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Original Article

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New onset tremor in patients with COVID-19: can be a possible link with parkinsonism?

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ABSTRACT

Aims: SARS-CoV-2 is a highly pathogenic member of the coronavirus family. We notice that some patients who were following in outpatient service have a new onset tremor. Our aim to describe these patients and interpreting new onset tremor after COVID-19 that possible link with parkinsonism.

Methods: Forty-two patients with tremor who applied to Alanya Alaaddin Keykubat University Hospital neurology outpatient clinic between the 2021-2022 years were included the study. The data related to demographic characteristics, reasons for application of outpatient neurology clinic, pre-diagnosis and treatment were collected retrospectively.

Results: The patients had a viral infection up to 3 months before the diagnosis of tremor was examined from the hospital system. It was determined that a total of 7 patients had viral infections due to upper respiratory infections and these were confirmed by polymerase chain reaction (PCR). Since two of these patients had concomitant thyroid dysfunction, one had diabetes and one had a history of acute cerebrovascular disorder, they were not included in the study. COVID-19 results were found to be positive wit PCR in 3 patients with a diagnosis of new onset tremor. It was determined in the neurology outpatient clinic notes of the patients that their complaints started after COVID-19.

Conclusion: We haven't enough data about COVID-19 yet but it should be included in the differential diagnosis of patients with new onset neurological symptoms, especially in epidemic situations.. Extensive clinical, neurological, and electrophysiological investigations of the patients may help to understand the virus's role in causing neurological manifestations

Keywords: Tremor, COVID-19, parkinsonism

INTRODUCTION

Since December 2019, the disease called "New Coronavirus Disease (COVID-19)" caused by the new type of coronavirus has spread rapidly from Wuhan province of the People's Republic of China to other provinces and then to the whole world. With this rapidly developing situation that threatens the existence of all humanity, the perspective of today and the future has changed. In this process, new concepts that had never been used before, were also used extensively.

Coronaviruses are approximately 125 nm in diameter, roughly spherical and moderately pleomorphic, single-stranded, positively polarity enveloped RNA viruses with rod-shaped spike protrusions on their surfaces.[1] They are a large family of viruses that are common in humans and animals.[2] Natural reservoir hosts such as wild animals and bats can be played an important role in the transmission of various viruses.[3]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly pathogenic member of the coronavirus family. SARS-CoV-2 is a beta-CoV with a genetic code that is nearly identical to SARS-nCoV.[4] According to recent studies, the virus is 96% similar to a bat coronavirus at the whole-genome stage, indicating that bats are the most likely hosts of the SARS-CoV-2.[5]

Patients with SARS-CoV-2 have a wide variety of clinical symptoms that are ranging from mild to serious. As more information about the SARS-CoV-2 virus has become available, most experts believe that COVID-19 is more than a respiratory disease and that it could affect other human systems. COVID-19's neurological role has been the subject of a growing number of studies recently.[6]

Various neurological symptoms including central nervous system (CNS) involvement, peripheral nervous system (PSS) involvement and skeletal muscle damage have been reported in

more than one third of the patients. Also SARS-CoV-2 nucleic acid component in the cerebrospinal fluid (CSF) of patients and the virus in the brain tissue at autopsies was detected.[7]

As symptoms and diseases that indicate CNS involvement; dizziness, vertigo, sleep disturbance, headache, loss of consciousness, ataxia, seizures, acute cerebrovascular disease, meningitis and encephalitis have been reported.[8,9] The most common complaints in patients with PSS symptoms are taste and smell distortions.[10]

Parkinsonism symptoms such as tremor and bradykinesia have been reported to develop during or after viral infections such as influenza A, HIV, Epstein-Barr virus, hepatitis C virus, varicella zoster, West Nile virus or Japanese encephalitis virus.[11] On the other hand, there are few parkinsonism cases which is possible linked with SARS-CoV-2 in the literature.

We notice that some patients who were following in outpatient service in Alanya Alaaddin Keykubat University Hospital, have a new onset tremor. Their complaints were started during COVID-19 and still going on. Below, you can see three patients who have been following for 3 months because of new onset tremor.

METHODS

This study was approved by Alanya Alaaddin Keykubat University, Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.10.2022, Decision No: 10-04). Forty-two patients with tremor who applied to Alanya Alaaddin Keykubat University Hospital neurology outpatient clinic between the 2021-2022 years were included the study. The data related to demographic characteristics, reasons for application of outpatient neurology clinic, pre-diagnosis and treatment were collected retrospectively. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

RESULTS

Whether the patients had a viral infection up to 3 months before the diagnosis of tremor was examined from the hospital system. It was determined that a total of 7 patients had viral infections due to upper respiratory infections and these were confirmed by polymerase chain reaction (PCR). Since two of these patients had concomitant thyroid dysfunction, one had diabetes and one had a history of acute cerebrovascular disorder, they were not included in the study. COVID-19 results were found to be positive wit PCR in 3 patients with a diagnosis of new onset tremor. It was determined in the neurology outpatient clinic notes of the patients that their complaints started after COVID-19.

Case 1

52 year old woman who have no chronic disease history, was diagnosed with COVID -19 three months ago. Her symptoms started with fever and myalgia, two days after symptoms onset she realized that her right hand was shaking slightly. She was treated by Favipiravir in five days (First day started with 1600 mg two times a day and four days 600 mg two times a day used) without any complication. She had an isolated right hand tremor that was progressively developed. No other abnormal findings were observed during the examination. Brain MRI, serology testing and a comprehensive laboratory analysis including tests for thyroid hormones all yielded a normal result. Her symptoms decreased after rasajilin 1 mg per day started and she can use her hand for daily activities.

Case 2

24 year old woman was diagnosed with COVID -19 four months ago. Her symptoms started wih fever. Before COVID-19 diagnosis, she had no tremor history. She was treated by Favipiravir in five days (First day started with 1600mg two times a day and four days 600 mg two times a day used). She had bilateral tremor that was getting worse day by day after the COVID-19. Brain MRI, serology testing and a comprehensive laboratory analysis were normal. Her symptoms decreased after propranolol 40 mg twice per day started.

Case 3

62 year old man who have diabetes mellitus history almost 2 year. He was diagnosed with COVID -19 three months ago. His symptoms started with dispnea and myalgia, He realized that his right hand was shaking. He was treated by Favipiravir in five days (First day started with 1600 mg two times a day and four days 600 mg two times a day used) without any complication. He had bilateral tremor that was started after COVID-19 treatment and tremor was more prominent in right hand. No other abnormal findings were observed during the examination. His blood sugar was 135 mg/dl and HgbA1C 6.8 mmol/L. Brain MRI, serology testing and a comprehensive laboratory analysis including tests for thyroid hormones all yielded normal. His symptoms decreased after propranolol 40 mg twice per day started and he can use his hand more effectively.

Possible Mechanisms of CNS Invasion of SARS-CoV-2

The coronavirus is thought to reach host cells via angiotensin converting enzyme 2 (ACE2) which is mainly expressed from respiratory tract epithelium, lung alveoli, vascular endothelium, renal cells and small intestine cells.[12] Although the presence of ACE2 in human CNS neurons is not clear, as are particular brain areas or cell types such as neuronal, astrocytes, microglia, immune and vascular cells, SARS-CoV-2 can be spread to the CNS via the ACE 2 receptors.[13,14] Coronavirus may also enter the CNS via the hematogenous or lymphatic system, though this is unlikely in the early stages of the disease.[15]

Blood-brain barrier (BBB) breakdown caused by the cytokine storm associated with peripheral viral infection is one possible mechanism for SARS-CoV-2 RNA presence in the CNS. It is well known that pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin 1 beta (IL-1beta), which are associated with inflammation and/or SARS-CoV-2, mediate BBB breakdown.[16]

Aerosol droplets allow coronaviruses to first locate in the infected host's nasal mucosa, then gain access to the CNS via a transcribrial path. After the strong adhesion of SARS-CoV-2, additional axonal transport promotes infection spread to the piriform cortex and other olfactory regions.[17] SARS-CoV-2 broadly diffuse to the CNS within a few days of infection, being detectable in the brains of infected mice or healthy patients.[17,18]

To determine how SARS-CoV-2 infection affects the CNS, researchers will need to conduct detailed neuropathologic studies and sample specific brain regions extensively. Autopsy studies will play a key role in identifying CNS pathology.

DISCUSSION

SARS-CoV-2, like other coronaviruses, has been linked to neurological complications. Such involvement has been observed in more serious cases and could be caused either directly by the virus or indirectly by the systemic effect. We haven't enough data about COVID-19 yet but it should be included in the differential diagnosis of patients with new onset neurological symptoms, especially in epidemic situations.

COVID-19 has a wide range of neurological symptoms from cognitive to cerebrovascular diseases. The most common neurological symptom were headache, myalgia, sleep disturbances and consciousness.[7,8] On the other hand, tremor which is one of the common sign of parkinsonism has only been described in a few COVID-19 related case reports.

Viral Parkinsonism is a neurodegenerative disease caused by a viral infection that causes encephalitis or brain inflammation. Tremor, loss of motor control, stiff movements and loss of balance or difficulty walking are Parkinson's-like symptoms. After viral infections, these symptoms can be appeared in high numbers.[19] The 1918 influenza outbreak and subsequent induction of von Economo's encephalopathy is one of the most well-known and controversial cases of viral parkinsonism.[20] Influenza virus, Coxsackie, Japanese encephalitis B, St. Louis, West Nile and HIV are known to cause parkinsonism.

Many mechanisms of viral parkinsonism remain unknown despite the fact that we know there is a link between viral infections and disease progression decades later. However, some researches have already focused on potential mechanisms between COVID-19 virus and neurodegenerative conditions like Parkinson disease. Some animal studies have shown that coronaviruses can enter the CNS via the nasal cavity and cause neuronal death.[21] Moreover, the presence of antibodies against other coronaviruses that cause the common cold in the CSF of parkinsonism compared to healthy controls suggests that viral infection may play a role in the pathogenesis of the disease.[22]

The mechanism that caused the nigrostriatal dopaminergic nerve terminals to degenerate is unknown, but angiotensin system, which has been linked to COVID-19 pathogenesis, may play a role in the neuroinflammation and neurodegenerative mechanisms seen in Parkinson's disease.[23] Perhaps genetic makeup made patients susceptible to immune-mediated mitochondrial injury and neuronal oxidative stress. Another theory is that the virus causes inflammation by activating microglia, which leads to protein aggregation and neurodegeneration. Another hypothesis is releasing of cytokines may activate immune cells in the CNS and/or allow them from the periphery to infiltrate the CNS and causing brain cell damage. Activated T cells and microglia are such cells that can kill neurons, astrocytes, and vascular cell types.[24]

We present three patients who have new onset tremor in the context of COVID-19. All of them treated with favipiravir. In the literature there is not any side effects like tremor of favipiravir.[25] After stopping the medication, there wasn't any regression in tremor of the patients. This is also supporting that symptoms aren't related with side effect of favipiravir.

More data from cases with similar features is required to determine a causal relationship between SARS-CoV-2 and tremor. In any case, our findings add evidence that is supporting the virus's possible role in the onset of neurological symptoms. Although the serious neurologic complications we've seen are unlikely to be caused by the virus, it's still important to be aware of common neurologic complications so doctors can be prepared, particularly when neurology isn't available.

Limitations

This study has some limitations. Neuroimaging techniques (fMRI, DTI, transcranial Doppler), electrophysiological tests, CSF tests were either not performed or were limited during the outbreak of COVID-19 because of the high risk of cross-infection. Furthermore, we were unable to determine whether these neurologic symptoms are caused directly by the virus or indirectly by another organ damage. Despite these limitations, neurologists should collaborate closely with other specialties through a multidisciplinary approach.

CONCLUSION

We are reaching new information about SARS-Cov-2 which poses a serious threat all over the world. COVID-19 doesn't limit itself to a simple lower respiratory tract infection but can cause serious systemic disease and affect the nervous system. Its neurological effect is mediated by a variety of mechanisms, including direct invasion and a maladaptive inflammatory response. Autopsies of COVID-19 victims, as well as extensive clinical, neurological, and electrophysiological investigations of the patients may help to understand the virus's role in causing neurological manifestations.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Alanya Alaaddin Keykubat University Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.10.2022, Decision No: 10-04).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

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Pathophysiology of parenchymal injury in ischemic stroke

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ABSTRACT

Stroke is rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with no apparent cause other than of vascular origin. By definition, symptoms should last a minimum of 24 hours or result in death. Clinic may occur in two ways: "ischemic" as a result of vessel (arterial or venous) occlusion and "hemorrhagic" (intraparenchimal or subaracnoid) as a result of distruption of vascular integrity. Treating a disease requires an understanding of its mechanism. Over the years much progress has been made in elucidating the patophysiology of ischemic stroke. Current treatment trials have concentrated on distrupting these mechanisms from various points, restoring circulation and preserving the surviving neurons (neuroprotection)).5,6 In this review, hemorrhagic events were excluded due to the breadth of the subject. Current information on the pathophysiology of ischemic stroke and suggestions for the use of said information in treatment were brought together.

Keywords: Stroke, ischemic stroke, parenchymal injury

INTRODUCTION

According to the World Health Organization (WHO)'s description; stroke is rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with no apparent cause other than of vascular origin. By definition, symptoms should last a minimum of 24 hours or result in death.[1-3] Clinic may occur in two ways: "ischemic" as a result of vessel (arterial or venous) occlusion and "hemorrhagic" (intraparenchimal or subaracnoid) as a result of distruption of vascular integrity.[2] Ischemic strokes account for 62.4% of all global stroke incidents (7.63 million [95% CI, 6.57–8.96 million]), while ICHs for 27.9% (3.41 million, [95% CI, 2.97–3.91 million]), and SAHs for 9.7% (1.18 million [95% CI, 1.01–1.39 million]).[3,4] These percentages may vary in accordance with race, etnicity and country's development level.

According to data from GBD (Global Burden of Disease) study and AHA (American Hearth Association); stroke, with an incidence of 11.71 million and a prevalence of 89.13 million worldwide, is the leading cause of morbidity and ranks fifth among all causes of mortality in USA.[4] Approximately 30% of stroke patients die within the first year and one-third of those who survive remain disabled in basic acitivites of daily life.[2] According to same sources, ≈795 000 people have a new or recurrent stroke each year in USA. 610 000 of these are new and 185 000 are recurrent.[4] Unfortunately, treatment options are still limited to revascularization techniques, which can only be applied to a limited group of patients in the acute period. Moreover, with these techniques, only damaged tissue formation is prevented and the damage that has already been done cannot be reversed. In addition, secondary cell death following primary damage increases long-term disability since it cannot be prevented with current treatment methods.[5,6] Therefore, new approaches in treatment is necessary.

Treating a disease requires an understanding of its mechanism. Over the years much progress has been made in elucidating the patophysiology of ischemic stroke. Current treatment trials have concentrated on distrupting these mechanisms from various points, restoring circulation and preserving the surviving neurons (neuroprotection).[5,6] In this review, hemorrhagic events were excluded due to the breadth of the subject. Current information on the pathophysiology of ischemic stroke and suggestions for the use of said information in treatment were brought together.

MECHANISMS OF BRAIN PARENCHYMA DAMAGE

1. Ischemia and Hypoxia

Brain is an organ with high metabolic activity. Although it constitues only 2% of the total body weight, the normal brain receives 15% of the cardiac output and garners 20% of body's oxygen consumption (750 ml/min). Neurons mostly

rely on glucose as their energy source. However their ability to store it in glycogen form is negligible. As a result, all these factors make the brain tissue highly susceptible to changes in blood flow and therefore amount of oxygen and glucose transported through the blood.[2,7,8] Ischemia occurs when the delivery of oxygenated blood is less than the level needed to meet methabolic demands of the brain tissue.[7,10]

The ischemic tissue is composed of two parts. The "ischemic core" in the center; which suffers maximum damage from ischemia, whose recovery is not possible under current conditions; and the area surrounding the ischemic core, "penumbra", where energy metabolism is disrupted, electrical activity cannot be maintained, but irreversible cell death has not yet begun because it can maintain the ion balance between intracellular and extracellular space. Penumbra region, which is known to be salvageable, forms the basis of early treatment studies in acute ischemic stroke. In individuals with good collateral leptomeningeal flow, the core area remains smaller and the salvageable penumbra tissue remains larger. Today, it has been proven that if the presence of penumbra is demonstrated with the current imaging techniques, it is possible for acute ischemic stroke patients to benefit from thrombectomy treatment even after the 6 hour limit.[2,3]

On a cellular level, all parenchymal injury mechanisms seen during ischemic stroke can be divided into two groups: primary and secondary. Primary injury is irreversible damage that occurs within a few minutes of the incident which forms the ischemic core. In the primary injury zone, cells undergo necrosis. Necrosis is a passive event characterized by initial cellular and organelle swelling- which causes uncontrolled water intake into cell or in other words "cytotoxic edema"-, subsequent disruption of organelle and plasma membranes, disintegration of nuclear structure and cytoplasmic organelles with extrusion of cell contents into the extracellular space. Scattered cell content paves the way for secondary injury.[7,10]

Secondary injury is the name given to all the changes that primary injury triggers or happens after primary injury. These include not only unrecovered penumbra tissue but also areas damaged by the compressive effects of edema or subjected to long-term mechanisms of neurodegeneration and neuromodulation. It may progress over days, weeks, months or even years. Many different mechanisms play a role in its formation; necroptosis, apoptosis, excitotoxicity, oxidative stress, mitochondrial dysfunction, calcium overflow are some of them. It is often observed in the adjacent area of primary injury and seldom in remote areas. The belief that it can be partially limited or reversed has made secondary injury mechanisms the main focus of current researches.[7,8,10]

Delayed cell death is one of the main elements of secondary injury. It occurs either as a continuation of primary cell death, by necrosis; or in a planned manner, through apoptosis. Apoptosis is an active process which requires some amount of energy. During apoptosis, cell contents are first neatly packaged. These packages, called "apoptotic bodies", are then removed from the area by phagocytosis. Apoptosis does not trigger inflammation.[7,9]

In ischemic process, the most important factor that determines the fate of the cell is the amount of ATP (adenosine triphosphate) that can be produced. Energy-dependent ion-gated channels on the cell membrane cannot function in regions where ATP is insufficient or blood flow is severly impaired, which in turn cause necrosis. Apoptosis occur when ATP remains partially accessible for a period of time.[7-9]

2. Cellular Energy Insufficiency

Brain tissue can only tolerate lack of ATP for several minutes. So much so that approximately 5-10 minutes of total occlusion of artery is enough for irreversible tissue damage.[7]

Aerobic glycolysis is a series of reactions in which a net 36 ATP are synthesized from glucose. It consists of glycolysis, Krebs Cycle and ETS (electron transport system) phases. Oxygen is necessary for transportation of electrons in the ETS. If oxygen depletes, transport proteins and cytochromes remain reduced. Since there is no potential gradient, energy cannot be synthesized. In this case, anaerobic glycolysis comes into play to close the energy gap in the affected area and regenerate the idle NADH and FADH2.[11]

Anaerobic glycolysis is a series of reactions in which a net 2 ATP are synthesized from glucose. However, the energy obtained from this is far from sufficient to sustain cell life. In addition, accumulation of its end product, lactate, deepens acidosis in the cell and increases H+ ion toxicity.[12]

Moreover energy deficiency causes the ion gradient across the plasma membrane to detoriorate. Because most of the ATP synthesized by cell is used to operate ion-gated channels localized on the plasma membrane, which are responsible for maintenance of electrolyte and fluid balance. The Na-K ATPase pump in particular uses a significant portion of the energy reserve of a normal neuron.[13] If the Na-K ATPase pump does not work properly, the potassium kept inside by the pump leaves the cell while sodium, chloride and calcium ions held outside enters the cell, dragging water with them. This is called anoxic depolarization. Thus, cell swelling, which is the first stage of necrosis, occur.[14]

Another process where energy is required is maintaining calcium balance. A healthy cell tries to keep the amount inside citosol constant by both storing it in the endoplasmic reticulum and mitochondria and excreting the excess out of the cell with energy-dependent pumps. Maintaining this balance is crucial for the cell because calcium is responsible for the regulation of many enzyme activities.

In case of ischemia, calcium tends to accumulate intracellularly by various mechanisms. Some of these include Na-K ATPase dysfunction; exchangement of the increased Na+ and H+ ions with calcium by using Na+/Ca+2 regulator (NCX) and acid-sensitive ion channels (ASICs, which exchange Ca+2/H+).

Mitochondria, together with the endoplasmic reticulum, are important regulators of intracellular calcium balance. It stores calcium and magnesium via vesicles in its matrix. It also limits the amount of calcium entering its matrix via channels called "mitochondrial calcium uniporter (MCU)" which are localised on its inner membrane. This way, the amount of calcium mitochondria contain is kept constant. However, in case of energy insufficiency micro-connections are formed between the endoplasmic reticulum and mitochondria. This process is activated by excess calcium in the endoplasmic reticulum. These connections open closed MCU channels. As a result, excess calcium enters the mitochondria from the endoplasmic reticulum and cytosol. Mitochondria's calcium overload triggers apoptosis and swelling of the organelle and activation of destructive enzymes such as phospholipase, protease and endonuclease. All of these eventually disrupt the functioning of the organelle and lead to "lipid peroxidation".[7,14]

3. Excitatory Amino Acids

Glutamate is the main excitatory neurotransmitter of the adult central nervous system. Overstimulation of neurons with glutamate causes cell damage, as it is an excitotoxin. This damage is mostly mediated by calcium overload. Energy is required for synthesis and reuptake of neurotransmitters. In normal conditions, the amount of glutamate in synapses is tightly controlled by the synthesis-reabsorption cycle. When neuronal injury occurs, cell integrity is disrupted and excessive amounts of glutamate are released. Due to the accompanying ischemia, this excess glutamate also cannot be reabsorbed as all of these processes are energy dependent. Excess glutamate increases tissue damage by overstimulating the surrounding cells.[7,16]

Glutamate binds to two separate receptors that mediate the opening of ion channels in the plasma membrane. NMDAR (n-methyl-d-aspartate receptor) is the most striking among them, but AMPA/kainate (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptors also have an important role in the neurotoxic effect. In fact, activation of the AMPA channel plays a key role in the activation of the NMDA channel. AMPA receptor is an ionotropic receptor permeable to many ions, especially sodium. It has the ability to turn on and off quickly and it is responsible for rapid communication between neurons under routine conditions. It needs only the presence of glutamat to activate. When the amount of glutamate increases as a result of neuronal injury, excess glutamate bind to the AMPA receptors of neighboring cells. This results in opening of ion channels in AMPA which leads to Na+ influx and depolarisation. Activation of the AMPA receptor causes magnesium ions, which block NMDAR, to get released from the receptor.[15]

NMDAR is responsible for attention and learning in physiological process, as well as neurodegeneration in pathological process. For it to open under normal conditions, it must be separated from the magnesium ion to which it is bound.[17] Excess glutamate in the environment binds to the NMDA receptor, which is freed from magnesium by AMPA activation and fast depolarisation. Then intense amounts of calcium and sodium enter the cell through the opened channel. As previously explained, calcium overload ignites a series of enzyme cascades that result in cell damage.[15]

Activation of the NMDA receptor also stimulates nitric oxide production in the neuron. Nitric oxide is essentially a vasodilator neurotransmitter; but when synthesized in excess, it combines with superoxide and mediates the production of strong reactive oxygen radicals.[7,15]

4. Reperfusion Injury

Ensuring perfusion to the ischemic tissue quickly constitutes the basic treatment approach in acute stroke and is of vital importance in terms of saving as many cells as possible. However, these cells, which have been deprived of oxygen and nutrients for a certain period of time faces new threats when blood flow is restored. Rapid increase in concentration of oxygen in the tissue brings the potential for oxygen free radical formation. In addition, restoring circulation of the tissue where the blood-brain barrier is damaged, causes inflammatory cells to invade the area. All of these injuries that follow the restoration of blood flow are called "Reperfusion Injury" and have an extremely important role in the formation of secondary injury.[7]

Mitocondria plays an important role in progression of reperfusion injury. It has been proven that ischemia-reperfusion process causes post-translational changes in oxidative phosphorylation proteins. Thus, the mitochondrial membrane potential increases and therefore reactive oxygen radicals [Hydroxyl (OH), superoxide (O_2-) and peroxide (H_2O_2)] are synthesized. In addition, substrates of oxidative phosphorylation (AMP, xanthine, hypoxanthine) tend to accumulate during the ischemic process. When oxygen re-enters the cell, rapid use of these substrates releases reactive oxygen radicals. The cell membrane undergoes lipid peroxidation as a result of free radical damage.[18]

The role of immune mechanisms in reperfusion injury is still subject to current research. Previously, the central nervous system was thought to be relatively shielded from immune system thanks to low permeability of blood brain barrier (BBB). But current studies have shown that, during stroke, BBB is distrupted due to capillary endothelial injury during ischemia. Microglia are also activated by stress and secrete signaling proteins that mediate both inflammation and tissue repair. As reperfusion occurs, leukocytes responding to the call of microglia flood into the tissue across the damaged barrier. These leukocytes contribute to tissue damage by secreting cytokines such as "TNF, IL-1, IL-6". Additionally, platelets activated by these prosseses aggregate and adhere to the endothelium. Thus, perfusion further decreases and the damage worsens as the "PAF" secreted from those platelets also increases the damage. Clinical and laboratory trials have shown that neuroinflammation plays a role in acute damage as well as in long term tissue changes after damage.[7,18,31]

5. Abnormal Autoregulation, Vascular Reactivity, Chemoregulation

Optimal maintenance of brain functions depends on the continuity of cerebral blood flow. Under normal conditions, cerebral blood flow (CBF) is determined by the ratio of cerebral perfusion pressure (CPP) to cerebrovascular resistance (CVR). Cerebrovascular resistance depends on blood viscosity and vessel diameter. Mean cerebral perfusion pressure (mean CPP) is equal to the difference between the mean arterial blood pressure (MAP) in the cerebral circulation and venous pressure (ICP-intracranial pressure); which is normally around 90 mmHg.[2,22]

The brain's ability to maintain a constant level of CBF despite changes in CPP is called "autoregulation." Constant blood flow can be achieved while the MAP is in the range of 60-140 mmHg.[19] However, these numbers are not absolute and vary from person to person. It has been shown that the lower and upper limits of autoregulation increase in people with long-term hypertension. Thus, as tolerance to high blood pressure values increase, so does sensitivity to hypotension.[2]

An autoregulation example is as follows: cerebral perfusion pressure decreases, as in systemic hypotension or increased intracranial pressure. With the dilation of the precapillary vessels, cerebrovascular resistance decreases and cerebral blood flow remains constant. On the other hand, in case of hypertension, the vessels constrict. The resistance increases and the cerebral blood flow remains constant yet again.[2,22]

Baroreceptors are sensitive to changes in perfusion pressure. Although these receptors are found in the walls of all arteries, especially the arcus aorta, they are most

commonly located in the regions called "Carotid Sinus" located on the walls of both internal carotid arteries.[32]

When the mean arterial pressure drops below 60 mmHg, the expansion capacity of the precapillary vessels is exceeded. As a result, collapse occurs and CBF decreases. Therefore, any pathology that prevents the vessels' ability to dilate results in ischemia. Aforementioned pathologies include, but are not limited to, thrombus, embolism, vasospasm, neutrophil aggregation and tissue edema. When the mean arterial pressure exceeds 160 mmHg, the narrowing of the vessels reaches its highest level. As a result, hyperemia and vasogenic edema develop. As edema grows in size, healthy tissues are pushed to the sides, intracranial pressure increases, herniation symptoms occur. Vascular damage disrupts the vasoconstriction function, causing hyperperfusion and increased brain edema.[2,7,21,22]

Another aspect that affects the vascular wall diameter is the quantity of components that reflect the state of cell metabolism. These include the partial pressure of carbon dioxide, oxygen and the amount of H+ in the environment. This is called "chemoregulation". It is particularly noteworthy that the response to changes in carbon dioxide levels is rapid and potent. As $PaCO_2$ levels decrease, the vessels constrict; vessels dilate as $PaCO_2$ levels rise. Moreover, this effect remains intact unless a serious global damage occurs in the cerebrum. Since arterial circulation is interrupted in ischemic stroke, oxygen is consumed rapidly; PaO_2 levels decrease. As the produced CO_2 and H+ cannot be excreted from the tissue, their partial pressures keep rising. Hypercarbia caused by respiratory depression that may accompany ischemic stroke significantly increases cerebral blood flow. Excessive increase in cerebral blood flow causes cerebral edema. Therefore, in a stroke patient, it is of utmost importance to check breathing functions. If respiratory depression is present, it is vital to intubate the patient and ensure effective ventilation. On the other hand, hyperventilation to lower $PaCO_2$ causes rapid vasoconstriction and therefore decreases intracranial pressure. As a matter of fact, hyperventilation has long been used as a standard treatment protocol in patients with increased intracranial pressure. However, the harm of prolonged hyperventilation tends to outweigh its benefits. The primary harm being that it significantly reduces blood flow in sensitive vessels and triggers ischemia in these areas. Therefore, it is recommended to use the hyperventilation technique for a maximum of 4-6 hours before decompressive surgery or in emergency interventions.[2,19,20,24]

Response to oxygen level changes is slower, less dramatic. Vasodilation occurs when the oxygen level in the tissue drops below 50 mmHg.[19,20]

6. Increased Intracranial Pressure

In a normal adult, average intracranial pressure is 0-15 mmHg. In fact, transient intracranial pressure changes are common in a healthy individual. Sneezing, coughing, laughing, straining, and changes in head position all increase intracranial pressure, but since the pressure returns to normal in a short period of time, there are no major consequences. Intracranial hypertension is when the pressure exceeds 22 mmHg for more than 5 minutes.[2,7]

The cranium consists of 3 major components: brain tissue, cerebrospinal fluid (CSF) and blood. As explained in the Monroe-Kellie Doctrine, a slight increase in the volume of any of these three components is compensated by a decrease in the volume of the other two. Reasoning being that cranium is surrounded by a hard skull and has little to no ability to expand.[25]

In ischemic stroke, the increase in brain tissue volume is often secondary to abnormal fluid accumulation in the intracellular or interstitial space, which is called "cerebral edema". Cytotoxic edema is characterized by accumulation of water and sodium inside the cell, ultimately causing cell swelling. Whereas vasogenic edema occurs as a result of disruption of the blood-brain barrier which leads to extravasation of electrolytes, water, albumin and similar intravascular proteins into the interstitial space. Processes that increase intravascular pressure, damage the capillary wall or cause vasodilation increase vasogenic edema. These include severe hypertension, hypercarbia, stroke and fever. Cytotoxic edema is observed within the initial hours of ischemic stroke. Vasogenic edema presents itself as a delayed effect of secondary damage to the brain as it usually begins to develop within the first 2-3 days and peaks on the fifth day.[7,26]

Cerebral edema, when severe, initiates a cycle in which the pressure gradually increases and the condition becomes increasingly severe. As edema fluid accumulates, it narrows the local vessels and prevents sufficient blood and oxygen from reaching the cells. This will lead to ischemia, vasodilation, increased capillary pressure causing even more fluid to leak into the damaged tissue, thus increasing edema even further.[2,7]

The most undesirable consequence of cerebral edema and therefore increased intracranial pressure is the herniation of brain structures. The word "herniation" refers to the protrusion of brain tissue through an opening between the surrounding dura sheets. In particular, compression of important midline structures (reticular activator system, vital regulatory center) and brainstem is associated with rapid brain death if not treated immediately. During this process, there is a risk of compression of the arteries and development of secondary ischemia (such as compression of the anterior cerebral artery and pericallosal artery in Subfascinal Herniation).[27] In addition, a significant increase in intracranial pressure and compression of the vessels cause the activation of the sympathetic system to maintain brain perfusion which is named "Ischemic Response" or "Cushing's Triad" . Cushing's triad is considered as the brain's last effort to ensure perfusion.[7]

TREATMENT

Current treatment of acute ischemic stroke includes stabilizing vital functions, restoring perfusion in the salvageable penumbra tissue with endovascular and iv thrombolytic therapy and, if present, treating cerebral edema and the accompanying increased intracranial pressure. First and foremost, it is essential to ensure the patient's airway, breathing and circulation are in order. Then glucose is measured from the fingertip, hypo-hyperglycemia is quickly intervened. Electrolytes, blood count, coagulation parameters, kidney and liver function tests are requested. Hypertension seen in the acute phase of ischemic stroke is most likely the body's attempt to reduce tissue damage by increasing cerebral perfusion. Therefore, hypertension should not be treated untill blood pressure reaches or exceeds 220/120 mmHg. However, if thrombolytic is to be administered, blood pressure should be maintained below 185/110. Hypotension, however, should always be treated immediatly.[33]

Occurences such as pain and fever should be prevented as they will accelerate metabolism and increase energy consumption. Hyperosmolar agents such as hypertonic saline, mannitol draw water from the brain tissue, reducing intracranial pressure. Such agents are used in the treatment of vasogenic edema. Mannitol dosage is calculated based on the patient's weight. First, a bolus dose is given, then maintenance dose is repeated every 4-6 hours. The target osmolarity is 320 mOsm/L and the maintenance dose is adjusted according to the patient's response and blood test results. Treatment should be reduced gradually since sudden stoppage may cause rebound edema and patients may develop resistance to mannitol during long term usage.[27]

Hypertonic saline can be administired as a bolus or as a continuous infusion. The serum sodium target is below 160. In case of infusion, sodium levels should be monitored by taking blood samples every 4-6 hours and the dose should be adjusted accordingly.[7,27]

Decompressive surgery is a life-saving treatment for select patients, especially in the first 48 hours.

Hypothermia's (32-33°C) use in treatment-resistant CIBAS is being researched due to its metabolism-slowing effect. Although it has been shown to reduce intracranial pressure, its significance in regards to clinical outcomes has not yet been confirmed. Moreover, the therapeutic window of effect, duration of application, safe rewarming protocols have not been fully defined. In addition, the shivering that occurs as a result of hypothermia neutralizes the positive effect of the treatment by increasing the oxygen demand in the tissue. Therefore more studies are required before hypothermia can be used reliably in the treatment of ischemic stroke.[7,28]

Finally, barbiturate coma may be attempted when all preceding options have failed. Pentobarbital infusion reduces cerebral metabolism while increasing membrane stabilization. The major downside of barbiturate coma is the inability to perform a neurological examination. Moreover hypotension is a common side effect in these patients.[7,29]

CONCLUSION

Ischemic stroke is an acute disease with high morbiditiy and mortality rates all around the globe. However, current studies come up short in many aspects. Current treatment algoritm only serves to preserve the penumbra tissue as much as possible in select patients, while aiming to limit secondary injury. Better understanding the pathophysiology of ischemia will not only open up new treatment options, but it may also help us understand the posibilities of reversing tissue damage. Studies conducted in the following years will both shed light on unanswered questions regarding the mechanism of the disease and reshape the treatment algorithm.

ETHICAL DECLARATIONS

Referee Evaluation Process

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

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Determination of the risk factors and delirium in the intensive care unit

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ABSTRACT

Delirium is a pathology that most frequently affects elderly patients, is the result of an underlying condition, increases patient mortality and morbidity, and places a significant financial burden on clinics. Prevention of delirium is the simplest and most feasible approach. Despite all these, the clinical diagnosis of delirium is still inadequate and overlooked. In this review, current clinical practices for delirium, including etiology, pathophysiology, diagnosis, and treatment management, are reviewed.

Keywords: Delirium, geriatric, consciousness, attention

INTRODUCTION

Delirium is a clinical condition that often develops in later life. In delirium, the ability to focus and maintain focus generally decreases, and in addition, loss of attention, consciousness, and cognitive changes may develop. Delirium frequently occurs rapidly in a short period of time and fluctuates during the day.[1] In the clinical picture, psychomotor behavioral disorders are mostly observed together with restlessness. Psychomotor behavioral disorders may manifest themselves as hypoactivity or hyperactivity. This condition is usually accompanied by an increase or decrease in sleep duration and a deterioration in sleep quality.[2]

Delirium does not develop under normal conditions in many patients. Typically, an underlying medical condition is what causes it. In the etiology, there may be simple conditions such as constipation, pain, and local infections, or life-threatening conditions such as systemic infections, sepsis, and postoperative conditions.[3]

As a result of studies on delirium, the main feature that stands out in prevalence data is that it is frequently observed in the advanced age group. Incidence figures that can reach up to 25%, especially after major surgeries, and exceed 50% after risky surgical procedures have been found. In the postoperative period, the development of delirium has been found to be an independent predictor of mortality, causing an increase in mortality risk of approximately 10%. On the other hand, it was observed that the development of delirium increased mortality rates 2-4 times in patients followed up in intensive care units.[4,5]

Delirium is a preventable clinical condition, and the most important approach is to prevent it before it develops. When it develops, it should be diagnosed early and rapidly, and its treatment should be performed carefully. Delirium is associated with increased morbidity as well as mortality risk. Consequently, it causes a serious cost increase for clinics.[6] Possible consequences of delirium, especially in intensive care unit patients, are summarized in Figure.

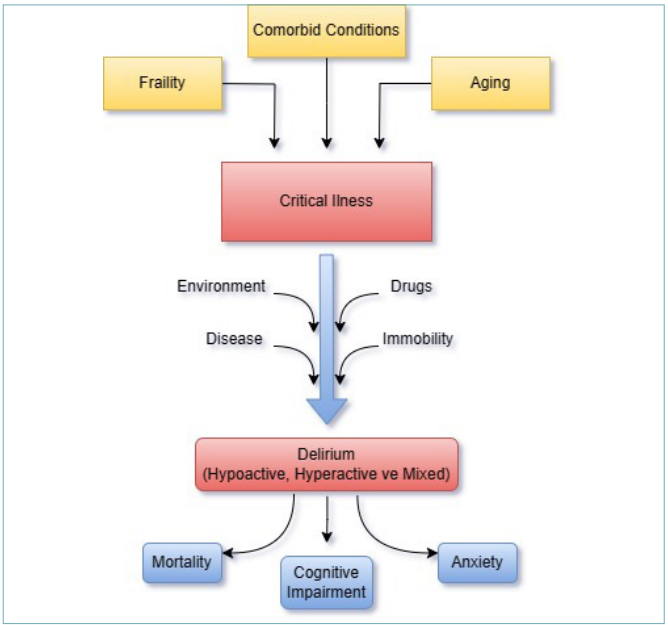

Figure. Risk factors and consequences of delirium in intensive care

ETIOLOGY AND RISK FACTORS

A new etiologic study in delirium is being added every day. However, the pathophysiology of many of the etiologic factors has not been fully elucidated. There are basically two groups of etiologies and risk factors related to delirium. These factors are roughly categorized as predisposing and accelerating factors. Delirium risk factors are summarized in Table 1.[7]

It should be kept in mind that the most common cause of predisposing factors is advanced age, and the importance of drugs among accelerating factors should not be forgotten. On the other hand, accelerating factors may consist of clinically overlooked symptoms such as constipation. Therefore, especially elderly patients should be approached carefully and holistically in terms of delirium, and all complaints of the patient should be given equal importance.[8]

Table 1. Delirium risk factors

Predisposing Factors	Accelerator Factors
• Advanced age (over 70 years) • Dementia (usually undiagnosed) • Functional disability • Male gender • Poor vision and hearing • Mild cognitive impairment	• Medicines (especially anticholinergics) • Postoperative period • Anesthetic substance use • Hypoxia • Untreated pain • Infections • Acute exacerbations of chronic diseases • Constipation • Dehydration • Insomnia • Urinary retention, bladder catheterization

PATHOPHYSIOLOGY

Delirium occurs pathophysiologically as a result of various mechanisms, and all of these conditions have not been fully elucidated. In studies, it has been determined that many conditions should occur simultaneously for delirium to occur.[8]

Advanced age, which is one of the most important points in terms of pathophysiology, comes to the forefront primarily due to loss of physiologic reserve and increased sensitivity to diseases and stress situations.[9] In addition, it has been demonstrated that inadequate perfusion of brain tissue with advanced age is effective in reducing the increase in neuronal degeneration and loss. It has been argued that the leading cause of neuron loss is the increase in endothelial permeability as a result of the loss of the effect of the endothelial barrier in the blood-brain barrier and the related increase in neuronal inflammation. In addition, it has been found that these cells are damaged at a higher rate than normal as a result of an increase in reactive oxygen species due to the high lipid content and low antioxidant capacity of central nervous system cells.[10]

One of the important factors in the development of delirium is sleep patterns. The function of the melatonin hormone has been determined as a result of many years of studies in order to elucidate hormonal mechanisms in this regard. Melatonin has many functions, including sleep-wake cycles, regulation of antioxidant defenses, and glucose metabolism. In cases of disruption of sleep duration, pattern, and structure, melatonin levels may be affected and lead to delirium.[11]

CLINIC

The clinical course of delirium may vary in many different ways. As a result of the studies, it is generally analyzed in three subgroups and summarized in Table 2. Delirium may present as hypoactive, with increased sleep duration, somnolence, and a depressive state, or hyperactive, with hallucinations, delusions, and an agitated general state. On the other hand, delirium may occur over a long period of time, such as days, or it may occur within hours. Therefore, the patient's general activity, condition, and mood must be evaluated in terms of delirium at each visit.[12]

Table 2. Delirium classification and clinic

Hyperactive Delirium	Hypoactive Delirium	Mixed Presentation
• Increased agitation • Hallucination • Fighting aggressive behavior	• Sleepiness • Increased sleep duration • Depressive appearance • Decreased excitability	• Clinical symptoms alternating between hyperactive and hypoactive

DIAGNOSIS

The starting point for the diagnosis of delirium is the suspicion of delirium. Clinical studies have shown that only 40% of all delirium cases are recognized, and many cases are not detected. It has been determined that most of the 60% of cases that are not recognized are in the picture of hypoactive delirium. Therefore, in patients with suspected delirium, the patient's companion or caregiver should be questioned in detail, and the presence of hypoactive symptoms should be detailed. It should be learned whether the patient has increased sleep, depressive appearance, and mood in recent days.[13]

A detailed physical examination must be performed on patients with suspected delirium. First of all, vital signs should be evaluated; if necessary, a complete blood count, blood biochemistry, electrolytes, urinalysis, and, if possible, arterial blood gas should be performed. If deemed necessary in line with the patient's clinical condition, chest radiography and an ECG should be ordered. The aim of all these tests is not to diagnose delirium but to determine the underlying etiologic cause. Although there is data showing that values such as CRP, some interleukins, and cortisol are correlated with delirium in clinical trials, they have no place in the diagnosis and are not recommended for follow-up.[13] The diagnosis of delirium is made according to DSM-5 criteria. These criteria are summarized in Table 3, and the presence of all criteria is required for diagnosis.[14]

Table 3. DSM-5 diagnostic criteria for delirium

Attention and discrimination disorder

a. Decreased ability to direct, focus, maintain, and shift attention. Decreased orientation to the environment.
b. Develops over a short period of time (hours to a few days) with fluctuations in severity during the day.
c. Additional impairment in cognition, memory, orientation, language, visuospatial competence, or perception

Impairment in criteria A and C;

- Is not better explained by another pre-existing, established, or developing neurocognitive disorder.
- It does not occur in the context of a severely reduced level of alertness, such as a coma.

TREATMENT APPROACH

In the treatment of delirium, primarily non-pharmacologic steps are applied. Identifying patients at risk for delirium in the foreground is seen as the most important intervention that can be done to prevent the emergence of delirium. The critical points to prevent delirium in these high-risk patients are to ensure that their rooms get enough sunlight, are frequently ventilated with enough fresh air, and are have a competent caregiver or a knowledgeable companion. In addition, unnecessary intravenous treatments

and urinary catheters that will tie the patient to the bed and prevent mobilization should be avoided. In addition, no medical agent that will not clearly benefit the patient should be started.[13]

In patients in whom delirium occurs, other causes that may lead to a similar picture should be rapidly ruled out. It should be ensured that the patient is not in sepsis, is not hypoxic, is not hypoglycemic, has no electrolyte imbalance, and all vital signs are stable.

After excluding all these causes, medical treatment can be administered to patients who are sure of the diagnosis of delirium. Especially due to the advanced age and patients with comorbid conditions, the qualities of the medical agents to be selected have been determined. The agent to be preferred must have a short half-life, low toxicity risk, no effect on seizure threshold, and minimal effect on the cardiovascular and respiratory systems.[7]

Any pharmacological agent is not recommended in hypoactive delirium since the agents in the treatment generally have the effect of reducing agitation and sedation. In hyperactive delirium, antipsychotics should be preferred as first-line treatment in the absence of contraindications. Frequently used agents can be listed as haloperidol, quetiapine, and risperidone.[15]

Haloperidol is used as the first-choice agent in the treatment of delirium and may cause mild hypotension in patients. It is available in oral, intramuscular, and intravenous forms. Because of the risk of QT interval prolongation, ECG monitoring is recommended. Prolongation in the QT interval is observed more frequently in the elderly, female gender, and patients with endocrine disorders such as diabetes mellitus.[16]

CONCLUSION

Although results are obtained with haloperidol and other agents in almost all patient groups, no response to these agents can be obtained in rare patient groups. This is called resistant delirium, and benzodiazepines, anesthetic drugs, and even electroconvulsive therapies are recommended in this group of patients.

In recent years, studies, especially on sleep patterns, have shown that melatonin treatment leads to a decrease in the frequency of delirium by providing sleep patterns. However, it has not been fully utilized due to controversial publications in the literature.[17]

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

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The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Hemorrhage in sinus vein thrombosis: the "cashew sign"

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ABSTRACT

Sinus vein thrombosis (SVT) has many clinical heterogeneity and diversity in misdiagnosis and inappropriate treatment due to many etiologic factors. The main factors for diagnosing SVT are good clinical skill and a good interpretation of the radiologic image. Intracerebral hemorrhages are quite common in sinus vein thrombosis. The morphology of these hemorrhages may vary from small localized juxtacortical lesions and subarachnoid hemorrhages to large hemorrhagic infarcts.[1] In this presentation, we aimed to emphasize venous hemorrhage and the "cashew sign" seen in SVT.

Keywords: Sinus vein thrombosis, cashew sign, hemorrhage

INTRODUCTION

Sinus vein thrombosis (SVT) is a rare cause of ischemic stroke. Nowadays, increased awareness of this disease and advancements in imaging methods have facilitated the detection of more cases. Its incidence is reported to be 0.2-1.2 cases per 100,000 individuals per year.[2] Most ischemic strokes have arterial origins, while venous strokes constitute only 1% of all strokes.[2] It can occur in all age groups, but it is more common in newborns and childhood than in adults. There is no gender difference in children and older age groups; however, in the young adult age group (20-35 years), it is three times more common in women than in men.[3] This gender disparity is mainly attributed to additional risk factors such as pregnancy, the postpartum period, and oral contraceptive use.[3] Despite being a potentially fatal condition, the prognosis for SVT is generally favorable.

CASE

A 43-year-old woman applied to the emergency department with a headache since last week and left-sided numbness and weakness for the previous three days. She had a history of thalassemia minor. A neurological examination revealed left hemiparesis (motor strength 4/5) and Babinski's sign on the left side. There were no meningeal irritation signs. Diffusion-weighted brain magnetic resonance imaging (DWI) revealed diffusion restriction with nodular infarction on the parasagittal area in the right frontal region (Figure 1A and Figure 1B). Brain computed tomography (CT) revealed hemorrhage in the right parietal region (Figure 2A). Computed tomography angiography (CTA) was normal. Brain magnetic resonance imaging (MRI) showed the presence of edema with T2 hyperintensity in the right frontal parasagittal area and hemorrhage in the parietal region (Figure 2B). Contrast-enhanced MR venography (MRV) revealed areas compatible with thrombus, showing filling defects in the superior sagittal sinus that are consistent with SVT (Figure 3). In the secondary intensive care unit, low molecular weight heparin, anti-edema, and warfarin therapy were started. Also, topiramate has been added to the treatment for headache. In the neuroradiology council, the images were evaluated, and it was concluded that hemorrhage resulted from venous hemorrhage. On brain CT and MR images, venous hemorrhages called "cashew sign" with high specificity for SVT were identified (Figure 2). Her headache was relieved with treatment, and warfarin was started on the 3rd day of hospitalization with daily INR control. No positive vasculitis markers were detected in the patient. Department of haematology suggested no additional recommendation for thalassemia minor. The patient's severity of headache decreased, and she was discharged on the 10th day of hospitalization with warfarin.

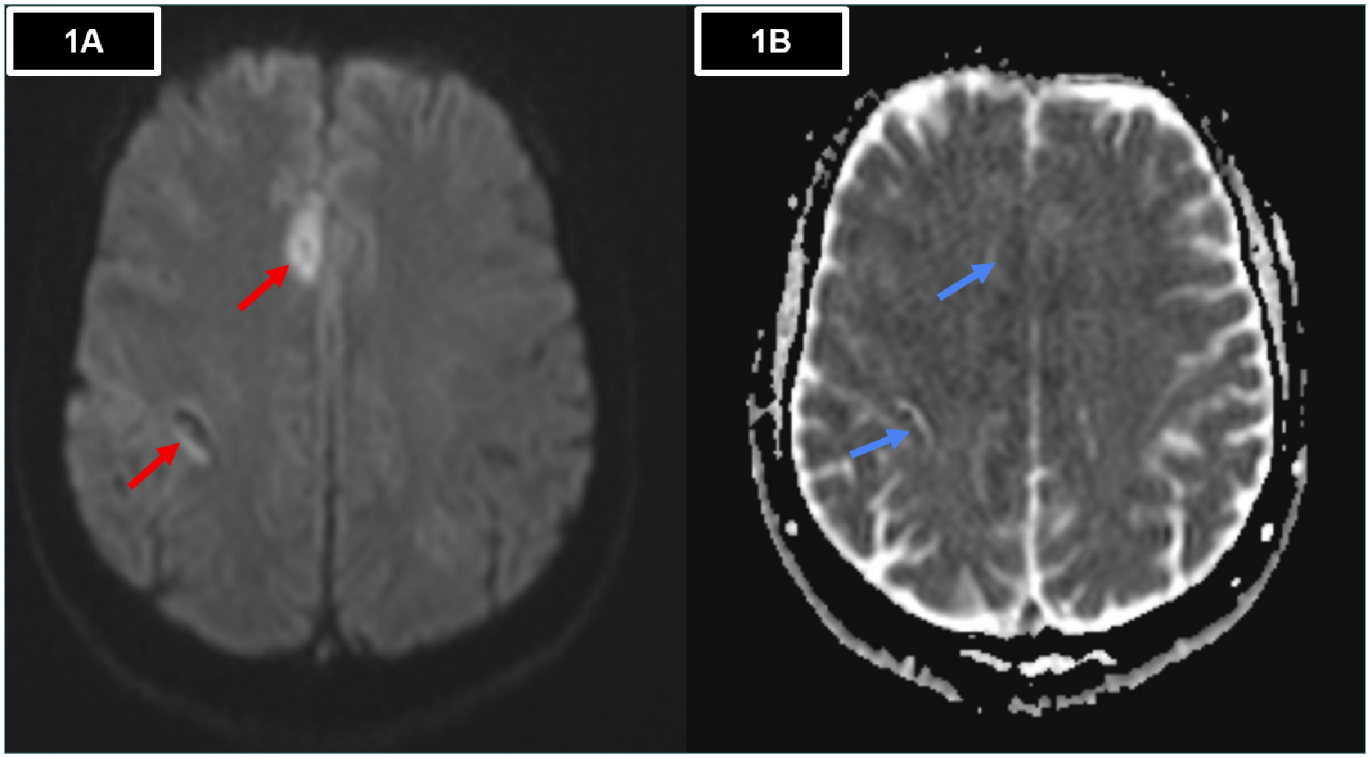

Figure 1A, and **1B.** Diffusion-weighted brain magnetic resonance imaging revealed diffusion restriction with nodular infarction on the parasagittal area in the right frontal region

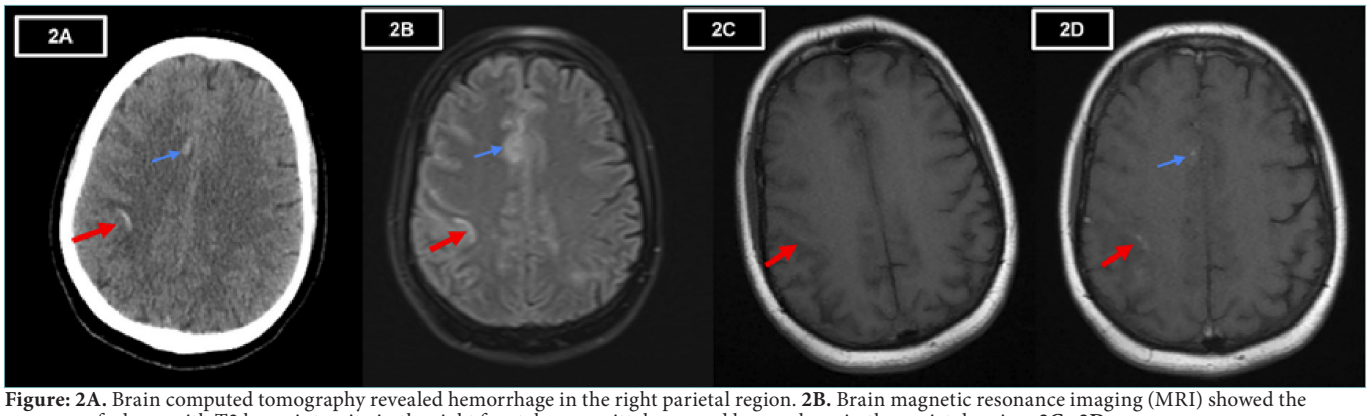

Figure: 2A. Brain computed tomography revealed hemorrhage in the right parietal region. **2B.** Brain magnetic resonance imaging (MRI) showed the presence of edema with T2 hyperintensity in the right frontal parasagittal area and hemorrhage in the parietal region. **2C , 2D**

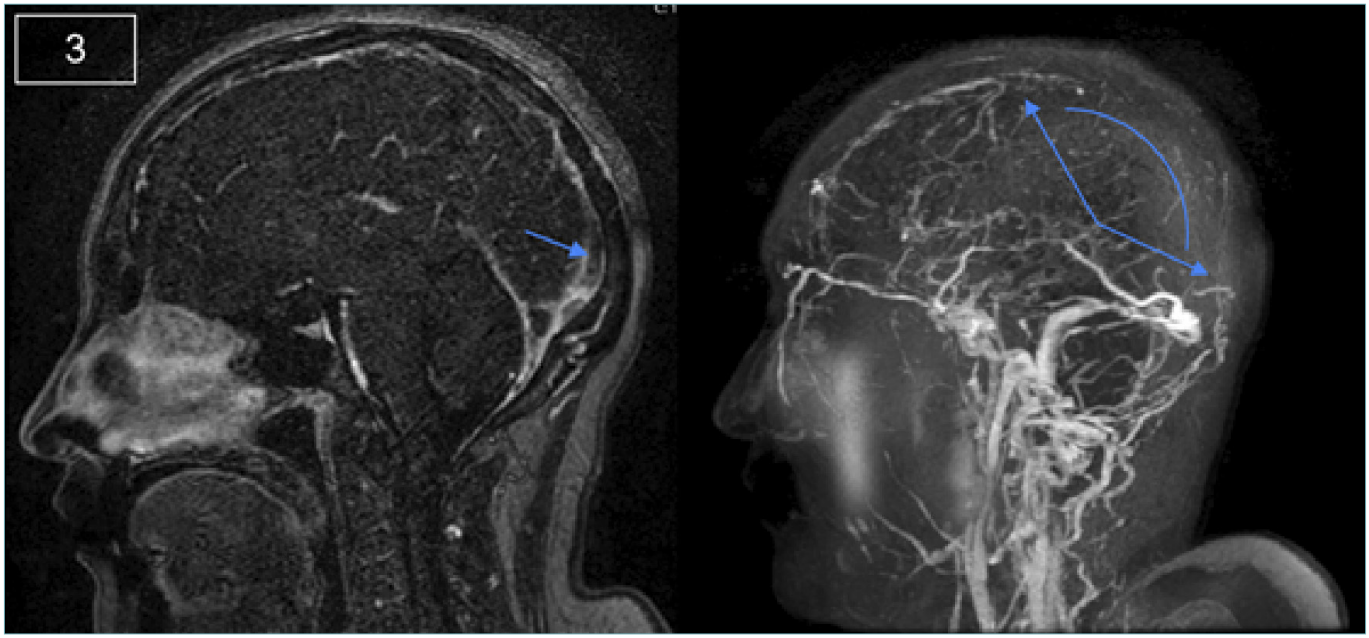

Figure 3. Contrast-enhanced MR venography revealed areas compatible with thrombus, showing filling defects in the superior sagittal sinus that are consistent with venous sinus thrombosis.

DISCUSSION

Intracerebral hemorrhage was found in 40% of patients, and juxtacortical hemorrhage in 26% of cases with intracerebral hemorrhage in patients with SVT.[1] In cases of SVT, a concave shape resembling a cashew nut called a "cashew sign" appears at the sulcus base in juxtacortical white matter hemorrhages. The "cashew sign" formed by hemorrhage of the juxtacortical veins is seen on CT and frequently in superior sagittal sinus thrombosis.[4] For non-traumatic SVT, the cashew sign shows relatively high specificity [specificity: 0.98 (95% CI 0.95 -1.0)].[1] Various imaging techniques, primarily non-contrast or contrast-enhanced CT with venous phase acquisition and MRI with MR venography, are employed for the evaluation. CT offers limited insights into the clot, vessels, and parenchyma, with minimal indicators for intracranial hypertension.[5] Conversely, CT venography demonstrates accuracy in diagnosing cerebral sinus thrombosis. In contrast, MRI provides comprehensive information on clot characteristics, vascular structures, parenchymal details, and potential indicators of intracranial hypertension.[5]

In general, symptoms of SVT include nausea, vomiting, headache, visual loss, seizures, and weakness. The diagnosis of SVT is based on radiologic and clinical findings. Symptoms in SVT vary depending on the location of the thrombosis, but the most common symptom is headache. The headache may intensify over days and become intolerable. It can be described as the most severe headache the patient has ever experienced.[6] Our patient also had an unbearable headache. The localization of the sinus thrombosis is a determinant in the clinical presentation. Superior sagittal sinus thrombosis is the most common localisation of SVT, as seen in our case.[7] Dinç et al.[8] presented a case with right-sided hemiplegia, aphasia, and cashew sign on the left frontoparietal area. Our case applied with left-sided numbness consists of a lesion on the right parietal lobe.

Our case had thalassemia minor as a risk factor for SVT. The most important risk factors for SVT are the classical Virchow triad of causes known as blood flow stasis, vessel wall changes and changes in blood content. An underlying cause can be found in approximately 80% of cases. SVT might relate to puerperium or pregnancy in young women.[9] SVT-related strokes account for 27-57% of all ischemic strokes associated with pregnancy.[10,11] Oral contraceptive use and coagulation disorders are important causes. Collagen tissue diseases and inflammatory bone diseases constitute a risk.[12,13] Genetic factors including homocysteine elevation, protein C-protein S-antithrombin 3 deficiency, factor V Leiden mutation, and prothrombin gene mutations, are responsible for 10-15% of cases.[14] As soon as the diagnosis is confirmed, treatment should be started immediately. Anticoagulation is the main treatment for SVT. Low molecular weight heparin therapy has been found superior to unfractionated heparin.[15] We have started warfarin sodium and low molecular weight heparin therapy after confirming of resorption of hemorrhage with CT.

CONCLUSION

Despite increasing awareness among clinicians, SVT is a complex disease to diagnose clinically and radiologically. This difficulty is because the neurologic picture ranges from objective focal neurologic deficits to subjective symptoms of weakness and headache. Small juxtacortical hemorrhages are characteristic of SVT and are rarely observed in other conditions. Recognizing these hemorrhages can greatly facilitate the diagnosis of SVT for clinicians.

ETHICAL DECLARATIONS

Informed Consent

All patients signed the free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Isolated eight-and-a-half syndrome associated with pontin hemorrhage: a rare clinical presentation with topological significance

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ABSTRACT

The eight-and-a-half syndrome is a critical clinical condition defined by peripheral facial palsy and the ocular symptoms mostly linked to ischemic cerebrovascular disease affecting the pontin tegmentum. We present a case of isolated eight-and-a-half syndrome with a pontine hemorrhage and discuss it's topological implications in context of neurological practice. This is the one of few cases presenting with eight-and-a-half syndrome following the pontine hemorrhage. Despite showing similar clinical features and clinical prognosis the our case is intriguing due to its unique topological anatomy demonstrating an initial improvement in ocular symptoms.

Keywords: Pontin hemorrhage, opthalmoplegia, eight-and-a-half syndrome

INTRODUCTION

The eight-and-a-half syndrome is a clinical condition defined by complete absence of horizontal eye movements in one direction, loss of inward eye movement in the other direction, involuntary eye movements during outward eye movement, and facial paralysis along with these symptoms. The syndrome, initially identified by Eggenberger in 1998, is characterized by peripheral facial palsy and the ocular symptoms as described by Fischer.[1] The dorsal tegmentum of the caudal pons is a critical region of the brainstem involving the median longitudinal fasciculus (MLF) and parapontine reticular formation (PPRF) with the nucleus and/or the fasciculus of the facial nerve. Within that context, horizontal eye movements are accomplished by connections between the PPRF, the nucleus of the sixth cranial nerve, and the MLF. There have been several etiologies leading to eight-and-a-half syndrome in the pontin region mostly related to the impairment of the dynamic interaction between PPRF, MLF and the facial nucleus and its fasciculus. Among them, the eight-and-a-half syndrome is mostly linked to ischemic cerebrovascular disease (CVD), specifically affecting the pontin tegmentum.[2] It is also worth mentioning that there are also exceptional cases of this syndrome related to some demyelinating disorders, vasculitis and some specific brainstem tumors, such as, brainstem tuberculoma.[1-5]

Here, we present a case of isolated eight-and-a-half syndrome with a pontine hemorrhage and discuss it's topological implications in context of neurological practice.

CASE

A 50 years old-male patient was admitted to the emergency services experiencing intense headaches, and fainting in the last 24 hours. His examination in the emergency room revealed stabil vital signs with the exception of elevated blood pressure of 180/120 mmHg. The patient's neurological examination revealed restricted abduction and adduction in the left eye, nystagmus in the right eye, and peripheral facial paralysis on the left side. The routine blood tests revealed no clinical symptoms, except for a slight elevation in blood urine levels. The brain computed tomography (CT) scan detected a hypertensive hemorrhage with the size of 16×20 mm in the posterior pontine region. Also gradient-echo T2-weighted magnetic resonance imaging (MRI) confirmed the bleeding in the left paramedian tegmentum of the pons while the CT angiography revealed no notable abnormalities except for the presence of plaque, resulting in a 50% narrowing of the left internal carotid artery (ICA). Treatment for pons hemorrhage targeting high blood pressure and brain swelling

has been started immediately after the diagnosis of pontin hemorrhage. The patient responded well to the treatment and on the fourteenth day of recovery, there was a partial but considerable resorbtion of the hemorrhage associated with partial improvement in clinical symptoms including mainly improvement in eye movements that was prominent after one month of the cerebrovascular accident with a sequele peripheral facial palsy that was only partially improved.

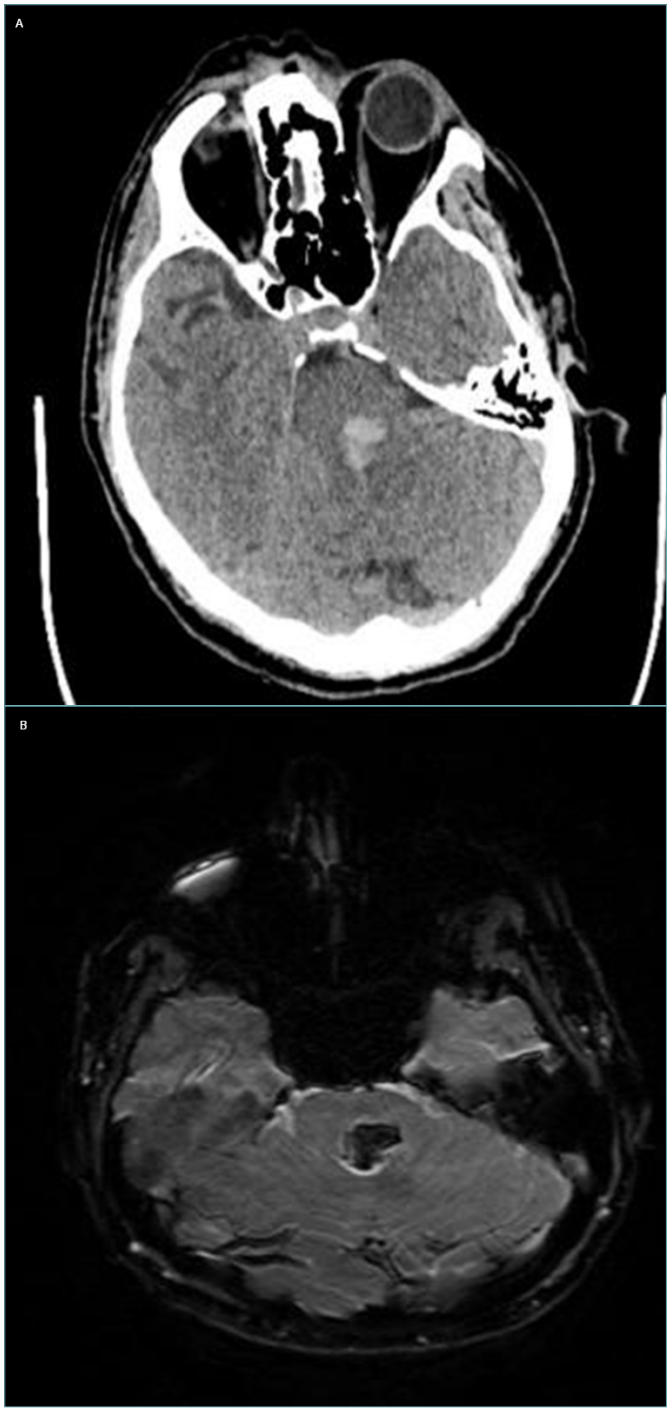

Figure 1a. Computarized Tomography (CT) consisted with pontin hemorrhage, **1b.** Hipointense area consisted with pontin hemorrhage on gradienr-echo T2 weighted MRI

DISCUSSION

The dynamic interaction between the MLF and PPRF are critical in regulating the horizontal gaze movements. However these regulatory structures are tightly located in the lower pontine tegmentum in a very small area leading to an accellerated functional impairment beyond the size of the lesion. Herein, the eight-and-a-half syndrome is a rare entity holding topological significance with its diverse clinical manifestation. For instance, eight-and-a-half syndrome might be also accompanied with some atypical clinical manifestations, such as vertical gaze palsy, however the typical clinical manifestation is a horizontal gaze palsy, central facial paralysis, hemiparesis and hemihypoesthesia defined in most of the cases, as was also described in our case. In this respect the most interesting ophthalmological finding is related to the involvement of PPRF and MLF leading to a clinical picture of a gaze palsy when looking to the contralateral side, where the nystagmus is seen in that eye and only the contralateral eye can abduct.[6,7]

Although ischemic stroke and demyelination are common etiologic factors, pontin hemmorrhage is an uncommon factor manifesting as eight-and-a-half syndrome.[3-5] Herein, there have been totally 21 cases presenting with eight-and-a-half syndrome in the literature related mostly to ischemic stroke and demyelinization with only few cases presenting with eight-and-a-half syndrome related to brainstem hemorrhage.[8] Similar to our case, a patient of pontine hemorrhage exhibited symptoms of left hemiparesis, right facial paralysis, and Fischer syndrome that improved within one month fitting well with the recovery pattern of our patient showing a considerable improvement in the clinical picture within the same time-frame.[9] Similarly, Yadegari et al.8 showed two patients presenting with eight-and-a-half syndrome related to right and posterior pontin ICH with a near identical clinical presentation characterized with an isolated eight-and-a-half syndrome and additional left hemiparesis. Our case's favorable recovery pattern align well with previous literature showing an earlier improvement in eye findings (i.e opthalmoplegia) defined also in previous case reports presenting with eight-and-a-half syndrome.[10]

To the best of our knowledge this is the one of few cases presenting with eight-and-a-half syndrome following the pontine hemorrhage showing similar clinical features and clinical prognosis as was previously reported by Xia and others.[9]

CONCLUSION

The eight-and-a-half syndrome is intriguing clinical syndrome due to its unique topological anatomy and clinical presentation demonstrating an initial improvement in ocular symptoms. Our case suggest a very rare diagnosis that should be considered if a patient is presented when gaze palsy is simultaneously seen with a facial paralysis especially when it comes to older patients with considerable vascular risk factors. Such an clinical appoach might require a special focus in these patients given the tight topological location of these regulatory centers in the pontin region.

ETHICAL DECLARATIONS

Informed Consent

All patients signed the free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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