invasive, microsurgical removal of intraventricular tumors or colloid cysts. This approach also minimized retraction and provided satisfactory visualization [25].
- In 2011, Yadav et al. described the use of a new inexpensive and simple tubular retractor deep-seated brain lesions in 40 patients. They commented that their retractor as simple, effective, lightweight and inexpensive. Also, their retractor did not require any holder while usage.
- Hong et al. (2016) compared microscope-assisted resection of deep seated cerebral lesions using tubular retractors with endoscope-assisted surgery. Their results favored use of the microscope rather than the endoscope due to a wider and 3D field of view [26].
- Eichberg et al. (2019) performed a retrospective analysis of 20 patients and concluded that the Tubular retractor systems had a favorable safety profile [27].

Tumor Treating Fields (TTF)

TTFs are low-intensity electric fields which alternate at an intermediate frequency. TTFs act by blocking cell division and interfering with intracellular organelle assembly. The device consists of a range of

transducers and a portable battery pack. The transducers are worn on the scalp during the procedure. They release mild electrical fields which pulse through the skin of the scalp, reach the brain and abort division of cancer cells. The advantage of TTFs is that it does not cause side effects typical of chemotherapy and radiation such as pain, nausea, fatigue or diarrhea.

Initially, it was seen that exposing a variety of malignant cell lines to TTFs exerted a profound growth inhibitory effect due to induction of cell cycle arrest and apoptosis, while there was no effect on cells which were non-dividing [28]. TTFs act by interfering with the spindle apparatus during mitosis. They target proteins with large dipole moments (ie, septins and the spindle microtubules, components essential in the metaphase and anaphase stages of the mitotic cycle for separation and equal distribution of chromosomes) [29]. Then they cause disruption of the microtubular assembly during mitosis and also prevent formation of the mitotic spindle apparatus. Thus, separation of the 2 daughter cells is blocked and cells fail to divide. This effect also results in abnormal chromosomal segregation in cells. Also, the clonogenic potential of the cell's progeny is decreased. Finally, apoptosis of the cells takes place. While using TTFs, prolonged exposure to the electrical fields is required for beneficial outcomes as cell division may occur at any time. A novel development has been development of a portable, battery-powered device that can create TTFs. During the procedure, the patients scalp is shaved and 4 transducer arrays (with 9 insulated electrodes each) and continuous temperature sensing are used to apply the electric field to the brain. Effectiveness of TTF was tested in randomized phase 3 trials in glioblastoma cases (GBM). TTF was found to prolong both progression-free survival and overall survival in patients with newly diagnosed GBM when administered along with standard maintenance chemotherapy (temozolomide).

Minimally Invasive Pediatric Neurosurgery

Hydrocephalus, craniosynostosis and intracranial mass lesions are the main pathologies for which minimally invasive pediatric neurosurgery is

employed. For infants with hydrocephalus, ETV (endoscopic third ventriculostomy) along with bilateral choroid plexus cauterization has been found to be effective [30]. For craniosynostosis, endoscopic excision of fused sutures is done with only a small incision. Customised springs are also implanted during the procedure and need to be removed on a later date. Initially this approach was used only for non syndromic and sagittal craniosynostosis, but recently it has been used also for syndromic and multiple craniosynostosis [31]. Intracranial masses are excised using transventricular or transsphenoidal route. Even paramedian middle cranial fossa lesions and posterior cranial fossa lesions have been operated using the transsphenoidal route.

Genetic Strategies (Human Gene Transfer)

Gene therapy is a modality to treat disease which involves the therapeutic insertion of nucleic acid into a patient's cells to modify genetic makeup of the host. It acts by achieving effective expression of transgene in patient’s cells while damage to surrounding normal cells is minimized. Viruses, chemicals, and cells have been used as vectors to transport genes to the patients. Prodrug activating genes, intracellular signalling molecules, inhibitors of angiogenesis and cell invasion immune modulators are some of the transgenes that could be useful in management of brain tumour. Gene therapy has been mostly used in patients of Glioblastoma multiforme [32].

The human brain has a blood–brain barrier which prevents significant amounts of most systemically administered agents to reach therapeutic parenchymal levels. The direct delivery of therapeutic agents locally into the brain is driven by diffusion, which results in unequal distribution of the agent, and that too restricted to a few mms from the source. In contrast, convection enhanced delivery (CED) distributes the therapeutic agent by bulk flow by using a pressure gradient established at the tip of an infusion catheter. Hence, an even distribution of highly concentrated agent over longer distances is produced. The volume of distribution during the

procedure depends on the structural properties of the tissue and other parameters of the infusion procedure.

Gene therapy can be used in two ways:

1. by directly transferring a gene into the patient's own cells (in vivo),

or

2. by genetically modifying cells to perform a specific function and then transplanting these cells into the host (ex vivo).

Biological therapies aimed to modify degenerated neural circuitry have been explored recently as an alternative therapy in patients with movement disorders. They consist of gene therapy, cell-based therapies or direct infusion of trophic factors.

In brief, DNA (that encodes a therapeutic protein) is inserted into a viral vector. This vector can be engineered to specific target cell types (dopaminergic neurons). The next step is injection of viral vector directly into the target region. The vector infects the desired cells and transfers the DNA into the host genome. This new DNA then produces the therapeutic protein leading to therapeutic benefit. There are published trials showing promising results in patients suffering with Parkinson's disease.

Gamma Knife Surgery (GKS)

GKS is a form of radiation therapy that is non-invasive and based on stereotactic principles. It employs highly sophisticated equipment to focus multiple tiny beams of gamma radiations on a tumour or other target of interest. As the beams converge at the target, the doses of all tiny radiations summate and a high dose is delivered to the target. The efficacy of GKS against various brain tumours has been established by many authors. Even the tumours resistant to traditionally used external beam radiation therapy

have been successfully treated using GKS. Daily quality assurance of the radiosurgical system needs to be done.

Leksell developed the first gamma knife device that used cobalt-60 as the energy source. He initially employed his invention for functional neurological surgeries. In fact, the first 2 human cases operated using radiosurgery were patients with trigeminal neuralgia. Leksell also gave the name “stereotactic radiosurgery” to this form of treatment.

As of today, four models of gamma knife machine are being used all over the world. It is estimated that there are a total of over 300 gamma knife machines presently in the world. The four available models are U, B, C, and the Perfexion models. The therapeutic team for gamma knife consists of neurosurgeons, oncologists, neuro-radiologists, medical physists and nurses.

The procedure of Gamma Knife radiosurgery consists of following steps:

1. Applying the stereotactic guiding device (Cosman-Roberts-Wells stereotactic frame) to the patient's head after injection of local anesthetics. It is followed by checking of Frame adaptor and frame cap fitting.
2. Stereotactic brain imaging- using either Magnetic resonance imaging (MRI), computed tomography (CT), angiography, or any combination of these.
3. Calculating and deciding upon the target volume and planning of the conformal radiosurgical dose by the radiosurgery team.
4. positioning of the patient's head inside the collimator system.
5. delivery of radiation to the target volume stereotactically.
6. Removal of the stereotactic guiding device.

Gamma knife surgery has been utilised in brain tumors like meningiomas, acoustic schwannomas, pituitary ademonas, brain arteriovenous malformations, Trigeminal neuralgias, functional disorders etc. In the latest Gamma Knife model (Perfexion), the accuracy of the mechanical versus radiation isocenter was seen to be as less as 0.05mm. This technical accuracy is superior to alternative radiosurgery techniques. Also,

GKS is said to have advantages like better geometrical accuracy, better dose gradient around the target, improved dose accuracy and the protection of extra-cranial tissue.

In addition to its applications in neurosurgery, CNS radiation oncology, and neurooncology, new advances of the CyberKnife have introduced radiosurgery into the general field of oncology. Now, GKS is being used to manage cancers of other body systems like pulmonary system, prostate ca etc.

Laser Interstitial Thermal Therapy (LITT)

LITT is an emerging, minimal invasive technique. It has been employed to treat primary and metastatic brain tumours which are otherwise hard to reach using conventional surgery. Briefly, the procedure consists of creation of a burr hole after administration of anaesthesia and navigation of wire into the area of interest under MRI guidance.

Thereafter, a laser catheter is implanted into the tumour. This catheter is then heated to temperatures high enough to destroy the tumour.

LITT achieves local tissue destruction using a catheter (which is placed stereotactically) and delivering focused thermal energy. LITT acts via the transfer of photon energy and achieves rapid photothermal heating. This heating then ablates neural tissues, causes protein denaturation and tissue coagulation [33]. To prevent undesirable side-effects, this thermal energy should be delivered in a reliable and predictable pattern. Also, heat generation must be controlled. So stereotactic guidance, temperature feedback, and prevention of overheating play an indispensible part in application of modern LITT.

The 2 most commonly used lasers are Nd:YAG lasers and diode lasers. The tumorous tissue differs from normal brain tissue in its optical properties. Hence, LITT is able to destroy timorous tissue while the normal brain tissue is not affected. In the acute phase, a rim of edema separates normal tissue from tumor. There is early neuronal swelling with defects in the cell

membrane and engorgement of the adjacent vasculature with thrombotic occlusion.

Later granulation tissue forms, followed by cyst formation with unresorbed necrotic tissue and a glial scar at the margin.

LITT is especially beneficial for patients who are too unhealthy to be able to tolerate cranial surgery. The most common complications of LITT include unintended thermal injury to eloquent brain tissue, hemorrhage and incorrectly positioned catheters. LITT has been used for tumors like gliomas, epilepsy surgeries, metastases and radiation necrosis [34, 35].

The advantages of LITT include no need of craniotomy, early discharge from hospital and early return to activity.

Indications of LITT

A) Deep seated lesions;
B) Lesions adjacent to eloquent structures;
C) Lesions resistant to alternative treatment modalities (e.g., radiation therapy);
D) Salvage therapy for lesions having reached a 'toxic threshold' with no other options for intervention.

Brief Clinical Review of LITT in Neurosurgery

- Carpentier et al. studied the safety and feasibility of real-time magnetic resonance-guided laser-induced thermal therapy for treatment of resistant focal metastatic intracranial tumors in 7 patients. They suggested that Real-time magnetic resonance guidance of LITT offered a high level of control and was a minimally invasive option for destruction and treatment of resistant focal metastatic intracranial tumors [36].
- Patel et al. described their experience of LITT in 102 patients suffering from glioma, recurrent metastasis, radiation necrosis, chronic pain, and epilepsy. They reported 27 cases of morbidity, including new-onset neurological deficits, and 2 perioperative

deaths. 14 of their patients developed new deficits after the procedure, and of those 14 patients, 9 had complete resolution of deficits within 1 month of procedure [37].

- Mohammadi et al. performed a retrospective review of 34 patients who had underwent LITT. LITT was delivered as upfront in 19 and delivered as salvage in 16 cases. After 7.2 months of follow-up, 71% of cases had demonstrated progression and 34% had died [38].

Robotic Neurosurgery

The word 'robota' was initially used by the Czech playwright Karel Capek in his play, Rossum's Universal Robots (RUR). Robots have been increasingly used in operation theatres now. Robots can consist of "effectors" and "sensors". Effectors are the artificial equivalents of human arms or leg while "sensors," perceive the environment and transfer it into information. This information is then used by a central processing unit, which works as the brain. Then there are several other electronic, electric or mechanical pieces of equipment, such as a screen with an interface, that complete the functioning apparatus of robots.

Robots range from being completely independent to fully dependent. Independent robots reproduce pre-programmed instructions without the control of the surgeon during the surgery. They are most commonly used for the purpose of stereotactic positioning in neurosurgery. In a fully controlled robot, the surgeon has full authority over the system for the particular procedure. Presently, most common systems in robot surgery are controlled systems; 'telesurgeries' are performed by the surgeon while sitting in a consolewhich is distant from the patient However, the surgeon has complete control over the motion of surgical instruments.

The CyberKnife was developed by John Adler of Stanford University and is considered by many as the first modern application of robotic neurosurgery [39]. The CyberKnife allowed for performing gamma knife surgeries without any direct surgeon-patient contact and with full control of

the surgeon while sitting at a remote location. Neuromate, Pathfinder, the NeuroArm, and the SpineAssist are other commonly used robots available for neurosurgery.

Commercially available hardware can be used by a robotic device to perform craniotomies. It can detect changes on its own and precisely create large numbers of craniotomies in a single patient. This technique can be adapted to automatically drill cranial windows as small as several millimeters in diameter. There have been reports of the use of even homebuilt hardware used in robotic surgeries. Robots in neurosurgery have been used in minimal invasive procedures in adults as well as pediatric patients. Minimally invasive supraorbital keyhole surgery with the 'da Vinci Surgical System' has been tried in cadaveric patients [40]. Robotic neurosurgery provides neurosurgeons with broader vision and articulable instruments, which are outside the reach of standard microsurgical systems.

Robots have been utilized for various procedures. The ROSA system has been used for ETVs and provides a more precise and a minimally invasive approach. Robotic 'manipulators' provide great precision along with reliability, and rapidity in the positioning of surgical instruments or devices in the brain.

However, improved outcomes and reduced adverse events using robotic technology are yet to be proven in clinical trials. Recently, a retrospective study which had compared the accuracy of spinal instrumentation with robot-guided screw insertion versus hand-guided (CT/fluoroscopic) screw placement could not suggest any advantage using robotic technology.

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Chapter 6

NONCONVULSIVE STATUS EPILEPTICUS IN NEUROSURGERY

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ABSTRACT

Nonconvulsive status epilepticus (NCSE) is a clinically cumbersome entity to cope with; however, accumulating cases suggest that it is much more pervasive than previously considered. This may also apply to neurosurgical cases, wherein common operative procedures, such as craniotomy or transient placement of subdural grid electrodes, are now regarded as potential candidates for NCSE. These cases, while few in number, raise questions about the potential underdiagnosis of NCSE, which might have been left untreated merely because intracranial lesions could not be identified. Furthermore, given that the use of intracranial electrodes or devices is becoming popular through technological development, caution must be practiced due to the potentially increased

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opportunities for NCSE. Although cutting-edge knowledge in the relevant field is currently limited to observational studies, basic knowledge on NCSE seems essential for neurosurgeons. This chapter summarizes the reported cases and observational studies of nonconvulsive SE in neurosurgical subspecialties of emergency and perioperative care, cerebrovascular diseases, neurotrauma, brain tumor, and stereotactic and functional neurosurgery. These papers strongly suggest the importance of obtaining relevant knowledge and making an accurate diagnosis of NCSE in the neurosurgical setting.

Keywords: nonconvulsive status epilepticus, neurosurgery, review

INTRODUCTION

Status epilepticus (SE) is semiologically classified as convulsive SE and nonconvulsive SE (NCSE). Although NCSE is often recognized in the form of impaired consciousness and neurological deficits (such as limb paralysis, aphasia, or sensory disturbance), the symptoms of NCSE are quite variable and complex (Kinney et al. 2018). In addition to cognitive dysfunction (Kinney et al. 2018) and atypical neurological symptoms (Kaplan et al. 2011, Kinney et al. 2018), it can manifest as psychiatric symptoms, such as psychosis, an altered mental status without any effect on the consciousness, mood disturbance, and hallucinations (Kinney et al. 2018).

NCSE is estimated to account for 25%-50% of SE (Knake S et al. 2001). It is becoming clear that the incidence of NCSE is higher than previously considered. In one study involving routine electroencephalography (EEG) for 2514 patients, the incidence of NCSE proved to be 0.8% (Seidel et al. 2012), which was once thought to be 0.2% in a large retrospective study (Shneker et al. 2003). While the majority of reported cases in NCSE seem to be amenable to conventional epileptic therapies, accumulating data have indicated that NCSE can have poor prognosis (Krumholz 1999, Jafarpour S et al. 2015, Yuan et al. 2018, Beretta et al. 2018). For example, one retrospective study targeting NCSE through acute medical causes reported death in 18 out of 100 patients (Shneker et al. 2003).

Given the high incidence of and potential risk associated with NCSE, adequate knowledge and an accurate diagnosis of NCSE are essential. Although the number of reported cases is currently limited, NCSE has been observed in common neurosurgical procedures, such as craniotomy (Al-Mefty et al. 2009) and the transient use of subdural electrodes (Fujioka et al. 2016). These facts cast some doubt on the possibility that NCSE has gone undiagnosed in neurosurgical settings. Furthermore, increasing opportunities to apply intracranial devices or electrodes may spur the possibility of encountering NCSE. While the clinical significance of NCSE in neurosurgical settings is apparent, data thus far have been limited to a small number of case reports and observational studies.

This chapter summarizes previously reported papers on NCSE associated with neurosurgical settings.

NCSE IN NEUROSURGERY

Emergency and Perioperative Care

A few cases suggest the substantial possibility of NCSE in neurosurgical emergency and perioperative settings. Previous cases have shown that NCSE was recognized in patients with coma (Trinka et al. 2015) and anoxic encephalopathy (Sakellariou et al. 2017) as well as those in critical conditions (Litt et al. 1998), such as cases of sepsis or uremia (Kubota et al. 2016).

Craniotomy *per se* seems to be associated with NCSE (Kubota et al. 2016), although the incidence is not fully established. Perioperative NCSE has been reported following craniotomy procedures in patients with brain tumor (Al-Mefty et al. 2009, Devarajan et al. 2011). As a rare but recurring syndrome, Al-Mefty et al. described a delayed, progressive deterioration of consciousness after skull-base craniotomy, which was associated with abnormal periodic discharges and abundant delta activity in EEG (Al-Mefty et al. 2009). Although they termed the phenomenon postoperative nonconvulsive encephalopathic status, this condition may also be regarded

as NCSE. Another study reported *de novo* NCSE in an 83-year-old woman following resection of meningioma. Since surgery was performed without intraparenchymal manipulation (Devarajan et al. 2011), the potential involvement of craniotomy with NCSE was more likely. Indeed, it has been pointed out that craniotomy is a potential cause of functional and metabolic derangements (Sayegh et al. 2014).

While relatively little is known about NCSE in the postoperative period, previous cases have shown a high rate of clinical and subclinical seizures (Freund et al. 2018), and NCSE may be associated with coma in neurosurgical intensive care (Kuchta et al. 2009). A single case study reported the involvement of fat embolism with NCSE as a post-operative complication (Arencibia et al. 2018).

A few studies have suggested that special care should be practiced with elderly patients due to the potentially high risk of NCSE (Canas et al. 2018). One prospective study among critically ill patients in intensive-care units (ICUs) found that 31 out of 239 patients had NCSE (Litt et al. 1998). Of these 31 patients, 24 (74%) were elderly, and 13 ultimately died (Litt et al. 1998). Another study showed that, among the elderly patients admitted to the emergency department, about 16% had NCSE (Cheng 2014). Our own experience is described below.

Case Presentation

The patient was a 90-year-old woman with a history of schizophrenia who sporadically presented peculiar behaviors and impaired consciousness that persisted over a few weeks. Following an investigation at the psychiatry department, she was introduced to the neurosurgery department. The baseline laboratory investigation findings were normal, and head CT findings were unremarkable. NCSE was suspected at this stage. Scalp EEG revealed slow wave bursts that were observed over a 30-min recording period, leading to the diagnosis of NCSE (Figure 1). Antiepileptic therapy using levetiracetam and lacosamide was effective.

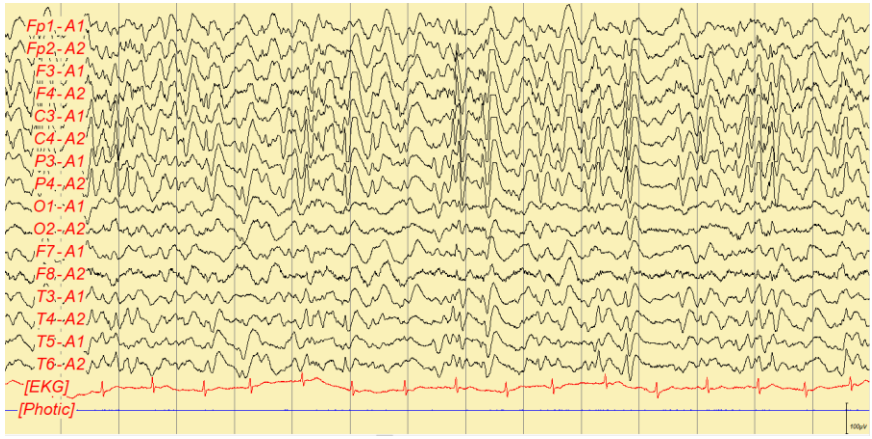

Figure 1. Scalp EEG (referential montage) indicating NCSE in an elderly patient.

Cerebrovascular Diseases

While stroke has been regarded as a potential factor for NCSE (Kubota et al. 2016), systematic studies or reviews in this field are scarce at present. One retrospective study of 50 stroke patients identified NCSE in 12 patients (24%). Of these, the potential risk factors determined through multivariable analyses were cardioembolic stroke and frontal lesions (Tomari 2018). Another retrospective study in a single local institute found NCSE during the perioperative period of cerebrovascular surgery in 7.4% (4 of 54 patients, Morioka et al. 2011). The authors considered the cause of NCSE in all patients to be multifactorial (Morioka et al. 2011).

NCSE in ischemic stroke is by no means rare, and it has been suggested that all types of ischemia have the possibility to develop NCSE (Kubota et al. 2016). In one prospective study, continuous EEG (cEEG) monitoring (>6 h) detected NCSE in 3.6% (32 of 889 patients) of acute ischemic stroke patients (Belcastro 2014). That study further indicated a significant association of NCSE with NIHSS scores, infarct size, and large atherothrombotic etiology (Belcastro et al. 2014).

The incidence of NCSE among subarachnoid hemorrhaging (SAH) patients varies according to studies, ranging from 3% to 31% (Dennis et al.

2002, Lyle et al. 2002, Little et al. 2007). Given that the nonconvulsive seizures after SAH reportedly show a poor outcome (Classen et al. 2013), extra caution must be practiced when dealing with SAH patients. Intracortical EEG in combination with surface EEG detected NCSE in 8% of comatose SAH patients (n=48), all of whom were highly refractory to treatment (Dennis et al. 2002). Another paper found that, among patients with nonconvulsive seizures after SAH, intracortical seizures were recognized in as many as 38% (Classen et al. 2013) and were also associated with an elevated heart rate, blood pressure, and respiratory rate (Classen et al. 2013). Despite these intriguing findings, whether or not these potentially autonomic changes contribute to the diagnosis remains unclear. Taken together, these results indicate that, if NCSE is suspected, assertive EEG should be performed in SAH patients associated with an impaired consciousness or neurological deficits through unknown cause.

One study directly investigated the issue of brain hemorrhaging-associated NCSE. According to the study by Matsubara et al., among the 228 patients investigated, NCSE was observed in 8.8% (Matsubara et al. 2018). The patients with NCSE had longer hospital stays, higher modified Rankin scale (mRS) scores, and a higher mortality rate than those without NCSE (Matsubara et al. 2018). The study further demonstrated that craniotomy and lobar involvement were independent factors associated with NCSE. As suggested by the authors, the induction of NCSE may be multi-factorial, considering the fact that craniotomy *per se* is an inducing factor of NCSE (Matsubara et al. 2018). Thus, careful attention must be paid to the identification of the factors responsible for NCSE.

Brain Tumors

Brain tumors *per se* can cause NCSE (Hormigo et al. 2004, Ruegg et al. 2008). One retrospective study documented that, among 259 patients who underwent EEG, NCSE was identified in 24 (2%), and a majority of the patients was successfully treated (Marcuse et al. 2014). Another retrospective study of 658 patients who underwent scalp EEG at a cancer

center found that NCSE was identified in 4% (25 patients). That study, however, reported that three patients died from NCSE (Spindler et al. 2013). Although the prognosis of brain-tumor associated NCSE remains unclear, it is not always a good prognosis.

At present, whether or not the benign or malignant characteristics of tumors can affect the incidence and prognosis of NCSE is unclear. The potential involvement of meningioma, glioblastoma multiforme (Litt et al. 1998), and metastatic CNS disease (Litt et al. 1998, Blitshteyn et al. 2006) has been reported. Furthermore, whether or not resection of a tumor can ameliorate NCSE is also unclear. Of note: there were two cases in which NCSE disappeared following surgical intervention of focal cortical dysplasia (Duane et al. 2004, Timer et al. 2018). However, given that focal cortical dysplasia is not a tumor, the accumulation of more data on brain tumors is desired.

Brain tumors are just one potential of cause of NCSE, and NCSE can be multifactorial (as mentioned above, craniotomy itself is a potential inducing factor). Caution must be practiced when attempting to determine the inducing factors, as described below.

1. NCSE has been observed in patients with (extracranial) cancer. One retrospective review showed that 4% of patients with cancer had NCSE (Spindler et al. 2013). As such, care must be taken when administering chemotherapy, as the use of ifosfamide seems to be associated with NCSE (Primavera et al. 2002).
2. Although quite rare, the possibility of tumor-associated encephalitis, such as paraneoplasmic limbic encephalitis (PLE; Gultekin et al. 2000), must be differentiated from NCSE. PLE is a neuro-oncological complication associated with personality changes, irritability, depression, seizures, memory loss, and dementia (Gultekin et al. 2000).
3. As described below, the use of intracranial electrodes for preoperative functional mapping can cause NCSE (Fujioka et al. 2016).

Neurotrauma

The incidence of NCSE in the acute stage of neurotrauma is reportedly high (Vespa et al. 2010). One study showed that approximately 10% of patients in the acute period of traumatic brain injury suffered from electrophysiologically detected seizures (Vespa et al. 1999). Another retrospective, small study indicated that 10 of 21 patients had abnormal EEG findings. Of those 10 patients, 2 were diagnosed with NCSE, and both were successfully treated with antiepileptic drugs (Lee et al. 2013). The usefulness of cEEG for the diagnosis of NCSE in adults (Claassen et al. 2004) and pediatric populations has also been demonstrated (Arndt et al. 2013).

NCSE in pediatric neurotrauma has received substantial attention in recent years, especially in the field of child abuse (Hansen et al. 2015, Greiner et al. 2015). It is associated with increased mortality and poor short-term neurological outcomes in critically ill children (Abend et al. 2013). In a retrospective study, 27.4% (20 of 73 patients) had nonconvulsive seizures, and 4.1% (3 of 73 patients) had NCSE (Greiner et al. 2015). This group also showed that NCSE was associated with children with SAH in 41% of cases. As neuroradiographic predictors of NCSE, they showed that the presence of SAH and cortical T2/fluid-attenuated inversion recovery signal abnormalities in magnetic resonance imaging (MRI) were significantly associated with nonconvulsive seizures or NCSE (Greiner et al. 2015).

A pathophysiological investigation by Vesta et al. in traumatic brain injury patients (n=20) showed the increased intracranial pressure (ICP) and metabolic disorders through microdialysis (Vespa et al. 2007). This study demonstrated, for the first time, that electrographic seizures were deleterious for patients with traumatic brain injury (Vespa et al. 2007). A subsequent investigation by the same group identified the potential association of NCSE with hippocampal atrophy (Vespa et al. 2010).

Stereotactic and Functional Neurosurgery

Stereotactic and functional neurosurgery is a field of active development, with chronically implantable intracranial devices being developed (Edwards et al. 2017). Currently used techniques include deep brain stimulation (DBS), responsive neurostimulation (RNS), and motor cortex stimulation (MCS; Levy et al. 2016, Fujioka et al. 2018). In addition, subdural electrodes have been used in epilepsy surgery and are now widely applied to identify the functional area of the brain (functional mapping) in brain tumor surgery. While cases of NCSE in this field are extremely rare, its potential incidence should nevertheless be monitored. We previously encountered a case in which NCSE was induced by the transient implantation of subdural grid electrodes in a patient with malignant brain tumor (Fujioka et al. 2016).

Case Presentation

The patient was a 69-year-old woman who complained of mild speech disturbance and gait disturbance. Contrast-enhanced MRI revealed a ring-enhanced tumor mass in the white matter under the speech and primary motor areas, which was associated with extensive vasogenic edema (Figure 1). Preoperative functional mapping was planned, and a sheet of subdural grid electrodes with a thickness of 0.8 mm was transiently implanted (Figure 2A, B). That evening, the patient became slightly lethargic with worsened motor aphasia and right hemiparesis.

Electrocorticography (ECoG) from the subdural electrodes clearly indicated NCSE, which was characterized by continuous slow waveforms of 1-3Hz (Figure 3A). Fast Fourier transform (FFT) analyses were performed exclusively using the data found in Figure 3A (settings and parameters used were as follows: FFT size, 4096 points; data window, Bartett; window overlap, 50%; mode, power attenuation [dB]; averaging, 15 times). The results showed a peak band power of 1-3 Hz (Figure 3B) with a gradually diminished frequency power distribution as the frequency increased (about 35-50 Hz). ECoG consisted of irregular bursts of activity with a different morphology from one burst to the next. Although the ECoG data on NCSE

have not been thoroughly investigated, our ECoG data were in agreement with the reports of surface EEG findings for NCSE, which have shown a mixture of triphasic waves with spikes and slow waves (Kaplan et al. 1999, Morioka et al. 2011). The magnified waveforms of Figure 3A comprised spikes and slow waves as well as triphasic waves (Figure 3C-3E).

NCSE in this case was resistant to conventional antiepileptic therapy and disappeared after the removal of the electrodes. The histological diagnosis was diffuse astrocytoma. The neurological deficits in the present case appeared to be associated with NCSE, possibly induced by cerebral ischemic changes due to compressive factors, such as grid electrodes, hematoma, and brain edema, in addition to an intrinsically increased metabolic demand through neuronal hyperexcitability (Fujioka et al. 2016).

The use of subdural grid electrodes in epileptic patients reportedly carries a significantly higher risk of complications than the use of strip electrodes (Hamer et al., 2002). Subdural electrode implantation in epileptic patients can cause various complications, such as infection, edema, increased intracranial pressure, cerebrospinal fluid leak, epidural and subdural hematoma, intracranial hemorrhaging, and transient neurological deficits (Hamer et al. 2002, Fountas 2011). Multiple factors were consider as the potential cause of NCSE in this case, including the brain tumor *per se*, the electrodes, or both. Although we judged that NCSE was induced by the implantation of the electrodes, it is difficult to determine whether or not the cause could be ascribed to a single factor.

At present, only one case study has reported the induction of presumable NCSE through intraparenchymal electrodes (Jochim et al. 2016). Jochim et al. were the first to report impaired consciousness following DBS surgery in a patient with Parkinson disease. Scalp EEG was associated with generalized sharp waves of 2 Hz (Jochim et al. 2016). The symptoms of DBS-associated NCSE seem to resemble those of peri-lead edema after DBS, which can also be associated with an impaired consciousness and neurological deficits (Whiting et al. 2018). A total of 191 leads were implanted and 6.9% of patients presented with symptoms, which were most often an altered mental status or neurological deficit (Whiting et al. 2018). The EEG characteristics of peri-lead edema after DBS have yet to be fully investigated.

Although electrical stimulation of the brain can induce convulsive SE, whether or not it can also induce NCSE remains unknown. Of potential interest is the review article that reported the possibility of NCSE associated with post-electroconvulsive therapy (ECT; Aftab et al. 2018). At present, the data are extremely limited, and potential risks for NCSE in this field cannot be denied; the accumulation of more data is desirable.

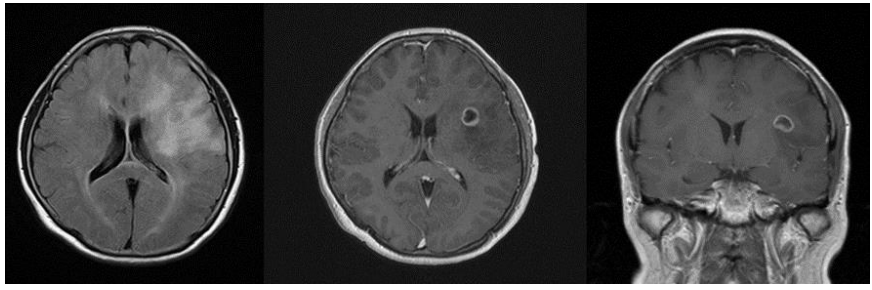

Figure 1. Head MRI showing extensive vasogenic edema. Contrast-enhanced MRI indicated a ring-enhanced tumor mass in the white matter under the speech and primary motor areas.

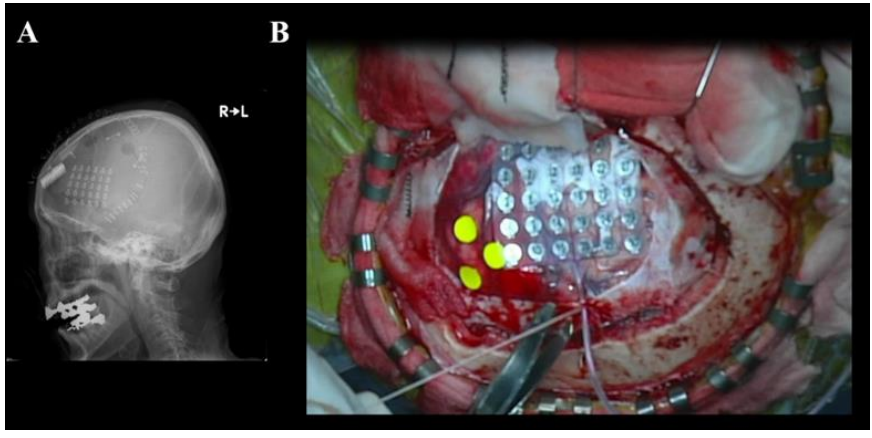

Figure 2. X-ray image (A) and an intraoperative image of subdural grid electrodes (B).

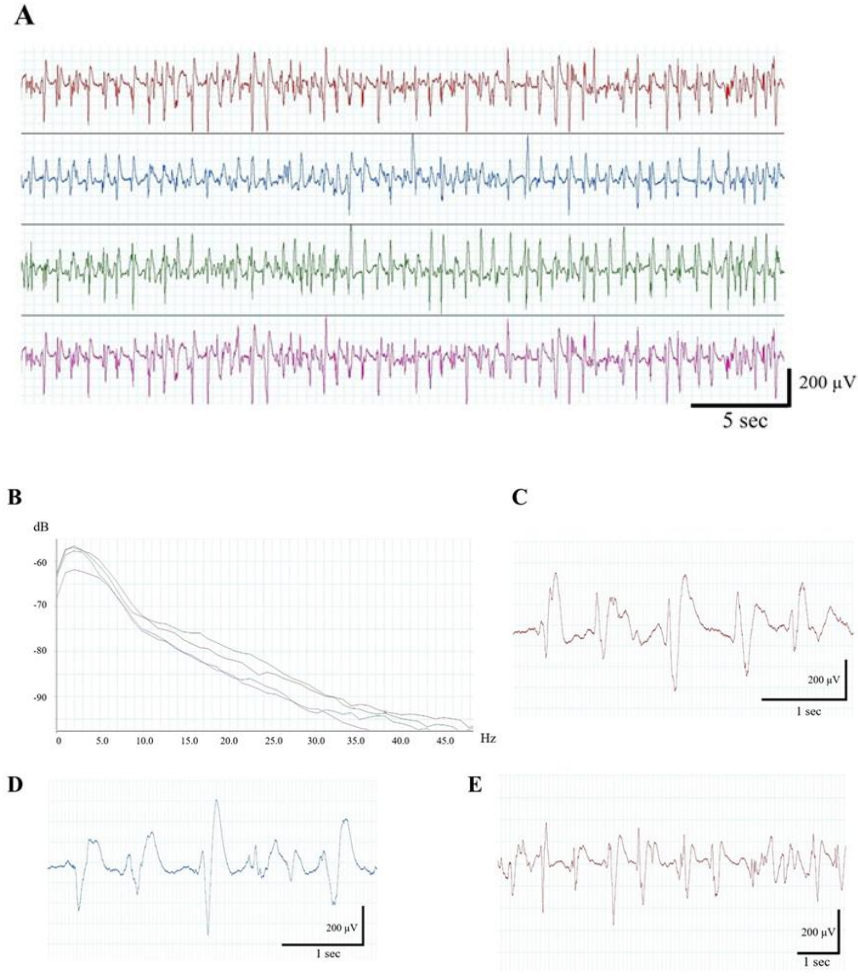

Figure 3. ECoG showing NCSE (A). FFT analyses showed the peak frequency bands around 1-3 Hz (B). Vertical line: frequency, horizontal line: power attenuation [dB]. Magnified ECoG in Figure 2A showing sharp spikes and slow waves (C), triphasic waves mixed with sharp spikes and slow waves (D). Note that the small-amplitude spikes hindered counting the exact number of waves (E).

THE DIAGNOSIS AND TREATMENT

At present, there are no established definitions of NCSE, and the diagnosis and treatment are empirically performed. The current golden

standard for the diagnosis is scalp EEG, especially continuous video-EEG (or cEEG, Freund et al. 2018). Indeed, about 80% of NCSE cases can be diagnosed following video-EEG for 12 h (Classssen et al. 2004). Although the clinical utility of modalities other than EEG remains to be investigated, other diagnostic tools may include MRI, MR spectrography, single-photon emission computed tomography (SPECT), and FDG-PET (Walker et al. 2005).

While electroclinical diagnostic criteria, or Salzburg consensus criteria, have been proposed for NCSE (Beniczky et al. 2013, Leitinger et al. 2016), it has been shown that waveforms of NCSE can take various forms (Holtkamp et al. 2011). For instance, scalp EEG in NCSE during the perioperative period of cerebrovascular surgery showed triphasic waves, with spikes and slow wave complex morphologies as well as periodic lateralized epileptic discharges (PLEDs) (Morioka et al. 2011).

Ideally, EEG should be performed as early as possible if NCSE is suspected (Husain et al. 2003). In reality, however, only a few institutions can perform EEG 24 h daily. Furthermore, the risk of a potential perioperative infection through scalp electrodes hampers the performance of scalp EEG after craniotomy. However, accumulating reports suggest that it may be not always necessary to perform scalp EEG with the conventional International 10-20 system. For example, a single case study described the successful diagnosis of NCSE using raw EEG findings of a bispectral index or BIS monitor (Ntahe 2018). In addition, the potential utility of a reduced number of recording electrodes (two or four channels) for the diagnosis of NCSE has also been suggested (Brenner et al. 2015, Yamaguchi et al. 2018).

In clinical practice, NCSE treatment is usually similar to that of convulsive SE, involving the intravenous administration of benzodiazepine or antiepileptic agents (Ruegg 2008, Holtkamp et al. 2011). While a majority of NCSE cases in neurosurgical settings have shown good prognosis with conventional therapies, refractory NCSE has recently been documented (Fernadez-Torre et al. 2015, Beretta et al. 2018). As in convulsive SE, aggressive treatment is desirable for refractory NCSE (Rossetti et al. 2019). Although firm conclusions have yet to be drawn, there are pros and cons to the aggressive treatment of NCSE (Rossetti et al. 2019). Potential drawbacks

of aggressive treatment include the possibility of overtreatment (Rossetti et al. 2019) or poor outcomes despite a considerable expense (Litt et al. 1998). Given the potential risks of NCSE, however, an aggressive trial of anticonvulsant therapy may deserve consideration (Hormigo et al. 2004).

In addition to pharmacological treatment, the surgical treatment will be a therapeutic option in the neurosurgical setting; surgical removal of implanted devices and/or treatment of the original disease may be necessary. In our experience, the removal of subdural grid electrodes helped improve NCSE (Fujioka et al. 2016). Therapeutic options include the administration of antiepileptic drugs (steroids in some cases) and the removal of implanted devices. No definite data on these approaches are currently available. Of note, only one study reported that surgical treatment was effective for refractory NCSE. The patient was a 7-year-old boy who developed NCSE and was refractory to multiple medical therapies, and hemispherectomy resulted in the complete cessation of seizures (Duane et al. 2004).

Whether or not NCSE is associated with permanent brain damage has been debated (Jordan 1999). As described above, accumulating data have shown the induction of brain damage following NCSE (Vespa et al. 2007, Vespa et al. 2010). While the physiological mechanisms of NCSE have yet to be clarified, empiric observation has suggested that it may be induced by cerebral ischemic changes due to compressive factors, such as grid electrodes, hematoma, and brain edema, in addition to an intrinsically increased metabolic demand through neuronal hyperexcitability. In a basic study in rodents, NCSE rat/mice showed a reduction in the synaptic protein level, further resulting in neuronal loss (Avdic et al. 2018).

CONCLUSION

Current issues associated with NCSE in the neurosurgical setting are, first and foremost, the dearth of reported cases and a lack of systematic analyses. While standard therapies have yet to be established, the above-mentioned therapeutic approach may be suitable. Our current understanding of the physiological mechanisms and the availability of epidemiological data

are far from satisfactory. Further investigations on NCSE are therefore required.

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Chapter 7

EPILEPSY AND NEUROINFLAMMATION

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ABSTRACT

Epilepsy is considered one of the major serious chronic neurological disorders, characterized by recurrent seizures. It is usually associated with history of lesion in the nervous system. Irregular activation of inflammatory molecules in the injured tissue is an important factor in epilepsy development. Although, it is unclear how the imbalanced regulation of inflammatory mediators contribute to epilepsy. So, recent goal in research is the identification of interconnected inflammation pathways which may develop epilepsy. The available drugs for epilepsy treatment have low effect and high adverse effects. So developing recent drugs which modulate epilepsy through recent mechanisms other than the

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traditional is a must. Alternative therapies and diet have recently reported positive outcome in epilepsy treatment. So the aim of this chapter is to review the associations between different brain inflammatory mediators and epileptogenesis, to strengthen the idea that targeting inflammatory pathway may be another effective therapeutic strategy to prevent or treat epilepsy.

Keywords: epilepsy, epileptogenesis, inflammation

INTRODUCTION

Epilepsy is considered one of the major serious chronic neurological disorders. It affects 0.5-1% of population (Haut et al., 2006). It is identified by impaired neuronal activity, seizures, and behavioral changes (Fisher 2015). High incidence of epilepsy was observed in children and geriatrics (Téllez-Zenteno and Hernández-Ronquillo 2012). Status epilepticus (SE) is considered the most dangerous form of epilepsy due to high mortality rate with it. It may be resulted from the deficiency of seizure termination mechanisms (Trinka et al., 2012). Status epilepticus is characterized by increased reactive oxygen species and excitatory neurotransmitters in the brain along with cognitive impairment (Coyle and Puttfarcken 1993).

Experimental animal models are used to identify new treatment strategies for improving therapy of SE (Martin and Pozo 2006). Pilocarpine (Pc) induces seizures which start in limbic regions causing structural damage and spontaneous recurrent seizures which resemble complex partial seizures in human (Schmidt-Kastner et al., 1996).

Previous studies on animal models (Folbergrová 2013; Noemí Cárdenas-Rodríguez et al., 2014) and patients (Carmona-Aparicio et al., 2015) with epilepsy have reported the imbalance between the oxidant and antioxidant system and high inflammation. Neuroinflammation is a critical part of brain's innate immunity. However, chronic inflammatory processes cause neurotoxicity and hyperexcitability. This evidenced the possible relationship between inflammation and epilepsy.

ROLE OF NEURO-INFLAMMATION IN EPILEPTOGENESIS

Neuro-inflammation has been reported by the up normal increase in proinflammatory mediators in the epileptogenic foci. Several mediators have been reported in epilepsy including interleukin-1β, toll-like receptor 4, transforming growth factor-β, and tumor necrosis factor-α, cyclooxygenase-2/prostaglandin E2 (Yifeng et al., 2016).

Brain tissues are extremely liable to oxidative stress which has been reported to play a vital role within the pathological process of seizures (Sudha et al., 2001). Oxidative stress is shown to participate in pathways resulting in neurodegeneration, which is considered the most vital factor in the epileptogenesis and cognitive behavior decline (Martinc et al., 2014). In cellular level, significant calcium influx leads to cascades, which induce reactive oxygen species (ROS) and stimulate acute neurons death during seizure activity (Fujikawa et al., 2000).

Previous studies reported that brain inflammation which developed after SE, may play a vital role in epileptogenesis (Gorter et al., 2006; Vezzani, 2014). Experimental studies on animal models of epilepsy have demonstrated rapid onset of release of inflammatory mediators which contribute to the pathogenesis of epilepsy (Riazi et al., 2010; Vezzani and Granata, 2005; Vezzani et al., 2011). During seizure neurons loss and destruction of BBB have been reported (Ravizza et al., 2008). Destruction of BBB can increase neurons excitability by increasing inflammatory mediators in brain tissue (Heinemann et al., 2012; Ransohoff et al., 2003). Uludag et al. (2015) reported that interleukin IL-6, IL-1β, and TNF-α are activated after seizures. In addition, IL-6 was found to be increased chronically in CSF than in plasma (Billiau et al., 2007, Riazi et al., 2010). The increased prostaglandins after epilepsy induction is confirmed by Takemiya et al. (2010), who noted that epileptic seizures rapidly induce COX-2 in excitatory neurons and increase brain PGE2 levels. COX-2 & PGE2 can enhance seizures by mechanisms which drive epilepsy, as stimulation of inflammatory processes, and neurons death (Salvadori et al., 2012). In addition, increased brain heat shock protein70 (HSP70) (Borham et al., 2016) proved that HSPs can induce the innate immune system through

their interactions with cell surface receptors, leading to the expression of proinflammatory cytokines, chemokines (Asea et al., 2000), and the activation of dendritic cells (Floto et al., 2006). HSPs are stress markers in temporal lobe epilepsy and are induced in response to some neurological diseases. Levels of HSP70 in serum and duration of epilepsy are positively correlated. Also, neuronal degeneration and disturbed memory function indicate that it may be used as biomarker for stress induced neuronal damage (Chang et al., 2012). Serum albumin extra vacation into the cerebral cortex microenvironment due to BBB gaps stimulates the transforming growth factor beta (TGFβ) receptor-mediated signaling cascade in astrocytes (Cacheaux et al., 2009). The pleiotropic effects of the TGF-β signaling pathway produce a reasonable mechanism for epileptogenesis following brain injury and promote a specific therapeutic target (Weissberg et al., 2015). In addition, IL-6 and IFN-γ are increased in patients having epilepsy (Mao et al., 2013). IFN-γ has vital role in developing brain excitatory seizure pathways (Getts et al., 2007).

Other studies have reported that epileptogenesis is associated with elevated levels of ROS, free radical generation, lipid peroxidation, NO and oxidative stress which lead to neuronal dysfunction (Sudha et al., 2001; Rauca et al., 1999, Arora et al., 2009; Xie et al., 2012; and Rathor et al., 2013; Bashkatova et al., 2003; Militão et al., 2010 and Tomé et al., 2010).

Mahfoz et al., 2017; Reddy and Kuruba 2013 & Tariq et al., 2008 have reported behavioral alterations of epileptic animals in Morris water maze test represented by deterioration of optical locative memory, cognition and higher time to reach the escape platform in Li-Pc-treated rats. In addition, epileptic rats spent lower time in target quadrant. Neurotransmitter alteration may be responsible for the observed neurobehavioral changes (Kubova et al., 2004; Nascimento et al., 2005). Paralleling this development of cognitive impairment, a number of morphological and physiological alterations occur in brain networks as a result of SE. Neuronal loss becomes apparent in hippocampus, dentate hilus, and entorhinal cortex (Kleen et al., 2012).

Oxidative stress biomarkers TBARS and NO were significantly increased in brain tissues isolated from SE group, and glutathione level was significantly decreased. Oxidative stress and inflammation may be

considered as possible underlying mechanism of epilepsy and also many neurodegenerative diseases characterized by progressive cognitive deficits (Coyle and Puttfarcken 1993; Mahfoz et al., 2017; Tariq et al., 2008).

Besides, increased excitatory neurotransmitter; glutamate and decreased inhibitory neurotransmitter; GABA was demonstrated in the brains isolated from SE group (Mahfoz et al., 2017). Glutamate was observed to be increased in human and animal models of epilepsy, and it is recognized that increased glutamate excitation leads to neurons' death in epilepsy (Coulter and Eid 2012). The glutamate-glutamine cycle is a main recycling mechanism of glutamate and GABA in the brain. Glutamine synthetase enzyme which is responsible for glutamate degradation was demonstrated to be decreased in epileptic patients (Eid et al., 2004).

In accordance, pathophysiology of different brain regions showed degeneration in neuronal cells of cerebral cortex and hippocampus in SE group. Besides, nuclear pyknosis associated with gliosis and plague formation in the striatum (Mahfoz et al., 2017).

CONCLUSION

It could be concluded that epileptogenesis is characterized by a complicated unregulated inflammatory mediators and pathways. Understanding these mechanisms will allow development of better treatment and prophylactic options against epilepsy.

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Chapter 8

DIABETES AND INSULIN THERAPY INVOLVING PRODUCTS WITH POTENTIAL USE IN POSSIBLE NEUROLOGIC DISEASE PROGRESSION

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ABSTRACT

Diabetes-induced hypoglycemia occurs because of inadequate insulin therapy. It is the main factor leading to brain biochemical dysfunctions, and neuronal death or oxidative damage-associated cognitive impairment. Some consistent evidences have shown that calcium plays a vital role in reducing the risk of diabetes and some neurological disorders have been

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implicated in dysregulation of Ca^{2+} homeostasis, and negatively affect high-affinity Ca^{2+} transport ATPase which plays a crucial role in controlling cytosolic Ca^{2+}. Besides, studies on the activity of enzymes, including ATPase enzyme have demonstrated changes in their actions when Ca^{2+} homeostasis is dysregulated. The impact of this dysregulation event on ATPase enzyme activity has been implicated in neurotoxicity and are possibly related to the pathogenesis in some clinical disorders. Currently, the major issue in glycemic control in neurocritical care patients is that tight glycemic control using intensive insulin therapy is associated with higher rates of hypoglycemia without an improvement in survival rate. On these bases, some authors have recommended adequate nutrition before and during insulin infusion. In fact, conventional pharmacotherapies have been associated with hypoglycemic state in old adult patients. However, the molecular metabolisms of these conventional drugs are still unclear. Therefore, it is necessary to carry out studies that could explain the molecular metabolisms of this common drugs that offer new treatment alternatives with trace elements for diabetic population as is described in this document.

INTRODUCTION

Diabetes is a threatening public health concern due to its high and increasing incidence, the associated healthcare costs, and threatening medical complications [1]. It is one of the priority non-communicable diseases with high impact across countries affecting both the young and the old. The variant, type 2 diabetes mellitus (T2DM), is globally witnessing an ever-increase growth. Hence, the need to put all hands on the deck in the prevention, diagnosis, and control of insulin resistance and most importantly T2DM [2].

Glycemia and insulin resistance are important regulators of multiple physiological processes and their dysregulation has wide-ranging consequences, including alterations in plasma concentrations of metal micronutrients [3]. Human studies have shown that zinc supplement is beneficial to offset pre-diabetic onset [4, 5], and the daily supplementation based on 50 mg zinc gluconate could be a useful approach for the management of overweight T2DM [6]. Zn (Figure 1) is involved in both insulin secretion and its action in peripheral tissues. Specifically, Zn has

insulin-mimetic properties that increase the activity of the insulin-signaling pathway.

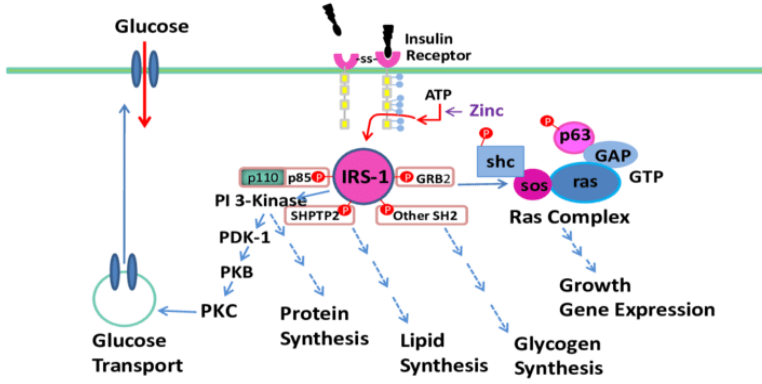

Figure 1. Zinc activities on insulin-signaling pathway.

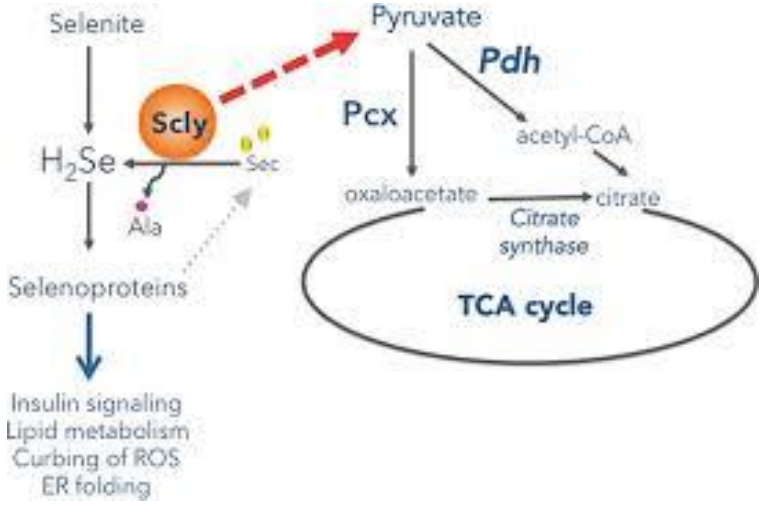

Figure 2. Positive association of selenium with metabolic syndrome.

Zn modulates long-chain polyunsaturated fatty acids levels through its action on the absorption of essential fatty acids in the intestine and its subsequent desaturation. Zn is also involved in both the assembly of chylomicrons and lipoproteins as well as their clearance, and thus, plays a

role in the regulation of lipolysis. Finally, Zn plays a crucial role in redox metabolism, and in turn, on blood pressure [7].

Serum copper has been demonstrated to be higher in obese and overweight individuals and is positively correlated with leptin, insulin, and the leptin/BMI ratio. When compared to lean controls, obese patients had elevated circulating cuproproteins, such as semicarbazide-sensitive amine oxidase (SSAO) and ceruloplasmin, and higher SSAO activity and copper levels in visceral fat [8]. Serum selenium levels were positively associated with metabolic syndrome (Figure 2). In adult patients with this syndrome, the mean serum selenium concentration was 96.34 ± 25.90 μg/L [9].

METABOLIC SYNDROME AND INSULIN RESISTANCE

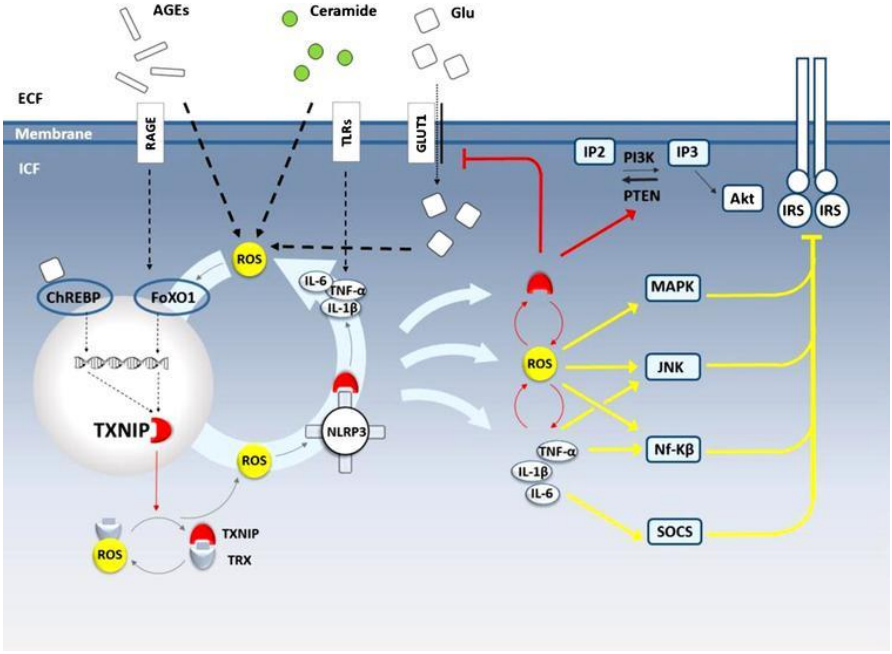

Figure 3. Metabolic syndrome and insulin resistance.

Chronic overconsumption of animal fats is a predisposing factor for diabetes mellitus and obesity. The underlying molecular mechanisms in these conditions encompass leptin resistance, a decrease in rewarding effects of physical activities, xanthine oxidase-induced oxidative stress in vasculature and peripheral tissue, impaired activation of incretin signaling, and deviation in food preference [10]. High-fat feeding and hyperglycemia, key risk factors for the development of metabolic syndrome (MetS), are becoming increasingly associate with high risk of developing dementia and cognitive decline. Increase in the levels of systemic inflammatory cytokines, gliosis in the hippocampus and immune infiltration in cerebral hemispheric tissue has been linked with high fat-consumption and hyperglycemia [11]. Hyperglycemia preferentially induces microglial numbers and astrocytosis in the hippocampus and it is associated with the peripheral recruitment of leukocytes to the cerebrovasculature. However, this situation has not been described in systemic inflammation (Figure 3).

INSULINE AND NEUROLOCIC DISORDERS

Central administration of insulin prevents cerebral cortex injury, brain edema and blood-brain barrier alteration induced by Kaliotoxin2 (KTX2); hence, brings about a significant decrease in systemic disorders, including serum cytokines, inflammatory and oxidative stress markers and tissue damage. The neuroprotective effect of insulin may be due to its crucial role in the regulation of inflammatory response [12]. Insulin resistance could be a risk factor for Parkinson's disease (PD) development, and this could be explained in the light of diminished capacity of dopaminergic neurons to cope with 6-OHDA mediated neurotoxicity due to insulin resistance [13]. High levels of circulating lipids and glucose imbalances has been found to amplify lipid peroxidation which gradually diminishes the antioxidant systems and cause high levels of oxidative metabolism that affects cell structure; thus, leading to neuronal damage. Accumulating evidence suggests that Alzheimer Disease is closely related to a dysfunction of insulin signaling (Figure 4) [14].

SIGNALING PATHWAYS

Insulin binds to the extracellular α subunits of the insulin receptor (IR), which leads to dimerization and autophosphorylation of the β subunits and to the activation of their kinase activity (Figure 5). Autophosphorylated β subunits of insulin receptors recruit molecular adapter proteins that belong to the family of insulin receptor substrates (IRS), as well as the SHC family of transformer proteins. Of the IRS family proteins, IRS1 and IRS2 are the best characterized and the most relevant for the classic metabolic actions of insulin.

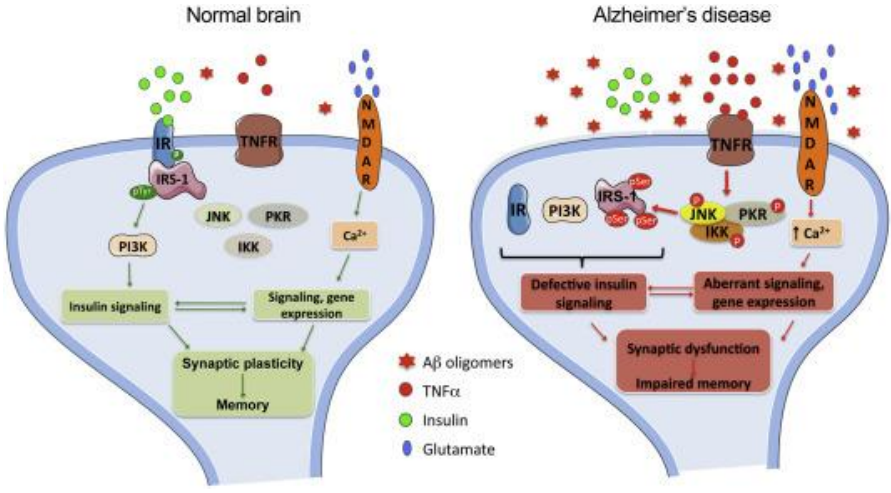

Figure 4. Dysfunction of insulin signaling and AD. Impaired neuronal insulin signaling in Alzheimer's disease (AD). Schematic outline of neuronal insulin signaling in normal brain (left) and AD brain (right).

IRS1 is especially important in skeletal muscle, adipose tissue and cerebral cortex, while IRS2 is important in the liver and hypothalamus. IRS1 and IRS2 recruit and activate the phosphoinositide 3-kinase complex (PI3K), which then phosphorylates and activates the AKT pathway (the main node of the insulin signaling cascade), as well as the protein kinase (PKCζ) and PKCλ. The activated AKT pathway has many subsequent effects of great relevance for systemic glucose control. In this pathway, AKT phosphorylates the 160 kDa AKT substrate, which controls the translocation

of the type 4 glucose transporter (GLUT4) to the cell membrane for glucose absorption in adipose muscle and some neurons. AKT-mediated activation of mTOR serves to regulate protein and lipid synthesis and many aspects of cell metabolism, growth, survival and autophagy [15].

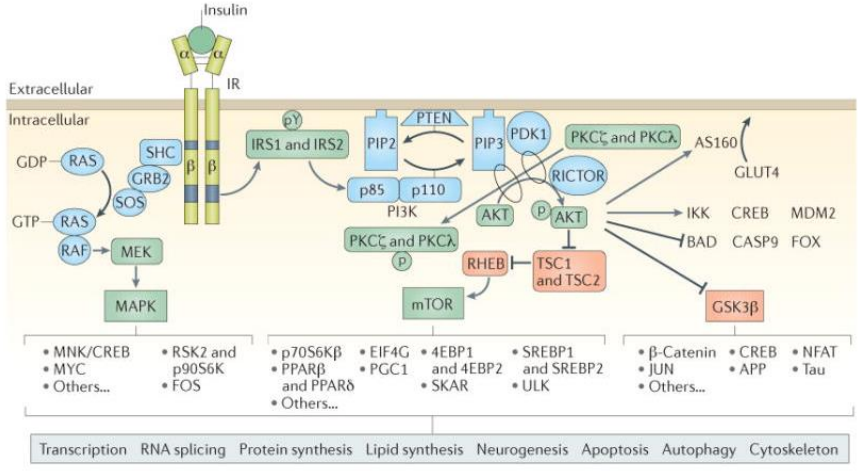

Figure 5. Insulin signaling pathways.

Under physiological conditions, insulin binding to its cell surface receptor (insulin receptor [IR]) triggers IR autophosphorylation and subsequently tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1). This results in phosphoinositide 3-kinase (PI3K) activation and downstream cellular responses that facilitate synaptic plasticity and memory.

Activity-dependent calcium (Ca^{2+}) influx via N-methyl-D-aspartate receptors (NMDARs) activates the signaling and the expression of genes involved in synaptic plasticity and memory. A crosstalk between NMDAR- and IR-dependent signaling may modulate the actions of insulin on memory. In AD, accumulation of amyloid-β (Aβ) oligomers leads to increased tumor necrosis factor-α (TNF-α) levels and activation of stress kinases (c-Jun N-terminal kinase [JNK], double-stranded ribonucleic acid [RNA]-dependent protein kinase [PKR], and IκBα kinase [IKK]), resulting in inhibitory serine phosphorylation of IRS-1. Aβ oligomers instigate additional removal of IRs

from the cell surface and redistribution to the cell body. These combined events block neuronal insulin signaling. Aberrant activation of NMDARs by Aβ oligomers results in excessive Ca^{2+} influx, neuronal oxidative stress, and the disruption in this signaling brings about impaired synaptic plasticity. Under these conditions, putative activation of protein tyrosine phosphatases may inhibit IRS-1 signaling further which ultimately leads to synapse impairment, memory failure, and decreased glucose metabolism in the brain; thus, leading to an insulin-resistant brain state [16].

It has been suggested that mechanisms leading to insulin resistance and diabetes, and their complications include high intake of refined and energy-rich food. These foods are usually accompanied by suboptimal intake of trace elements such as zinc (Zn), selenium (Se), chromium (Cr), and copper (Cu) that are essential and crucial for various biological processes [2]. Although, Zn, Se, and Cu are involved in the pathogenesis of diabetes, but in excessive amount, these trace elements can be toxic.

NEUROENDOCRINE CHANGES

Changes in glucose levels mobilize a neuroendocrine response that prevents or corrects glycemia. The hypothalamus is the main area of the brain responsible for the regulation of glycemic homeostasis. Consequently, metabolic diseases such as obesity and diabetes are related to the imbalance of this control [17]. This condition induces oxidative damage and hyperglycemia which can be interpreted as evidences of increased brain oxidative stress, impaired brain mitochondrial function, increased brain apoptosis, increased tau protein expression, increased phosphorylation of tau protein expression and amyloid beta levels, and decreased dendritic spine density [18]. Oxidized DNA, RNA, protein and lipid products can be used as possible disease progression markers.

The antioxidant system and the generation of FR coexist in a balanced way. When this equilibrium is altered, the result is oxidative stress. This condition causes cell injury and triggers physiologic disorders, as well as promotes pathologic processes such as human neurodegenerative disorders.

This later event is characterized by the accumulation of 8-oxo-7,8-dihydroguanine (8-oxodG) in the DNA of affected neurons, which can occur through direct oxidation of DNA guanine or via incorporation of the oxidized nucleotide during replication [19].

PHYSIOLOGY OF OXIDATIVE STRESS

The major site of production of superoxide radicals is the respiratory chain in the mitochondria, but the exact mechanism and the precise location of the physiologically relevant reactive oxygen species (ROS) generation within the respiratory chain have not been disclosed (Figure 6) [20].

The generation of reactive oxygen species (ROS) within the respiratory chain could be relevant, because evidence indicates that oxidative stress is a crucial factor in the pathogenesis of neurodegenerative diseases [21]. The excessive production of ROS or reactive nitrogen species (RNS) has been found to be deleterious to target cells, and this could play a role in a variety of degenerative processes of some human diseases in the Central Nervous System (CNS). ROS or RNS can have either beneficial or deleterious effects, depending on the species and cellular target on the neuronal signaling pathways involved in the pathophysiology of the neurodegenerative disorders [22]. Ischemic stroke is a major cause of neurological damage and brain dysfunction with consequent strong cerebral oxidative imbalance, inflammatory and apoptotic responses.

INSULIN RESISTANCE AND NEUROLOGIC DISORDERS

Insulin performs variety of functions in the neurons that are mediated through signals in its two main effector pathways: the insulin-IRS-AKT and MAPK pathways [23, 24]. Insulin receptors are located both in the presynaptic terminal axon 60 and in postsynaptic density compartments [25, 26], and have important effects on neurosynaptic functioning [27, 28]. Briefly, insulin improves the growth of neurites and modulates the release

and uptake of catecholamines. It also regulates the traffic of ionic channels activated by ligand, as well as the expression and localization of GABA, N-methyl-d-aspartate (NMDA) and acid receptors α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA). It plays a modulating role in the activity-dependent synaptic plasticity [i.e., long-term potentiation (LTP) and long-term depression (LTD)] through NMDA and AKT receptor signaling [29].

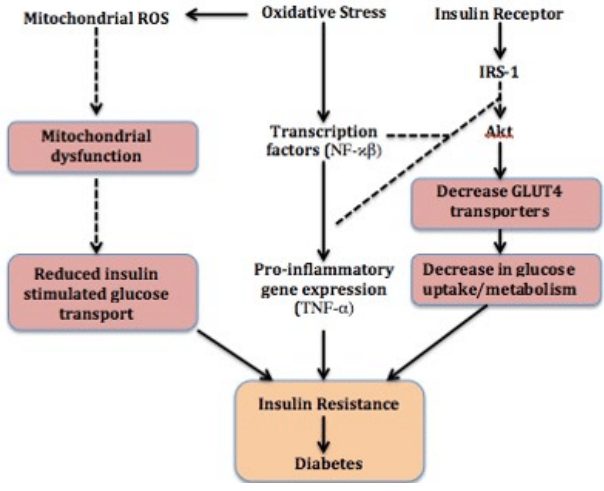

Figure 6. Insulin receptor and oxygen species (ROS) generation within the respiratory chain.

GLUT3 insulin-independent glucose transporter, which is present in very few cells in the body, is the main glucose transporter in the neurons. The density and distribution of GLUT3 in axons, dendrites and neuronal soma correlates with local brain energy demands [30].

Insulin resistance in DM2 is defined as “reduced sensitivity of the body tissues to the action of insulin.” Similarly, the brain insulin resistance is defined as “the failure of brain cells to respond to insulin.” Mechanically, this lack of response is due to negative regulation of insulin receptors, inability of insulin receptors to bind to insulin or defective activation of the insulin-signaling cascade.

Table 1. Natural or synthetic substances used in the treatment of diabetes

Substances	Effect	Ref.
Vildagliptin	Reduces malondialdehyde (MDA), elevates reduced glutathione (GSH) and phosphotylinosital 3 kinase (PI3K), and phosphorylates protein kinase B (p-AKT). It induces the activation of PI3K/AKT/mTOR pathway, and its anti-apoptotic effect.	[38]
Sanbai melon seed oil (SMSO)	Mitigates oxidative stress and alleviates the liver and renal injury in diabetes. It also protects islet cells from apoptotic damage by suppressing ER mediated and mitochondrial dependent apoptotic pathways	[39]
Yucca schidigera extract (YSE)	Decreases the levels of inflammatory markers including tumor necrosis factor (TNF-α), nitric oxide (NO), and transforms growth factor-β1 (TGF-β1) and vascular endothelial growth factor (VEGF).	[40]
Flavonoid glycosides as Isoorientin	Reverses dexamethasone-induced decrease in mitochondrial membrane potential (MMP) and intracellular ATP production. It reduces accumulation of intracellular reactive oxygen species (ROS), and protects mitochondrial DNA (mtDNA) from oxidative damage	[41]
Cilostazol or sildenafil	Treatment with these drugs improve anti-oxidative capacity and ameliorate lipid peroxidation and pro-inflammatory iNOS expression in testicular tissue of diabetic subjects.	[42]
Resveratrol (RES) and insulin	Mechanism of actions revealed a synergist effect of both drugs due to hypoglycemic effect of insulin and the ability of both drugs to increase renal cortex antioxidant enzymes activities, inhibit lipid peroxidation, and up-regulate Na^+/K^+-ATPase, independent of each other.	[43]
Thymoquinone (TQ),	Decreases glucose, glycosylated hemoglobin (HbA1c) levels and alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transpeptidase activities.	[44]
Black soybean seed coats	Plays a role in controlling blood glucose and lipids levels by promoting insulin secretion and restoring islet β-cell function.	[45]
Limonene, a major component of Citrus oils,	Decreases DNA damage, GR enzyme activities and MDA levels and significantly increases GSH levels and CAT, SOD and GSH-Px enzyme activities and altered lipid and liver enzyme.	[46]
Bamboo leaf extract (BLE)	Ameliorates diabetes-induced myocardial morphological changes and cardiac inflammation, and reduces protein levels of TGF-β1, IL-6, Cleaved-caspase-3 and the nuclear transcription of NF-κB in the hearts.	[47]
Malvastrum tricuspidatum (MT)	The increase in oxidative stress in synaptosomes and brain mitochondria marked by an increase in lipid peroxidation and protein carbonyl content and decline in reduced glutathione was restored by the MT extract	[48]
Crocin	Reduces the oxidative stress and pro-inflammatory response of podocytes	[49]

At the cellular level, this dysfunction is manifested by deterioration of neuroplasticity, decline in the receptor regulation or decreased release of neurotransmitters in neurons. Moreover, the manifestation may include deterioration of the processes most directly involved in insulin metabolism, such as neuronal glucose uptake in neurons that express GLUT4, or homeostatic or inflammatory responses to insulin [31, 32].

Midlife obesity may be an important modifier of brain atrophy in individuals who are developing cognitive impairment and dementia, while it has little effect on structural brain integrity in no demented older adults [33]. Metabolic disturbances as insulin resistance, diabetes and obesity, and neuropsychiatric disorders have been demonstrated in both human and animal studies, suggesting the possibility that they have shared pathophysiological mechanisms. Insulin is a pleiotropic peptide, critical to neurotrophism, neuroplasticity, and neuromodulation. Moreover, the role of insulin underscores its importance in the development of several neuropsychiatric disorders, including, but not limited to, mechanisms involved in the pathogenesis and progression towards diabetes, obesity, and neurodegenerative disorders, such as Alzheimer's disease [34]. The peroxisome proliferator-activated receptor (PPAR) are improvements often attributed to anti-inflammatory effects of PPAR activation. PPAR induces metabolic changes as a potential mechanism of regulation of immune cell function through these nuclear receptors. Together, immune cell-specific activation of PPARs presents a promising therapeutic approach to treat both metabolic and neurodegenerative diseases [35].

THERAPEUTIC OPTIONS

Lixisenatide is a new potent glucagon-like peptide-1 (GLP-1) analogue that has been used clinically in the treatment of type II diabetes [36]. This drug produces suppression of oxidative stress parameters (catalase, reduced glutathione, malondialdehyde and NO), inflammatory marker (tumor necrosis factor-alpha) and apoptotic marker (caspase-3) in ischemic animal models. However, Metformin is the most frequently used oral anti-diabetic

drug, which apart from having hypoglycemic activity, improves serum lipid profiles and positively influences the process of homeostasis and exhibits anti-inflammatory properties [37]. Table 1 shows a list of other substances with similar effects.

CONCLUSION

Indeed, the prevalence of diabetes continues to increase despite advances in detection and insulin therapy. Therefore, to achieve optimal glycemic control, it is necessary to embark on beneficial lifestyle interventions, particularly physical activity, coupled with the choice of an insulin regimen, timely initiation and intensification of insulin therapy with adequate combination of antidiabetic agents.

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Chapter 9

VISUAL EVOKED POTENTIALS AND OUR STUDIES

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ABSTRACT

Evoked potentials are electrical responses of the brain to light, sound, or electrical stimuli. Depending on the type of stimulus, they emerge as visual, auditory, or somatosensorial evoked potentials. Visual evoked potentials (VEPs) are electrophysiological signals taken from the electroencephalographic activity of the visual cortex and recorded the scalp over the cortex. VEPs depend on the functional integrity of the visual pathways at any level including optic components of the eyes, retina, optic nerve, optic chiasm, optic radiations, and the visual cortex. On the pattern VEP recordings, 3 main components are observed which are called N75, P100 and N145. There are two types of recordings, known as pattern VEP and flash VEP.

The presence of dopamine in the inner plexiform layer of the retina in mammals including humans and the fact that dopamine is not known to be

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an important transmitter anywhere in the visual system except for the retina, suggests that VEP abnormality is of retinal origin.

Factors affecting VEP latency and amplitude include inflammation, hypoxia, and atherosclerosis. We have several publications on this topic on different groups of patients. This chapter of the book was intended to be written in order to explain and comment on our studies as well as the others on the definitions, types, recordings, waves, commenting normal and abnormal responses. Physiology and the pathophysiological mechanisms underlying abnormal VEPs will also be discussed.

Keywords: visual evoked potential, flash VEP, pattern VEP, latency, amplitude

1. INTRODUCTION: EVOKED POTENTIALS

Evoked potentials (EPs) are electrically recorded responses of the brain to external stimuli such as light, sound, or electric current [1]. EPs are responses of the brain to electric, light, or sound. They are recorded from the electrodes on the scalp, spine, or peripheral nerves. Each of them is in the wave form with unique latency, amplitude, or other features. They are defined based on their polarity, latency, or sequence number. As they are potentials of very low amplitude, they are amplified and averaged [1, 2].

Evoked potentials are used to show sensorial system dysfunctions detected by history and/or physical examination, to reveal subclinical pathologies of the sensorial system, to determine neuroanatomical distribution, or location of the disease, and for purposes of clinical follow-up and intraoperative monitoring [1, 2].

It is a non-invasive method. Recording these potentials is used in evaluating normal or pathological functions in the nervous system.

Evoked potentials are applied in three main ways:

(a) Visual evoked potentials (VEPs),
(b) Brainstem auditory evoked potentials (BAEPs), and
(c) Somatosensory evoked potentials (SSEPs) [1, 2, 3].

1.1. Visual Evoked Potentials

Visual evoked potentials (VEPs) are visually evoked electrophysiological signals originating from the electroencephalographic activity of the visual cortex recorded from the scalp. Because the visual cortex is primarily activated by the central visual area, the VEPs are dependent on the functional integrity of the visual pathways at any level including the eyes, retina, optic nerve, optic radiations, and the occipital cortex [1, 2, 3]. VEP is a useful diagnostic modality providing important information on function of the visual system. It reflects dynamic alterations in the visual pathways with advantages of being non-invasive and having temporal resolution at the level milliseconds [4]. The brief aim of the VEP is to yield data reflecting status of the higher afferent visual areas involving the retino-cortical transmission and activity in the visual cortex [5].

The optical components of the eye which are the retina, optic nerve, optic tract and all structures to the occipital cortex are reviewed in VEP's neuroanatomical information [4, 5].

1.1.1. The Visual Pathways

The retina's function is to serve the information given in the form of light to the brain. When transducing the light to electrochemical energy, the retina converts the information consisting of dark and light contrast to neural signals which is meaningful in the visual cortex. Photoreceptors are the main functional components of the retina

1.1.1.1. Photoreceptor Cells

Light energy falling onto the photoreceptors (the rods and cone cells) are transduced to electric energy (action potential) by photochemical reactions

Seeing in the dark is the function of the rods whereas seeing in the light is the function of the cone cells. The retina contains about 120 million rods and about 6 million cone cells. The cone cells are located on the central retina. They enable sharp and color vision in the light. The fovea contains only the cone cells. Density of the cone cells is decreased toward the

periphery. The rods are responsible for seeing in the dark and twilight. They are located on the peripheral retina.

1.1.1.2. Bipolar Cells

The photoreceptor cells make synapse with the bipolar cells. Bipolar cells are the first neuron of the visual pathways.

1.1.1.3. Ganglionic Cells

These are the second neuron of the visual pathways. Nerve fibers released from the ganglionic cells emerge on the internal surface of the retina and illustrate the layer of nerve fiber by running parallel to the retinal surface. The optic disc consists of ganglionic cells extensions (Figure 1). Nerve fibers which leave the eye as optic nerves reach the chiasm. In the chiasm, the fibers come from the temporal retina and pass through, whereas the fibers originating from nasal retina decussate to make the optic tract. Optic tract fibers reach corpus geniculatum laterale in the brain and make another synapse. The third neuron of the visual pathways is located in the corpus genitaculum laterale (Figure 2). To sum up, the visual pathways that begin from the optic nerve consist of axons of the ganglionic cells and extend to the occipital cortex (Figure 3).

Corpus geniculatum laterale has two fundamental functions: First, to transmit visual information of the optic tract to the primary visual cortex via optic radiation (geniculocalcarin tract), and second, to control how much signal of visual information will pass to the visual cortex [6, 7].

Fibers of the third neuron originating from the lateral geniculate ganglion make the optic radiation and project to the striatal (the primary visual cortex, Brodmann area 17), peristriatal (Brodmann areas 18 and 19), and midtemporal areas. Similarly, they project from area 19 and mid-temporal area to the posterior parietal area. Because transmission is spread on such a wide area, VEP can be recorded from a wide area on the scalp from the vertex to the inion [3, 8, 9, 10]. That is to say that the visual pathways don’t activate only the occipital lobe. They project on a wide area on the temporal and parietal lobes as well. Based on this information, the

reference electrode should be placed in front of the vertex, away from the active area [3, 8, 9, 11].

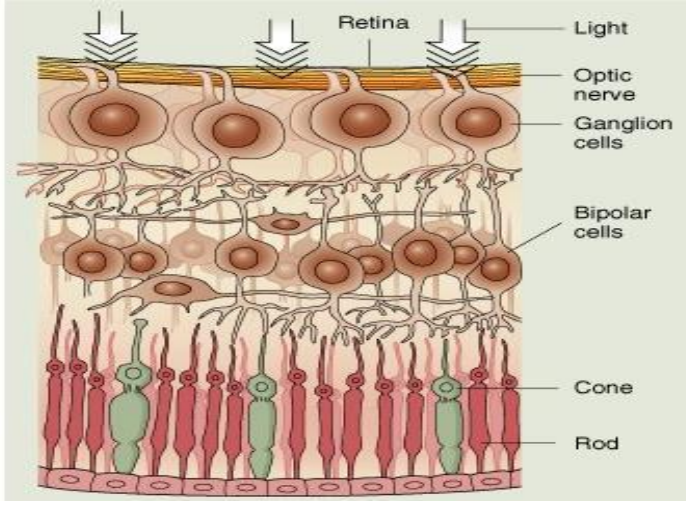

Figure 1. Cells in the retina (NEUROANATOMY BOOK-SNELL).

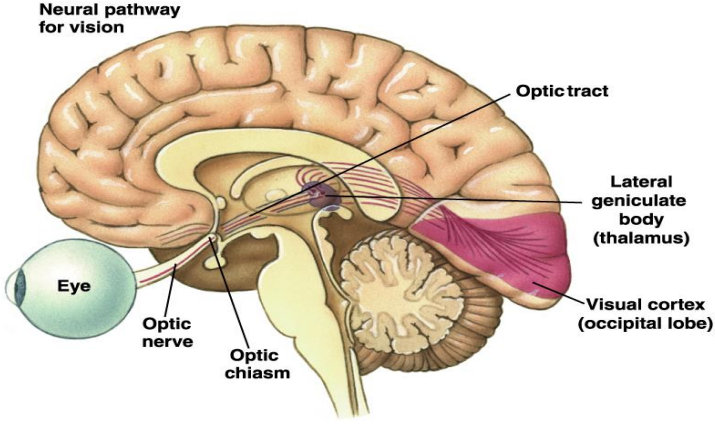

Figure 2. Map of the optic pathways (NEUROANATOMY BOOK-SNELL).

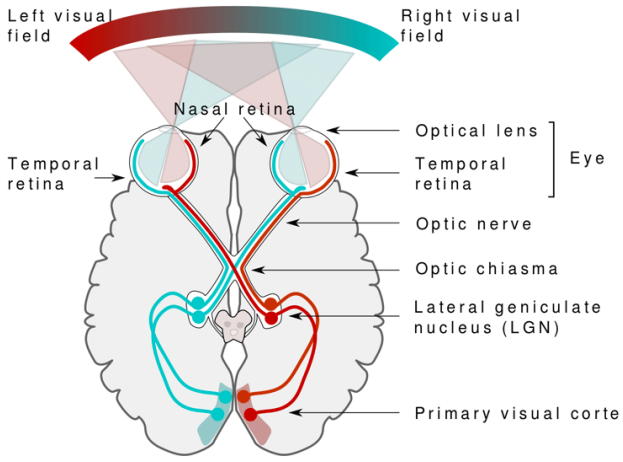

Figure 3. The visual pathways (NEUROANATOMY BOOK-SNELL).

1.1.2. Procedures of VEP Recording

Certain equipment is required for recording VEP. General equipment electrodes, stimulation, amplification, filtering machinery and an average computer are required.

1.1.2.1. The Electrodes

For recording VEPs, various skin electrodes are recommended such as silver-silver chloride, standard silver-silver chloride, or golden disc electrodes. The skin is cleaned with alcohol and it is freed from oil and dead skin tissue. The electrodes are used with an appropriate paste or gel to reduce the resistance of electrode and to enable a stable electrical connection. Impedance of the electrodes should be lower than 5 kΩ as measured at 10 and 100 Hertz (Hz) and no more than a 20% difference should exist between the electrode sites in order to avoid electrical interference [12].

1.1.2.2. Placing the Electrodes

According to the international 10/20 system, the scalp electrodes should be placed on the bony landmarks proportional to size of the head [12]. Anterior/posterior midline measurements are dependent on the distance

between the inion and nasion over the vertex. The reference electrode is placed on the Fz point. The active electrode is placed on the Oz point 2 to 3 cm above the protuberencia occipitalis. The active electrode records the neural signals and environmental noise. The inactive electrode is placed on the Cz point according to the 10-20 EEG recording system. It records all potentials except for the neural ones (Figure 4). The difference between these two electrodes reflects neural activity of only one area of the occipital cortex [13, 14].

1.1.3. Stimulus Types

There are two important standard classes of VEP stimulation, being pattern and flash stimuli.

1.1.3.1. Pattern Stimulus

The standard pattern stimulus is black and white checkerboard with high contrast. Sight distance ranges from 50 to 150 cm and it may be adjusted to allow an appropriate visual field and to provide the grid sizes required for screens of any size [13].

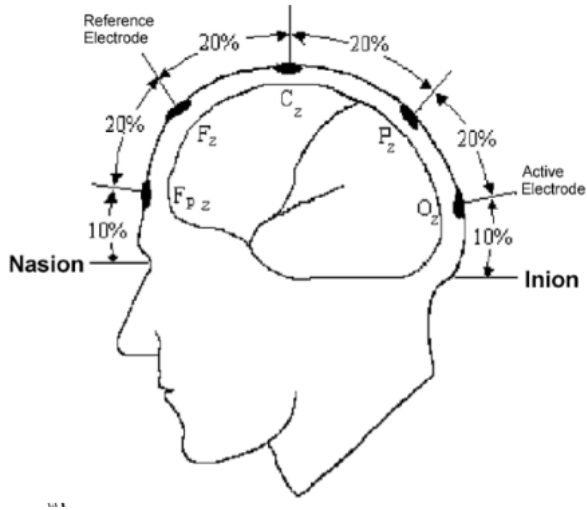

Figure 4. Placing the scalp electrodes according to 10/20 electrode system.

1.1.3.2. Field and Size of Grid

In pattern VEP recording, the visual stimuli are usually applied using grids of two different sizes. The smaller grids rather stimulate the fovea while the bigger ones rather stimulate the peripheral areas of the retina.

The angle of entry of the stimulus varies depending on size of the grids and distance from the subject [15]. For example, the stimulus from a grid with an edge of 4 mm reaches the eye with an angle of 14' from a distance of 100 cm, an angle of 18' from a distance of 75 cm, an angle of 30' from a distance of 50 cm, an angle of 1º from a distance of 25 cm, and with an angle of 2º from a distance of 12 cm [9]. The visual angle is a function of distance from the eye of the subject to the pattern (check) and width/height of the pattern [9]. It equals the arctangent of division of the pattern width to the distance to the screen. It is calculated as follows:

$$B = \text{Arctan}(W/D)$$

where B is the visual angle, W is the width of the pattern in centimeters, and D is the distance between the eye and the screen in millimeters.

Two components of control are used for the VEPs in the standard pattern. It is 1° ± 20% and 0.25° ± 20% on both sides. All grids should be in the shape of square and contain equal numbers of light and dark squares. It is not mandatory to use a field in the shape of a square but the ratio of width to height shouldn't exceed 4:3 and the size of field should be at least 15º at its narrowest dimension [13].

Grid size determines latency and amplitudes. A decrease in grid size increases N70 and P100 latencies. But its relationship with P100 latency isn't linear. It has been shown that P100 latency increases if the size of the grid is above 30º [4].

The size of the box and field should be chosen to evaluate the clinical condition in the best manner. Small boxes (12 to 16 inches) and small fields (2° to 4°) selectively stimulate the central vision. These responses are sensitive especially to non-focusing and decreased visual acuity. Bigger boxes (40 to 50 inches) and bigger fields (16° - 32°) create bigger stimulation

of peripheral vision. These responses are less affected by non-focusing or decreased visual acuity [16].

1.1.3.3. Determining the Location of Types of Stimulation Fields

For the subject, another fixation point other than reversing the pattern itself to the subject should be provided. The location of the fixation point relative to the stimulation field determines the part of the visual field to be stimulated [16].

1. Pattern full-field stimulus: This is the pattern spreading to both sides of the fixation point equally.
2. Pattern central-field stimulus: It is a pattern restricted to such a small part of the central vision of 2-4°.
3. Half-field stimulus: It is a pattern in which the visual field is reflected to one side of the fixation point, i.e., to left or right of it.
4. Alternate half-field stimulus: It is a type of half-field stimulus in which a central fixation point and the right and left half-fields are reversed consecutively in an alternate manner.
5. Partial-field stimulus: Any pattern reflected on a small sector of the visual field is called a location defined by the fixation point.

When half-field or partial field stimuli are used, the fixation point is displaced slightly to the unstimulated side of the visual field. This helps avoiding stimulation of the areas out of the partial field or retinal half-fields by involuntary eye movements. When alternate half-field stimuli are used, both half-fields should be separated from each other with a non-turning back band and the center of the fixation point should be on the band. Additionally, the distance of the fixation point from the stimulus pattern (retinal eccentricity) should be noted [16].

1.1.3.4. Evaluation of the Luminance (Level of Light) and Contrast

Brightness of dark and light elements of any pattern directly affect the amplitude and latency of the waveform of VEP. Absolute illumination (illumination, light) should be measured by a photometer in cd/m^2. The

average illumination of the checkerboard should be 50 cd/m2 (40 to 60 cd/m2) and contrast between the dark and light squares should be high (defined as 80% or higher co-efficient of Michelson). Illumination and contrast of the stimulus should be uniform between the center and the periphery of the field. Ambient illumination is average value of illlumination measured at several points around the unit. Isoluminance is of importance in preventing light scattering on the retina. Many optic and electronic systems, however, don't provide truly uniform fields. Thus, a variation (difference) up to 30% between the center and periphery is considered as acceptable. PVEP is relatively insensitive to the effects of changes in the ambient illumination but it should be kept fixed as much as possible (Table 1) [13].

Another important parameter is the contrast. The contrast of the pattern is a ratio calculated as follows:

Contrast = (max – min) x 100/(max + min)

A decrease in the light reaching the retina causes a decrease in amplitude and an increase in latency. Retinal illumination (I) is calculated as follows:

I = L x A

where L is the ambient illumination and A is the field of the pupil.

Table 1. Parameters affecting the latency and amplitude values during VEP recording

Stimulus Rate	1-2 Hz. Latency increases with rate
Contrast	50%-80%: Latency increases as contrast decreases.
Luminance	100cd /ml: Latency increases as luminance decreases
"Check size"	Full-field: 28-31 (central retina) Half-field:50-90 (peripheral retina)
Filter	1-250/300hz
Average	200 times

Contraction of the pupil creates the same effects with the illumination on amplitude and latency. Changes in pupil size has prominent effects on

retinal illumination. P100 latency varies between 96 and 107.5 msec depending on the pupil size.

2. TYPES OF STIMULATION

2.1. Pattern Reversal Stimulus

For the purpose of pattern reversal protocol, black and white grids are reversed every second, thus they alternate suddenly and repeatedly (Figure 5). No overall change should occur in illumination of the screen; for this purpose, an equal number of black and light elements should be present on the screen and no transient change in the illumination should occur during reversal of the pattern. Big grid (1º) and small grid (0.25º) stimuli is determined by grid width (visual angle), stimulus rate (number of alternation per second), number of reversals, mean illumination, pattern co-efficient, and field size.

It is the preferred stimulus for most clinical purposes. It is less variable than other VEPs evoked by other stimuli in terms of wave form and timing [13].

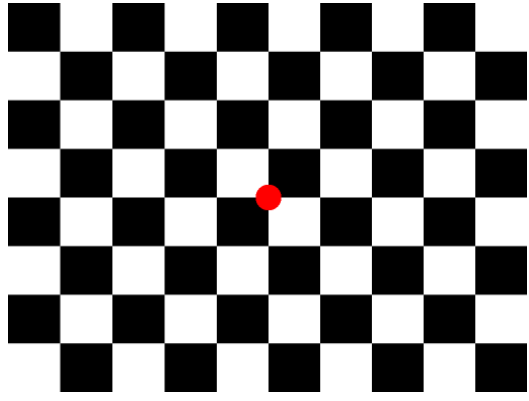

Figure 5. Checkerboard used for VEP recording.

2.2. Pattern Onset/Offset Stimulus

For purpose of pattern onset/offset, the checkerboard pattern is suddenly switched to a diffuse gray background.The average illumination of the checkerboard and diffuse gray background should be similar and no change should occur in the illumination during switch from the pattern to the black screen. This may be hard to achieve. Onset time for the pattern should be 200 msec later than to diffuse a background of 400 msec. At least two sizes of pattern components should be used in the shape of grids of 1° and 0.25° on both sides [13].

This stimulus is appropriate for detecting the malingering cases and to be used in patients with nystagmus.

2.3. Flash Stimulus

Flash VEP should be evoked by a short-time flash given in a dimly enlightened room making a visual angle of at least 20º. The flash rate should be one per second. It is useful in the cases of poor optics, poor cooperation, and for the cases being inappropriate for pattern stimulation with poor visual conditions [13].

In terms of stimulus frequency, the VEPs are divided in two groups as transient and stable. The waveform of any VEP depends on the temporal frequency of the stimulus. The waveform becomes near sinusoidal at high rates of stimulation and this is called “stable state”. The frequency of the stimulus raises up to 10 per second. Multiple different deflections occur at lower temporal frequencies, called “transient VEP” [13, 17].

Normal values of the latency are as follows: 50 to 100 msec for wide positive waves and 100 to 250 msec for the wide negative waves with the limit for interocular latency being 6 msec [13, 17].

3. RECORDING THE PARAMETERS

3.1. Amplification and Filtering

For recording VEP, amplification of the input signal by 20,000 – 50,000 times is usually appropriate. The input impedance of the pre-amplifier should be at least 100 MΩ and the common mode rejection rate shouldn't exceed 120 dB. In order to exclude the signals of which the amplitude exceeds ± 50 – 100 μV, automated artifact rejection based on the signal amplitude should be used. The amplifiers should start over rapidly after the artifact signals [13].

Analog high-pass and low-pass filters [-3 dB points] should be set to ≤ 1 Hz and ≥ 100 Hz, respectively. The roll-off slope of the analog filter shouldn't exceed a 12 dB/octave for the lower frequencies and a 24 dB/octave for the higher frequencies. Filter adjustments should be made in certain situations. In the case of using any analog filters, especially those with low-pass under 100 Hz, it is of importance to know that they can alter the timing or peak time of the VEP components significantly. A filter set is recommended as 1-3 Hz for the lower filter and 100-300 Hz for the upper filter. Scanning time should range between 300 and 500 msec. Shorter scanning time causes abnormal responses in P100 peak time [18].

3.2. Averaging and Signal Analysis

The number of sweeps of each average depends on the signal to noise ratio between the VEP and background. In many clinical conditions, the minimal number of sweeps per average should be 64. At least two averages should be taken to confirm the repeatability of each VEP. In infants and young children, less sweeps per average may produce clearer responses at times. A longer recording time which is required to increase the sample size brings about possibility of variability due to attention loss and/or increasing movements. At least 100 potentials should be averaged. Occasionally, it may be required to average 200 or 500 potentials [13].

3.3. Analysis Time

Minimum analysis time (sweep time) for all adult flash and pattern-reversal VEPs is 250 msec after the stimulus. Analysis time (sweep time) should be extended to 500 msec in order to analyze both initial and final pattern responses evoked by the initial/final stimuli. In infants, peak latency of the VEPs is longer and a longer sweep time will be required to better demonstrate the response [13].

4. PREPARATION BEFORE VEP

a. The patient should sit in a comfortable armchair. The chin and neck should be in a comfortable position in order to avoid muscle artifacts (Figure 6) [8]
b. If the patient is using spectacles, he/she should be wearing them or his/her vision must be corrected by lens [10].
c. The patient mustn't have used hair spray or hair gel.
d. The patient mustn't have used mydriatic drops for purpose of ophthalmic examination in the last 12 hours. Mydriasis causes a decrease in visual acuity, increase in P100 latency, and alterations in P100 amplitude [9].
e. Variation in the pupil size may alter test results. The constricted pupil (myosis) decreases P100 amplitude whereas dilated pupil decreases P100 latency [9].
f. The visual stimulus is given by a television screen or monitor. During the examination, the room should be dimmed.
g. For mono-ocular stimulation, the other eye is closed by an eye-band.
h. There must be a fixation point in the middle of the screen.
i. In order for the procedure not to be affected by the artifacts, the response should be averaged from the first few stimuli.
j. Half-field stimulation is performed either by darkening half of the screen or by placing a dashboard in front of the screen to close it.

k. The stimulation rate should be 1-2 per second (usually 2 per second) during VEP recording. A slower rate of stimulation may cause distraction of the patient [16].
l. During the examination, the patient is asked to fix his/her eye on the point marked in the middle of the screen for full-field stimulation and on either left or right edge of the pattern for the half-field stimulation (on the right corner for the stimulation of left half-field and on the left corner for the stimulation of the right half-field) [8, 16].
m. For pattern-reversal stimulation, the patient should sit 1 meter away and for flash VEP stimulation, the storoscobic flash should be placed 10 cm away [10].
n. It is critical for the patient to focus on the pattern and to analyze it in regard to performing PVEP test. Alterations in focusing on the pattern may affect latency, amplitude and waveform of the response. Tiredness may alter focusing on close objects. In order to avoid this effect, the patient shouldn't be placed less than 70 cm from the stimulus [13, 14].
o. Wakefulness of the subject and attention level against the test stimulus are critically important in performing VEP test and should be noted. Changes in these factors during the test may affect comparing the measurements of the consecutive stimulations between the right and left eyes or in the same eye [13, 14].

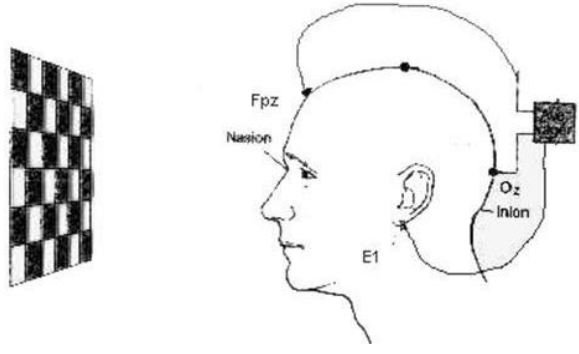

Figure 6.

5. STANDARD VEP WAVEFORMS

The time from the beginning of the stimulus to the positive or negative deflection or to the occurrence of VEP is called peak time.

In the past, the term “latency” was used to express the time from the beginning of the stimulus to the biggest amplitude of the positive or negative wave. In many areas of physiological recordings and in electroretinography, the time between the beginning of the stimulus to the peak of the next deflection was termed “implicit time” and the term “latency” was expressed as the time from the beginning of the stimulus to initiation of the response. The recent ISCEV standards tend to replace the peak time or peak latency with implicit time [19, 20].

According to ISCEV, VEP waveforms are divided in three.

5.1. Pattern-Reversal VEP

They are obtained in response to visual stimuli consisting of black and white grids in the form of a checkerboard and the grid alternates 1-3 times per second. The pattern stimulus is usually applied to the subjects with a computer screen.

In the pattern VEP records, three components are observed which are called N75, P100, and N135. The letters P and N imply positive or negative voltage recorded from the active electrode over the occipital cortex relative to the reference electrode (Figure 7A and 7B). The VEPs consist of an array of waveforms including a negative wave (expressed as N) and a positive wave (expressed as P). P100 amplitude is measured from peak to peak between N75 and P100. P100 wave latency shows less variability between the subjects. Its variability between two eyes and between the repeating measurements in the same subjects is less. Thus, it is one of the most frequently used parameters in evaluating the VEP [13, 19, 21].

VEP trace consists of positive and negative waves although it varies depending on several individual factors. The first negative wave is defined as N75 (N1), and the second one N145 (N2). The N75 wave isn’t observed

in some subjects while it may be as wide as P100 latency in others [22]. These negative waves give information rather on the nerve fibers serving in conduction function [23].

The N75 wave reflects activity of the fovea and primary visual cortex whereas the N145 wave reflects activity of the visual association area. P100 peak time is affected by the parameters not being pathophysiological such as size and contrast of the pattern, ambient illumination, signal filtering, age of the subject, refractive errors, poor fixation, or myosis [13].

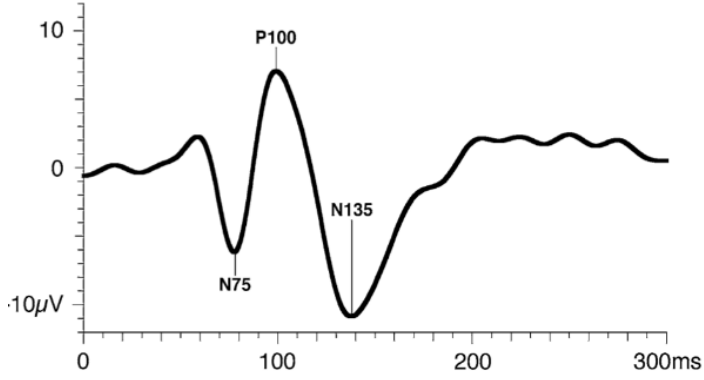

Figure 7 A. Latencies used in pattern VEP stimulation (ISCEV Criteria).

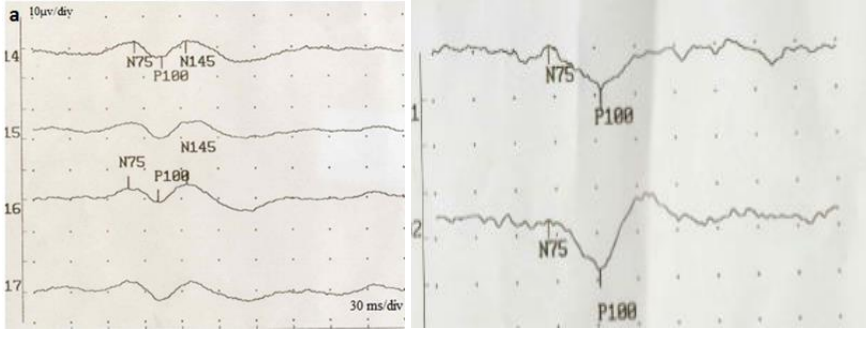

Figure 7 B. Latencies used in pattern VEP stimulation (MEDELEC /IECA "Sapphire Celal Bayar University Neurology Department).
First The ISCEV standard recommends displaying positivity upwards -opposite from neurological standards.

The size of the grids in the pattern stimuli in the form of a checkerboard used in pattern VEP varies depending on the purpose of the field. In pattern VEP recording, visual stimuli are usually used when grids of two different sizes are used. The smaller grid rather stimulates the fovea whereas the bigger one rather stimulates the retina. The latency and amplitude of the waves are more stable in VEP recordings obtained with pattern stimuli [4, 19].

5.2. Pattern Onset/Offset VEPs

There is a special form pattern VEP called "Onset-Offset Pattern VEP" in which the images appears on the screen and then disappear after awhile. During this test, illumination of the screen is kept unchanged. Negative effects on the waves are avoided by keeping the illumination in standard manner [24].

Pattern onset-offset VEPs show more intersubjective variability than the pattern-reversal VEPs. Pattern onset-offset stimulation is useful in detecting or confirming cases of malingering and in evaluating the patients with nystagmus because this technique is less sensitive to compounding factors such as poor fixation, eye movements, or voluntary non-focusing. Standard VEP against the pattern onset-offset stimulation typically consists of three main peaks: C1 (positive, about 75 msec), C2 (negative, about 125 msec), and C3 (positive, about 150 msec) (Figure 8). The amplitudes are measured from the last peak [24].

5.3. Flash VEP

Flash VEP occurs in response to flashing stimuli applied by photostimulators such as xenon, light emitting diode (LED). Light intensity, frequency, and wavelength of the flash given by the photostimulator shows variability. It allows for comparing both eyes and both cerebral hemispheres [15].

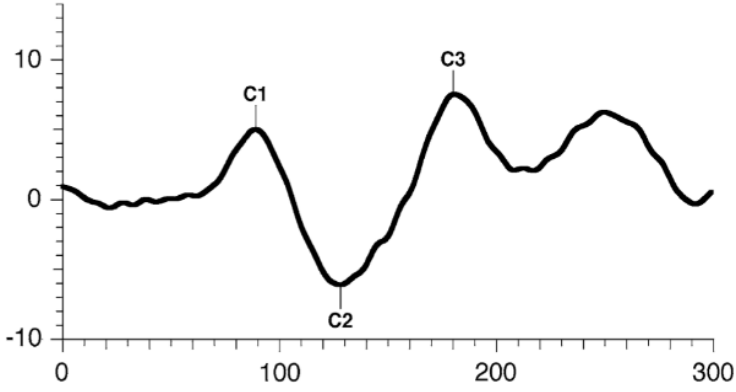

Figure 8. Pattern VEP onset-offset assessment (ISCEV Criteria).

Flash VEPs show more variability compared to the pattern VEPs but they are quite similar between two eyes of any subject. They are especially useful for the subjects who are not able to or unwilling to cooperate and in the cases of accurate use of the pattern stimuli being prevented by optic factors such as media opacities.

Flash VEPs consist of positive and negative components called N1, P1, N2, P2, N3, and P3. This denomination enables easy distinction of the flash VEPs from the pattern VEPs. In clinical practice, N2 and P2 waves which are easier to observe and more stable, are usually assessed because N1 and P1 waves with shorter latency and smaller amplitude are harder to distinguish in the records. Latency of the N2 component is about 90 msec while that of P2 is about 120 msec (Figure 9) [15, 19, 21].

Flash VEP is preferred in children and in individuals with mental problems and refractive media. The width of distribution of flash VEP in a normal range is more than that of pattern VEP. Thus, flash VEP should be preferred in the case of intraocular comparison being required [14].

Rarely is the site of a lesion at the level of the sheath of the optic nerve when pattern VEP is normal, but the flash VEP is altered (increased latency, decreased amplitude) in the presence of optic nerve lesions [14].

As a result, latency and amplitude of the waves are more stable in VEP recordings obtained with pattern stimuli. On the other hand, latency and amplitude of the waves show more variability in the recordings taken from

normal individuals using flash VEP. In both flash and pattern VEP records, however, variability between two eyes of the subject is lower in the recordings taken in the same session. Thus, pattern VEP recording is usually preferred in clinical practice. A flash VEP recording is more appropriate in infants and young children and in non-cooperating subjects, [4, 19].

5.4. Special Methods of VEP Recording

The following methods are preferred and give more information in certain clinical conditions although they aren't compatible with ISCEV standards:

- Steady state VEP
- Sweep VEP
- Motion VEP
- Color VEP
- Binocular VEP
- Stereo-elicited VEP
- Multichannel VEP
- Hemi-field VEP
- Multifocal VEP
- Multi-frequency VEP
- LED Google VEP [13, 14]

6. EVALUATING THE VEP

6.1. Normal Values

Even though standardization should provide similar VEP waveforms between the laboratories, each laboratory should determine its own normative values using its own stimulus and recording parameters.

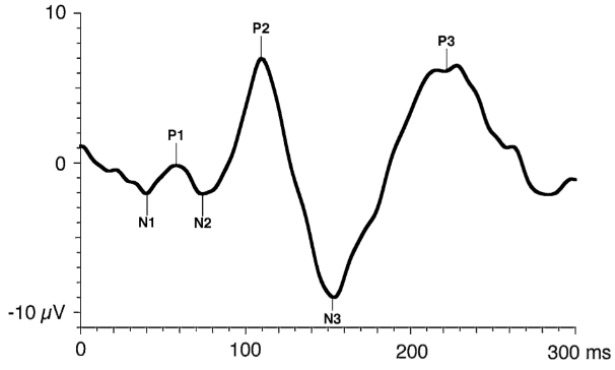

Figure 9. Sample of flash VEP (ISCEV Criteria).

For laboratory norms, the structure of a normal sample should contain factors of age, sex, and interocular asymmetry. Normative values for adults cannot be applied to the pediatric or elderly population. Comparing the amplitude and peak time between two eyes increases sensitivity of the VEP to monocular conditions.

Normal laboratory values, descriptive statistics, not assuming normal distribution, but based on calculations of the medians and percentiles from the observed sample distribution should be used. As a limit of normal, a 95% confidence interval (i.e., the interval of 2.5% and 97.5%) is recommended [13].

Reports using the standard VEP protocols should contain the following stimulus parameters: field size of the stimulus, power of the flash (time-integrated luminance) or average illumination of the pattern, pattern component size and contrast of the pattern stimuli, stimulation frequency, and the eye parameters tested. Recording parameters such as filter sets and location of the positive (active), negative (reference) and ground electrodes should also be noted.

The traces should contain a net polarity indicator, time in milliseconds, and amplitude in microvolts. VEP traces are recommended to note as positive when they are upward. All VEP reports including those for the non-standard responses should contain their own normal values and ranges as well as peak time and amplitude measurements. The reports should note whether the records are compatible with these ISCEV standards [13, 14].

In pattern VEP investigations, P100 latency is about 90 to 110 msec with its limit being 117 msec. The interocular difference of latency should be less than 6 msec, N75-P100 amplitude limit value should be 5 microvolts. The interocular difference of latency should be less than 50% [13, 14].

6.2. Interpreting VEP

VEP abnormalities aren't specific and may occur in very different ophthalmological and neurological conditions. Comments should contain explanations on normality or abnormality based on comparison of the result with normative values as well as interocular comparisons and previous records. The type of abnormality should be specified and this abnormality should be linked to clinical presentation and electrodiagnostic results [13, 14].

6.2.1. Normal VEP Findings

Pattern VEP consists of consecutive waveforms. These waveforms are in the shape of consecutive positive or negative waves and they're evaluated with their polarity and latency. The positive waves are expressed with letter "P" and a number indicating the peak latency (P60, P100) and the negative ones are expressed with letter "N" and a number again indicating the peak latency (N75, N145). P100 is the dominant wave in the VEP (Figure 10). The wave before P100 is N75. The N75 wave is not observed in some individuals and may be as big as P100 in others, so it isn't accurate to include it in routine evaluation.

Very rarely, P100 may be seen in the shape of a "W" in the normal population. Usually, only one P100 peak is obtained by using patterns of wide checkerboard and a decision may be made. In normal individuals, it may occur as a result of the mixing of positive activation occurring on Oz with negative activation from the upper visual field or as a consequence of visual field defects such as scotoma impairing the positive peak by creating negative activity. In the former, a bifid (double peaked) pattern is seen to recover when only the lower visual field is stimulated [3].

6.2.2. Abnormal VEP Findings

The most common VEP alteration is increased latency of the P100 or N75 waves. Decreased amplitude may be encountered less frequently. The most serious abnormality is not recording a wave at all, called "absent VEP". A delayed P100 response is not specific for any disease condition. It is useful to divide diseases that may cause abnormal VEP responses as pre-chiasmal, chiasmal, and retro-chiasmal [3].

Several combinations of the monocular and half-field stimuli yield information on whether the lesion is pre-chiasmal, chiasmal, or retro-chiasmal [8].

6.2.2.1. Pre-Chiasmal Lesions

Decreased amplitude is more remarkable in the ocular lesions such as corneal opacity, cataracts, or refractive errors while increased latency is more prominent in the case of lesions of the optic nerve. Tumors causing compression of the optic nerve may lead to decreased amplitude and distortion of the waveform. In the case of increased latency, the increase is usually less than 30 msec. VEP is normal in the tumors not directly compressing the optic nerve but causing papilledema [3].

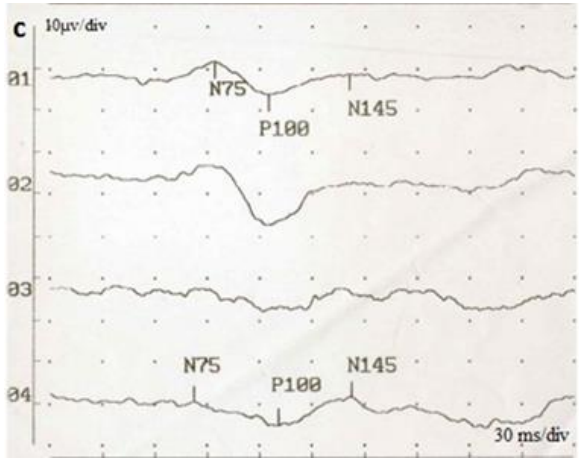

Figure 10. Pattern VEP waveform **(**(MEDELEC /IECA "Sapphire Celal Bayar University Neurology Department).

Total lesion of an optic nerve results in ipsilateral loss of VEP response. Partial lesions cause increased latency and decreased amplitude. The lesions involving only nasal or temporal sides of the retina cause abnormal VEP response (abnormalities in the amplitude and latency) in stimulation of the half-field of the contralateral eye. Bilaterally decreased amplitudes or slight difference of amplitude isn't a reliable index [8].

6.2.2.2. Chiasmal Lesions

Since the chiasmal lesions involve medial fibers of the optic nerve, they result in a pathological response in the half-life stimulation. A normal response is obtained in the nasal half-field stimulation (although being of higher amplitude in the hemisphere contralateral to the stimulated eye) because stimuli from the nasal visual field are conducted normally [3, 8]. The presence of an abnormal VEP response to temporal half-field stimulation is used for purpose of postoperative follow-up in the lesions compressing the optic chiasm such as pituitary tumors and cranipharyngioma [8].

6.2.2.3. Retro-Chiasmal Lesions

VEP is usually preserved in the bilateral retro-chiasmal lesion leading to cortical blindness despite severity of the clinical presentation. Morphology and latency of VEP are preserved in the cases of bilateral hemianopsia. Reasons for this may include that VEP originates from the visual cortex or undamaged occipital cortex [3, 8]. If more than one electrode is placed over the occipital cortex, it may be possible to compare both hemispheres. Chiasmal and retro-chiasmal lesions not detected by a single electrode in the midline may be revealed by asymmetric VEP obtained using more than one electrode [3, 8].

6.2.2.4. Abnormalities of P100 Waveform

Rarely, P100 peak may be in the shape of "W" in normal individuals. In the case of double pattern, some authors recommend considering the first peak and others recommend considering the midpoint. Increased amplitude of P100, however, is always associated with abnormal latency and/or amplitude and considered to be pathological [9].

A P100 peak in the shape of "W" may have been caused by two reasons. It occurs in the case of positive activation on Oz mixing with negative activation from the upper visual field. A double pattern is observed to be corrected when only the lower visual field is stimulated. Or, it may occur in the case of visual field defects such as scotoma altering the positive peak by causing negative activity [9].

7. NON-PATHOLOGICAL AND INDIVIDUAL FACTORS AFFECTING VEP

a. Stimulation Frequency: A subnormal rate of change of the visual stimulus in the form of a checkerboard doesn't change the VEP response. It leads, however, to an increased duration of the test procedure. High rates may cause increased latencies in the pattern VEP, especially those above 4 msec.
b. Contrast: In pattern stimulation, the effect of changes in contrast on the VEP is usually small, but increased latency and decreased amplitude occur in the case of low contrast. Contrast has two main contents: contrast between the grids and acuity of the grid margins.
c. Fixation: Pattern VEP depends on fixation. Alterations in fixation cause decreased amplitude.
d. Stimulus Intensity: In flash VEP, the increasing intensity of stimuli in a normal range causes increased amplitude and decreased latency.
e. Pupil Diameter: Increased diameter of the pupil tends to increase intensity of the stimulus.
f. Advanced age: P100 latency remains constant during most of adulthood but it increases after age 60. Thus, age-based normal values are especially important in the elderly. Aging influences responses at the retinal level [14].
g. The effect of aging is more prominent when small grids are used. Additionally, it causes increased latency of N70 and P100 components. This can't be explained simply with delayed retinal responses because the retino-cortical time corresponding to peaks

of N70 and P100 reflects the events occurring out of the retina and to a lesser extent, the events in the optic nerve, optic pathways or visual cortices.

h. The retino-cortical time increases in the grids of 15' whereas it doesn't increase in the case of using grids of 31'. Accordingly, age-dependent increase in latency is associated with alterations in the visual pathways and cortex. This has been noted to be due to ganglionic cell loss, dismyelination, axonal swelling, and loss of nerve fiber in the optic nerve or alterations in neurotransmitter function and increased synaptic delay [4, 15].
i. Gender: P100 latency is shorter in the group of women compared with men, albeit the difference being insignificant. Small gender-dependent differences in the latency has been attributed to smaller cerebral size and shortness of the visual pathways in women [15, 17, 25].

8. Pathological Conditions and Diseases Affecting VEP

With VEP, it has been possible to objectively measure the conduction and function of the optic stimuli in the central nervous system. Psychogenic visual disorders may be distinguished by normal VEP findings because normal VEP indicates not only that the function of the peripheral receptors is good but also that there is healthy conduction in the afferent system and equal integration of the stimuli exists in the cortical neurons.

In the case of demyelination, waveform isn't influenced much whereas latency increases obviously. In the case of axonal lesion, latency isn't influenced much whereas amplitude decreases substantially [26].

Alterations in VEP occur in many pathological conditions and diseases seen in clinical practice involving the optic system and visual pathways. Although VEP findings recorded in the cases of these disease conditions aren't pathognomonic, they may be useful in diagnosing and following these diseases (Tables 2 and 3) [4, 15].

Table 2. Pattern VEP findings occurring in some diseases

Disease	**Amplitude**	**Latency**
Optic Neuritis	Normal/Decreased	Remarkably increased
Optic Nerve Compression	Minimally Decreased	Intermediately increased
Anterior ischemic optic neuropathy	Intermediately increased	Minimally increased
Leber's Hereditary Optic Neuropathy	Decreased	Minimally increased
Dominant Hereditary Optic Neuropathy	Minimally Decreased	Normal/Minimally increased
Papiledema	Normal/Minimally Decreased	Normal/Minimally increased
Toxic Optic Neuropathy	Minimally Decreased	Normal/Minimally increased
Deficiency of Vitamin B12	Normal	Minimally increased
Glaucoma	Normal/Minimally Decreased	Normal
Amblyopia	Normal/Decreased	Normal/Minimally increased
Opacities of the Cornea and Lens	Decreased	Normal/Minimally increased
Leukodystrophy	Normal/Minimally Decreased	Intermediately-remarkably increased
Friedrich's ataxia	Decreased	Intermediately-remarkably increased
Optic Nerve Tumors	Decreased	Intermediately-remarkably increased
Injury to the Optic Nerve	Decreased	Normal/Minimally increased
Retinopathy	Decreased	Increased

In evaluating the disease conditions listed in Table 2, full-field VEP examination gives information on the presence or absence of P100 and whether it is increased or decreased while half-field VEP examination indicates absence of ipsilateral or contralateral response on the stimulated side [4].

A flash VEP response consists of a series of positive and negative wave peaks. Its latency and amplitude show individual and age-related variations. Latency is found to be increased in premature babies and infants compared to the adults; it normalizes when myelination is complete [15, 19, 21].

Table 3. Pattern VEP findings occurring in some diseases

Bilateral absence of VEP	Technical issues, ocular disorders, fixation or refractive errors, severe bilateral optic nerve lesion
Unilateral absence of VEP	Optic neuropathy, Ocular disorders
Increased VEP latency	Optic nerve lesion
Increased difference of interocular latency	Optic nerve lesion
Unilaterally decreased amplitude	Ocular lesion
Bilaterally decreased amplitude	Ocular, bilateral chiasmal or prechiasmal lesions

9. SAMPLES FROM SOME DISEASE CONDITIONS – RESPONSE OBTAINED IN VEP

9.1. Optic Neuritis and Multiple Sclerosis

Until the 1970s, P VEP was known to present with increased latency usually without altered amplitude in demyelinating diseases of the optic nerve (optic neuritis). It is currently accepted that an increase in the latency is permanent even in the periods during which the disease recovers [27]. Visual acuity decreases during acute attacks but recovers in a period of several months until myelination is completed [28, 29].

Permanently decreased amplitude and visual acuity (in later stages) may be due to axonal loss [30]. Flash VEP is usually preserved in optic neuritis but wave formation may be delayed. In rare cases, no delay occurs. Central fibers have been shown to be most frequently involved fibers in demyelinating processes. Flash VEP abnormalities give limited information because it shows a narrow range of functional disorders of the optic nerve rather than showing all of them [31]. The biggest challenge is in detecting the relationship between the acute attacks and axonal loss leading to permanent damage in MS [32].

The layer of nerve fibers in the retina contains only unmyelinated axons. Measuring the thickness of this layer is considered and used as a measure of backward axonal loss [32].

9.2. Anterior Ischemic Optic Neuropathy

In VEP, investigation in non-arteritic anterior ischemic optic neuropathy (NAAION) decreased the amplitude and is present typically without a "change in latency." VEPs have been found to be completely normal in uninvolved eyes [33].

9.3. Tumors

Glioma of the optic nerve may cause painless, silent, and slowly progressive visual loss, and even may be completely asymptomatic. In these cases, amplitude is decreased and widespread distortion and delay may occur in waveform in the PVEPs. The value of VEP has been defined well in evaluating the function of the chiasm. Lesions causing compression in the earlier stages lead to increased latency but this is less prominent than in the demyelinating diseases. In a study on this topic, it was found that an increase in latency exceeds the upper limit of normal by 20 msec at most in the compressive lesion, while it ranged between 35 and 45 msec in optic neuritis due to Multiple Sclerosis (MS) [34]. Additionally, abnormalities in the waveform are more often seen in the compressive lesions than in the demyelinating diseases. Asymmetric VEP traces may be seen as well in pituitary adenomas [35].

9.4. Albinism

Although not being a disease of the optic nerve, there is misdirection of the intracranial pathways in patients with albinism. Most of the fibers making the optic nerve decussate at the chiasm. Albinos have many different phenotypic appearances. Young children are hard to exam. The misdirected nerve fibers in young patients with oculocutaneous and ocular albinism may be revealed easily by VEP [36].

Flash VEP is more useful and easier in younger children whereas PVEP yield better results in adults. In the onset-offset pattern of VEP, the eyes are examined separately with electrodes placed on both hemispheres on the occipital lobe (the electrode is placed on the midline, to 4 and 8 cm right- and left-handside. It appears at 100 msec in length and disappears 400 msec later). A recording is made from each electrode. In testing one eye in albinos, a positive wave component is taken from the contralateral hemisphere on 85 – 88 msec whereas a wave with lower amplitude and shorter latency is obtained from the ipsilateral hemisphere.A positive wave from the contralateral side is of higher amplitude and decreased latency. This is because of more nerve fibers decussating at the level of chiasm in the albinos. If this investigation is made with flash VEP no such a difference is found and similarly, normal waves are obtained on both sides. This investigation is useful particularly in the cases of suspected albinism and especially in diagnosing the cases of ocular albinos and can explain decreased visual acuity. It is also useful in the cases of suspected albinism in the presence of nystagmus [36].

10. Functional Diseases (Malingering and Hysteria) and VEP Investigation

A case of malingering may be encountered as an individual, exaggerating any present health problem. On the other hand, occurrence of acclaim of decreased vision intentionally or unintentionally is called “hysteria” or “conversion reaction”. Hysteria occurs as a result of any psychological problem. In either case, a normal trace obtained with a pattern VEP test indicates that visual pathways from the retina to the occipital cortex is healthy [37].

Being an objective psychophysical test, VEPs are used in evaluating non-organic cases of visual loss, that is to say in determining that the retina and the visual pathways are intact. Halliday made symmetric pattern VEP recordings from both eyes in a case of unilateral hysteric visual loss first in 1973 [38]. In the case of visual loss due to hysteria, a normal foveal response

is taken when flash VEP is performed with red light. Nevertheless when the test is applied to a subject with suspected malingering or hysteria, taking abnormal responses doesn't mean evidence of an organic disease. In contrast, results of the test being within normal limits are more valuable. In clinically suspected cases, pattern VEP and recently onset-offset pattern VEP and Sweep VEP tests are used and it is distinguished from other organic causes by obtaining normal results. Thus, the subject may be clarified without further investigations.

It should be kept in mind that especially pattern VEPs are affected by refractive errors, wearing opthochromatic spectacles and opacities in the refractive media and abnormally weak responses are obtained in such conditions. Similarly, abnormal traces may be obtained in the case of subject closing or squeezing his/her eye, looking to wrong target and even creating blurred image on the retina by looking faraway. VEP traces, obtained without considering such issues and considered as pathologic, mislead us. Thus, an attendant should accompany the patient during the investigation and observe the patient continuously, should warn him/her when necessary. Notes should be written on the traces of the subjects not following the warnings. In particular, the reference forms should be reviewed first of the subjects without goodwill and coming for gaining something illegally, the purpose for reference of the subject should be understood well, and if the subject has been referred from another center then he/she should undergo investigation by us again. An important conclusion for pattern VEP is that we may sign the trace as normal without any debt if a normal trace has been obtained. Because it is impossible to mimic a normal trace. Because of the facts above, it is possible to mimic a pathological trace even in a healthy individual.

11. Is Pathological Data on the VEP Originating from the Retina?

Pattern VEP pathologies aren't specific to diseases of the optic nerve. The VEPs may be affected negatively in the diseases widely involving the

macula and in the diseases of the optic nerve or chiasm. As can be seen, ERG is also used to detect location of the event and even which layer it involves because VEPs are also affected in some diseases in the visual system originating from the retina.

In the case of necessity, PERG and mfERG should be used since some retinal diseases manifest as optic nerve diseases. ERG yields finding in widespread abnormalities of the retina whereas abnormality of PERG and mfERG is found in the diseases involving only the macula. Again, pallor may occur in the papilla secondary to some retinal diseases. In these patients with pale papilla, pattern VEP will be found to be impaired. For example, dysfunction of the cone cells may be revealed in the ERG in cone dystrophies leading to pigment alterations in the macula [14, 39].

The VEPs reflect the quantity and quality of the information conducted to the occipital cortex by the nerve fibers rather reflecting the central retina. In the ERG, the share of the cones in fovea is less than 2% whereas most of the potentials recorded by VEP is made of the stimuli from cones in the fovea. The share of the area of 2 degrees in the central retina is 65% in VEP [40]. In VEP, especially the variability of the P100 wave may be of the origin of optic nerve lesion as well as of macular origin. Additional investigations such as ERG (electroretinography) is required to demonstrate whether it is due to possible macular lesion in VEP investigation [14].

In the classical electroretinography (ERG), flash light stimulation is used and the total response of the retina is recorded through the cornea or conjunctiva. Information is obtained on the situation of different cell groups or layers depending on the eye being light or dark adaptation and differences in the light parameters. Bioelectric waves recorded by ERG arise from photoreceptor and bipolar cells [14].

In the pattern ERG (PERG), the same square screen as the checkerboard in the VEP test is used and with the total response from “ganglionic cells”, the macula area reflects the health status of this layer [14].

In multifocal ERG (mfERG), the cones on the macular and paramacular areas are evaluated by stimulation with 61 to 102 hexagonal figures [14, 41]. Each part is illuminated by “pseudo-random double consecutive” system, and a recording is made with a single electrode using the “cross relationship

technique". Using PERG and mfERG, we can understand whether the VEP abnormality we have is of macular origin or not. PERG may provide advantage in understanding the situation of the ganglionic cells in the macula developing secondary to the optic nerve diseases [42]. It is less affected than mfERG than in the mild losses of fixation. If a lesion involving only the macula is being suspected or present, it is possible to compare to a normal ERG result because classical ERG reflects whether a condition involving entire retina is present [14, 43].

Abnormal ERG indicates retinal cell dysfunction. Abnormal mfERG in the presence of normal ERG indicates macular dysfunction [14].

Another version of the VEP is multifocal VEP (mfVEP). mfVEP may give further information to understand features of diseases of the optic nerve. But this method can't be compared to classical VEP technique because it has quietly big issues of interpretation [44].

Additionally, in most situations the ideal stimulation parameters, recording techniques, insertion points of the electrodes, variabilities in the case of repeating the tests, and the best stimulus parameters haven't been established yet [14, 45].

Methodology varies between several studies and main points of the topic are absent in the ISCEV and IFCN protocols. Additionally, abnormalities of mfVEP may originate from retinal problems [14, 46]. There are studies in which alterations especially in the macula have been investigated using multifocal VEP investigation [14].

According to the ISCEV criteria, mfVEP has been shown to demonstrate the lesions of the optic nerve more clearly and to reveal its exact pathology. mfVEP is in the forefront, especially in detecting the chiasmal and retro-chiasmal lesions [14].

In the future, however, it will be possible for mfVEP to become available in more promising devices and methods than the available routine clinical applications today[14].

12. OUR STUDIES

Other reasons for the altered latency and amplitude of the visually evoked potential (VEP) include inflammation, hypoxia, and atherosclerosis. We have publications and projects on this topic including those on different groups of patients. Our biochemical parameter related to dopamine is iron. Decreased cerebral iron content may decrease activity of several neurotransmitters such as dopamine, serotonin, and noradrenalin by altering enzymes involved in synthesis of these neurotransmitters. Apart from demyelination, synaptic dysfunction or receptor blockade due to neurotransmitter deficiency should also be considered as a mechanism underlying delayed VEP responses [47, 48].

Iron deficiency during a rapid myelination process may impede the normal function of the oligodendrocytes and may impair the myelination process [49, 50, 51].

The increase in latency observed in infants with iron deficiency anemia also supports the hypomyelination hypothesis. Latency of P100 wave was found to significantly increase in the children with iron deficiency anemia compared to the controls [52]. These findings also suggest that anemic hypoxia in children might be a possible factor affecting VEP waves [53].A decrease in VEP latency was observed at the end of an iron treatment of 12 weeks [54]. Wave latencies in the evoked potentials are considered as a function of the myelination status of the corresponding pathway [50].

The fact that dopamine is present in the interplexiform layer of the retina in vertebrates including man and that dopamine isn't known to be an important transmitter elsewhere in the visual system, suggests that the VEP abnormality is of retinal origin [55].

Similar studies have been conducted on patients with thalassemia and deficiency of vitamin B12 [56, 57]. No difference was found in VEP latency between the patients with a diagnosis of thalassemia and the control group ($p > 0.05$). Similarly, no difference was found in VEP latency among different therapies given to the patients with thalassemia ($p > 0,05$). [57].An increase was found in latency in the VEP investigation in the patients with deficiency of vitamin B12 compared to the normal control group ($p < 0.05$)

[56]. It was emphasized that latency is normalized in about 85% of the patients following vitamin B12 replacement therapy of 3 months ($p < 0.05$). There isn't any study, however, comparing VEP latency and amplitude before and after treatment during iron deficiency anemia in adults. The presence of developed myelin in adults causes such studies to be performed with more difficulty. It has been suggested that studies comparing the results before and after long-term treatment would also be possible in adulthood.

Another disease related to dopamine is Parkinson's disease. VEP latencies were compared before and after giving dopamine to the patients with Parkinson's disease [58]. A decrease in latency and increase in amplitude of the VEP were found after giving dopamine ($p < 0,05$) [58]. A similar situation was also seen in restless leg syndrome. Our study was conducted with the objective of determining whether visual evoked potential could be used qualitatively as a monitoring method in terms of presence and development of neurodegeneration in the patients with restless leg syndrome (RLS). RLS is a disease condition characterized by a type of dysesthesia, an abnormal sensation impossible to describe especially in the limbs.

Our study included 3 groups and pre- and post-treatment VEP latencies and amplitudes were evaluated (the subjects with only diagnosis of restless leg syndrome, those with association of restless leg syndrome and iron deficiency, and those with only diagnosis of iron deficiency). In our study, alterations in VEP latency and amplitude were looked for the first time in patients with a diagnosis of restless leg syndrome. In contrast to the literature, our study evaluating VEP latencies and amplitudes in the patients with restless leg syndrome also evaluated VEP latencies and amplitudes before and after treatment in the patients with iron deficiency anemia in adults, albeit being in low numbers [59].

The patients with iron deficiency anemia were given iron replacement therapy. All patients with only a diagnosis of RLS received dopamine agonist in concordance with their symptom scale. Treatment of the patients with RLS associated with iron deficiency was given as combination therapy. In in-group comparisons, it was seen that latencies were decreased and amplitudes were increased at controls on months 0-3 and 0-6 and especially after month 6 of therapy in all three groups (the subjects with only diagnosis

of restless leg syndrome, those with association of restless leg syndrome and iron deficiency, and those with only diagnosis of iron deficiency), although increased latency and decreased amplitude were seen in all three groups at month 6 of therapy compared to the normal control group. These values were statistically significant ($p < 0,05$). VEP investigation was repeated on months 3 and 6 in order to evaluate dopaminergic receptors in the retina following dopamine treatment [59].

Iron treatment increased the enzyme tyrosine hydroxilase and thus dopamine synthesis. Similarly, decreased latencies and increased amplitudes were seen. Better responses are achieved with the given treatments in childhood because myelination is not completed. In adults, it was observed that no complete recovery occurred in latency and amplitude at month 6 following iron and dopamine treatment compared to normal controls because myelination was completed [59].

The best recovery was seen in the group with iron deficiency, and the patients with RLS and RLS associated with iron deficiency were seen to have less recovery similarity. When the data were compared at month 6 between the groups with RLS and RLS associated with iron deficiency, no statistically significant difference was found ($p > 0,05$) [59].

Another study we conducted is a VEP study in the prediabetic period. There are many VEP studies in the literature on patients with diabetes mellitus while no studies exist conducted in the prediabetic period [60].

VEP alterations in diabetes mellitus are known to originate from the vascular and metabolic disorders involving the macula, retina, optic nerve, and visual pathways. An increase in latency in VEP has been explained with several mechanisms such as widespread axonal loss, direct effect of ischemia, Wallerian degeneration is due to retinal ganglionic cell loss and demyelination due to death of oligodendrocytes. Accumulation of neuropoietic cytokines in the central nervous system such as interleukin-1 (IL-1), IL-6, leukemia inhibitory factor, ciliary neurotrophic factor, tumor necrosis factor-alpha, and transforming growth factor-beta possibly delay transmission in the visual pathways. This is a reason for increased latency in VEP found in the diabetic patients compared to the healthy controls [61, 62].

Prediabetic period (impaired glucose tolerance and impaired fasting glucose) is an important clinical course defined as the period before diabetes. Considering the presence of poor glycemic control, it is known that prediabetes may lead to micro and macro-vascular complications similar to diabetes [63, 64].

In order to detect degeneration and progression in the retinal ganglionic cells using VEP tests before the retinopathy findings become detectable with ophthalmic examination in the prediabetic period, the present study included the subjects with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) detected in routine controls without any symptoms and signs in the visual and other systems. It was aimed at evaluating variabilities in latency and amplitude values in VEP of these subjects. It was planned to investigate whether damage began in the central nervous system in IFG and IGT, both of which having different physiopathology, and whether alterations of VEP latency and amplitude were affected in the prediabetic period. It was planned to decide whether VEP could be used as a predictive value and whether it could be used in detecting neurodegeneration in the visual and macular pathways in early period and in monitoring its progression. Mean P100 latency in the right eye was 110.03 msec in the IFG group, 111.43 msec in the IGT group, and 107.75 msec in the control group while in the left eye it was 110.17 msec in the IFG group, 112.33 msec in the IGT group, and 107.80 msec in the control group. A significant difference was found when the IGT group was compared to the control group for both right and left eyes. ($p = 0{,}003$ and $p = 0{,}001$, respectively). No statistically significant difference in P100 latency was found, however, when the IFG group was compared to the control group for the right and left eyes ($p > 0.05$). These values indicated that there was an obvious increase in P100 latency in the IGT group similar to the diabetic group. These findings emphasized that the patients in the IGT group should be more careful and should undergo periodic controls and further investigation in terms of retinopathy [60].

Electrophysiological studies we performed showed that visual evoked potentials could have a predictive value in detecting retinopathy in the prediabetic period. An increase in VEP latency is indicative that

neurodegeneration has started. It will be possible to monitor neurodegeneration and possible regeneration with the treatments given. Thus, it is possible to follow the patients for development of diabetes and retinopathy. It will also provide an additional contribution for early treatment and avoiding the possible complications [60].

Our study has two conclusions. First, VEP is a sensitive, reliable, non-invasive and reproducible method used to detect early alterations in the central optic pathways in prediabetic patients without any clinical visual symptom or any retinopathic finding detected in ophthalmic examination. Second, VEP is important in evaluating neurodegeneration especially in the early period and should be added to the screening tests in order to provide an appropriate disease management along with early diagnosis and follow-ups in patients with a diagnosis of prediabetes [60].

Other studies we conducted and planned are those on Obstructive Sleep Apnea Syndrome (OSAS) and VEP.

VEP latency and amplitude are altered in patients with obstructive sleep apnea syndrome (OSAS) because edema and inflammation are obvious secondary to intermittent hypoxia in different stages of the condition (mild-intermediate-severe). These alterations are due to multisystemic consequences such as metabolic, neurocognitive, and inflammatory ischemic events originating from harmful effects of nocturnal intermittent ischemia. Intermittent hypoxemia may affect the optic nerve by altering axonal and myelin components due to recurrent microischemic injury. Decreased VEP amplitude may be explained with intermittent hypoxia where increased latency may be attributed to inflammatory processes that may damage the optic nerve myelin [1, 2, 65, 66].

Hypoxemia, due to respiratory impairments from OSAS, increased intracranial pressure and vascular resistance cause glaucomatous optic nerve injury by altering perfusion and oxygenation of the head of optic nerve [67, 68].

Changes in the circadian ocular perfusion pressure lead to endothelial dysfunction by decreasing nitric oxide and increasing endothelin-1. This atherosclerotic background, the inflammatory mediators, increased intracranial pressure during snoring, presence of hypoxia and micro-

angiopathies lead to thinning of the retina detected in optic coherence tomography (OCT) and latency and amplitude alterations in the visual pathways on the VEP investigation [65, 66].

The experimental and animal studies have emphasized that nocturnal intermittent hypoxemia has multisystemic consequences such as metabolic, neurocognitive, and inflammatory ischemic events. Accordingly, intermittent hypoxemia may affect the optic nerve as well by altering axonal and myelin components due to recurrent microischemic injuries [65, 66]. Consistent with this study, the patients with OSAS show decreased amplitude and increased latency in P100 wave of VEP. In the studies on human subjects and groups of patients, in the VEP investigation which is more widely used because of its sensitivity in demonstrating optic nerve lesions increased latency indicated myelin injury whereas amplitude changes seem to be related to axonal loss [1, 2]. Neurological consequences of OSAS probably cause axonal as well as demyelinating damage in the optic nerve [67]. These findings might have been explained with intermittent hypoxia provoking decreased VEP amplitude whereas increased latency has been considered to be due to inflammatory background that might damage the optic nerve myelin [69, 70, 71, 72].

When the severe OSAS group was compared with the control group, both P100 and N145 latencies were found to be significantly and remarkably increased ($p < 0.001$). When mild OSAS was compared with the control group, P100 latency was found to increase ($p < 0.05$). When both mild and severe OSAS groups were compared with the control group, N75-P100 amplitudes were found to be significantly decreased ($p < 0.001$) [73].

Especially when the retina was investigated, a correlation was found between retinal values obtained by optic coherence tomography and VEP latencies and amplitudes. No correlation was found, however, between values of the macular layers and VEP latencies and amplitudes [73].

In a comparison of the patients with OSAS before and after treatment (CPAP treatment), it was remarkable that VEP latency decreased. Similarly, a correlation was found after the treatment between retinal layers obtained by optic coherence tomography and VEP latencies and amplitudes. In VEP

comparisons, decreases in the latency (N75, $p = 0.002$; P100, $p < 0.001$) and increases in the amplitudes (N75-P100) were observed ($p < 0.001$) [74].

In previous electrophysiological studies on the patients with chronic obstructive pulmonary disease (COPD), which is a disease similarly related to hypoxia, increased latency and decreased amplitude have been shown in P100 wave of VEP. In light of this information, it is considered that the reason for the common occurrence of optic neuropathy in the patients with COPD is chronic hypoxemic damage to the vasa nervorum [75].

In several studies on OSAS, it has been shown that increased latency in the VEP investigation is more prominent in OSAS [62, 76, 77]. It has also been suggested that VEP latency might be used as a marker in evaluating the retinal ganglionic cells [62].

In our study, it was shown that both amplitude and latency parameters (P100, N145) were altered in VEP in patients with the diagnosis of OSAS alone after excluding clinical co-morbidities that may involve the visual pathways such as ocular pathologies, hypertension, and diabetes. Taken together, all these data indicate that optic nerve injury is caused by inflammation, in addition to chronic hypoxemia, secondary to non-glaucomatous involvement in the OSAS group

When VEP data before and after treatment were compared in the patients with OSAS, a significant recovery (decrease) was observed in N75 and P100 latencies whereas a significant increase was seen in N75-P100 amplitudes ($p < 0.001$). Thus, inflammation and myelin damage is reduced and both latency and amplitude normalized in VEP when inflammation caused by hypoxia is reversed [74].

VEP studies have been conducted with the same pathophysiology and similar results (increased latency and decreased amplitude) were found. Our other project on VEP is investigating the correlation between the cognitive tests, magnetic resonance imaging (atrophy evaluation protocol) and VEP studies in the patients with diagnosis of vascular dementia. When the group with vascular dementia was compared to controls, it was observed that VEP latency increased bilaterally (in both eyes) and amplitude decreased in the group of patients and these values were statistically significant ($p < 0.05$). It was concluded that these latency values are correlated with atrophy in the

hippocampus on magnetic resonance imaging (MRI) (ADNI protocol) and thus, P100 latency might be used as a reflection of cerebral atrophy on the eye [78].

CONCLUSION

Visual evoked potentials depend on the functional integrity of the visual pathways at any level including optic components of the eyes, retina, optic nerve, optic chiasm, optic radiations, and the visual cortex. With the advantage of being non-invasive and having an excellent temporal resolution at the level of milliseconds, it reflects dynamic changes of the visual pathways.

On the pattern VEP recordings, 3 main components are observed which are called N75, P100 and N145. P and N denote negative or positive voltage recorded from the active electrode on the occiput relative to the reference electrode. These negative waves provide information about nerve fibers involved in transmission. P100 wave latency shows less variability among individuals. Thus, it is one of the most frequently used parameters in evaluating the VEP. P100 amplitude is measured from one peak to another between N75 and P100. N75 wave reflects activity of the fovea and the primary visual cortex while N145 wave reflects activity of the visual association area. The difference between the two eyes and the test variability in repetitive measurements in the same individual is negligible.

Peak P100 latency is affected by non-pathophysiological parameters such as the pattern size, pattern contrast, average luminance, signal filtering, age of the patient, refraction errors, poor fixation, and myosis. Increased VEP latency in the elderly is caused by cellular loss within the ganglion cells, dismyelinization, axonal swelling, and loss of nerve fiber or alterations in neurotransmitter function and increased synaptic delay.

There are two types of recordings, known as pattern VEP and flash VEP. The size of the checkerboard squares used in the pattern for VEP can be adjusted depending on the purpose of the recording. In pattern VEP recording, two different sizes of squares are generally used. The small

squares reflect activity of the fovea and the bigger ones reflect the activity of the peripheral retina.

More stable latency and amplitude values can be recorded by using pattern stimuli. On the other hand, amplitude and latency values of the flash VEP, are more variable. Variability between two eyes of the same individual is less in the recordings taken in the same session in both pattern and flash VEP recordings. Thus, pattern VEP recording is usually preferred in clinical practice. Flash VEP recordings are more appropriate for babies and young children and for the individuals being unable to cooperate.

The most common VEP alteration is increased P100 and N75 wave latencies. Less commonly, decreased amplitude may be seen. The most serious abnormality is the absence of all the waves, called "Absent VEP". Delayed P100 response is not specific for any disease. It is useful to classify the disease that may cause abnormal VEP responses as pre-chiasmic, chiasmic, and retro-chiasmic. Factors affecting VEP latency and amplitude include inflammation, hypoxia, and atherosclerosis. We have several publications on this topic in different groups of patients.

The presence of dopamine in the inner plexiform layer of the retina in mammals including humans and the fact that dopamine is not known to be an important transmitter anywhere in the visual system except for retina suggests that VEP abnormality is of retinal origin. Dopamine-2 receptors in the retina are known to be effective in showing the pathology of VEP. VEP values were compared in the patients with Parkinson's disease before and after dopamine administration. Decreased latency and increased amplitude were found in VEP after giving dopamine. A similar situation was observed in one of our studies on restless leg syndrome. Dopamine is a neurotransmitter which is related to iron metabolism. In children having a diagnosis of iron deficiency anemia, decreased latency and increased amplitude of VEP were observed following iron supplementation.

Alterations of VEP in diabetes mellitus are known to originate from vascular and metabolic impairments that may affect the macula, retina, optic nerve and the visual pathways. An increased latency of VEP has been reported with several processes such as axonal loss, direct effect of ischemia, Wallerian degeneration due to cellular loss in the retinal ganglion, and

demyelination due to death of the oligodendrocytes. Accumulation of the neuropoietic cytokines such as Interleukin-1, Interleukin-6, leukemia inhibitory factor, ciliary neurotrophic factor, tumor necrosis factor-alpha, and transforming growth factor probably delays transmission in the visual pathways. This is the reason for delay of the VEP latency in diabetic patients. In the patients with obstructive sleep apnea syndrome, VEP latency and amplitudes are affected because of the edema and inflammation secondary to hypoxia seen in several stages of the disease. Intermittent hypoxia with repeated micro-ischemic injuries may alter axonal and myelin components of the optic nerve. Amplitude changes can be attributed to intermittent hypoxia whereas delayed latencies are considered to be due to inflammatory changes.

VEP studies have been conducted in the patients with dementia and similar results (increased latency, decreased amplitude) have been gathered in general.

In this chapter of the book, we aimed to explain and comment on definition, types, recording, waves, interpreting, normal and abnormal values, and pathophysiology of VEP and to increase awareness on VEP by explaining our studies and others on this topic.

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