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Subthalamic Nucleus Degeneration As A Dark Cause of Parkinson's Disease After Subarachnoid Hemorrhage: A Preliminary Experimental Study

Subaraknoid Kanamaya Bağlı Parkinson Hastalığının Karanlık Bir Nedeni Olarak Subtalamik Çekirdek Dejenerasyonu: Deneysel Bir Ön Çalışma

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Abstract

Aim: Although the subtahalamic nucleus degeneration has been accused of Parkinson's disease, the obscure roles of subtalamic nucleus degeneration induced by subarachnoid hemorrhages has not been adequately studied. The aim of the study is to examine the histopathological changes in the subthalamic nucleus after subarachnoid hemorrhage.

Material and Method: Twenty-one wild male healthy rabbits were included in this study. The test subjects were divided as: control (GI, n=5); SHAM 1.2 cc of saline injected (GII, n=6) and 0.75 cc of autologous blood injection into cisterna magna (GIII, n=10). They followed up for three weeks and sacrificed under general anesthesia. Vasospasm index (VSI) was estimated by the circle surface estimation method, degenerated neuron densities of the subthalamic nucleus were estimated by Stereological methods and analyzed by Mann Witney U test.

Results: Two rabbits dead in the study group were represented by meningeal irritation signs and unconsciousness. Prolonged QT intervals, ST depressions, and low voltage QRSs were noticed in GIII animals. Numerical documents of heart-respiratory rates (n/min), VSI values, and degenerated neuron densities of the subthalamic nucleus (n/mm3) as follows: 1.05±0.03/ 219±324/21±4/8±3 in GI; 1.75±0.23/209±14/15±4/16±4 in GII; and 2.03±0.14/175±19/19±5/123±21 GIII. P values between the VSI values and degenerated neuron densities of the subthalamic nucleus were nearly eqund: p<0.005 in GI/GII; p<0.0005 in GII/GIII and p<0.00001 in GI/GIII.

Conclusion: Subarachnoid hemorrhage causes spasm of the arteries supplying the subthalamic nucleus, leading to ischemic injury, and hydrocephalus leading to mechanical stress injury.

Keywords: Subarachnoid hemorrhage, Subthalamic nucleus, Parkinson's disease, Neuronal degeneration

Öz

Amaç: Subtalamik çekirdek dejenerasyonu Parkinson hastalığı ile suçlanmış olsa da, subaraknoid kanamaların neden olduğu subtalamik çekirdek dejenerasyonunun belirsiz rolleri yeterince çalışılmamıştır. Bu çalışmanın amacı, subaraknoid kanama sonrası subtalamik çekirdekte meydana gelen histopatolojik değişiklikleri incelemektir.

Gereç ve Yöntem: Bu çalışmaya 21 adet yabani erkek sağlıklı tavşan dahil edildi. Denekler şu şekilde ayrıldı: kontrol (GI, n=5); SHAM 1.2 cc salin enjekte edildi (GII, n=6) ve sisterna magnaya 1.2 cc otolog kan enjeksiyonu (GIII, n=10). Üç hafta takip edildiler ve genel anestezi altında sakrifiye edildiler. Vazospazm indeksi (VSI) daire yüzey tahmin yöntemi ile, subtalamik çekirdeğin dejenere nöron yoğunlukları Stereolojik yöntemlerle tahmin edildi ve Mann Witney U testi ile analiz edildi.

Bulgular: Çalışma grubunda ölen iki tavşan meningeal iritasyon bulguları ve bilinç kaybı ile temsil edildi. GIII hayvanlarında uzamış QT aralıkları, ST çöküntüleri ve düşük voltajlı QRS'ler fark edildi. Kalp-solunum hızlarının (n/dak), VSI değerlerinin ve subtalamik çekirdeğin dejenere nöron yoğunluklarının (n/mm3) sayısal belgeleri aşağıdaki gibidir: GI'de 1,05±0,03/ 219±324/21±4/8±3; GII'de 1,75±0,23/209±14/15±4/16±4; ve 2,03±0,14/175±19/19±5/123±21 GIII. Subtalamik çekirdeğin VSI değerleri ile dejenere nöron yoğunlukları arasındaki P değerleri hemen hemen eşitti: GI/GII'de p<0.005; GII/GIII'de p<0,0005 ve GI/GIII'de p<0,00001.

Sonuç: Subaraknoid kanama, subtalamik çekirdeği besleyen arterlerin spazmına neden olarak iskemik yaralanmaya, hidrosefali ise mekanik stres yaralanmasına neden olur.

Anahtar Kelimeler: Subaraknoid kanama, Subtalamik çekirdek, Parkinson hastalığı, Nöronal dejenerasyon

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INTRODUCTION

Recently, the tendency towards cerebral ischemic pathologies, which should be investigated in the etiology of Parkinson's disease, has been increasing. The obscure importance of cerebral ischemic injuries and subarachnoid hemorrhage (SAH) in the etiology of Alzheimer's and Parkinson's disease is increasingly being clarified.[1] It is now well known that the movement disorders seen in Parkinson's disease are caused by traumatic and spontaneous deep brain center hematomas.[2,3] From this top it is interesting that the subthalamic nucleus has not been adequately studied in subarachnoid hemorrhages. According to current knowledges, anosmia and ageusia is the earliest and most common symptom of Parkinson's disease.[4] As a matter of fact, pathologies that are the cause of the anosmia and ageusia like findings are now included in the list of causes.[5] Parkinson's disease is accompanied by neurodegeneration, neuronal loss, reactive gliosis and synuclein (Lewy bodies) accumulation in the substantia nigra. Dying neurons undergo phagocytosis by microglia or neuronophagia.[6] Blood brain barrier disruption is an important stimulator on the development of Parkinson disease.[7] Magnetic resonance images detected gray matter, hippocampus, amygdala and basal ganglia atrophy.[8] The subthalamic nucleus is anatomically and functionally connected with important regions of brain such as cerebral cortex, basal ganglia, brainstem, limbic system and also spinal cord.[9-11] For the functonal connectivity of subtahalamic nucleus, deep brain stimulation and focused ultrasound applications directed to that nucleus are becoming widely accepted as a therapeutic option in Parkinson's disease. Because they allows closed focal blood-brain barrier opening.[12] The blood flow of subthalamic nucleus can be constructed because of subarachnoid hemorrhage induced various mechanisms and obliged to ishemic insult.[13,14] The deep mechanisms of ischemic pathologies, which will be investigated more effectively in the future. Increasing research on the loss of olfactory taste signals as the cause, not the result, and understanding the deep mechanisms of ischemic pathologies will create profound revolutions in the etiology and treatment of Parkinson's disease.

MATERIAL AND METHOD

Ethical approval for this study was given by Atatürk University Faculty of Medicine, HAYDEK Ethics Committee (Date: 09/11/2022, Decision No: E-42190979-050.01.04-2200370519). This study was conducted on twenty-one, aged wild rabbits collected from mountains nourished in a natural farmers. Vital signs, body measurements were recorded. The test subjects were divided into three groups as: control group (GI, n=5); SHAM group 0.75 cc of saline injected (n=6) and study (GIII, n=10) object to SAH with autologous 0.75 cc blood injected in tapering doses into their cisterna magna [15]. After 6 hours of non feeding period before surgery and sacrified after general anesthesia with isoflurane by a face mask, 0.2 mL/kg; KetamineHCL, 150 mg/1.5 mL; Xylazine HCL, 30 mg/1.5 mL; and distilled water, 1 mL. Craniectomy performed and cerebral tissues were resected just after intracardiac formaline injection and then fixed in 10% of formaline solution. Microsections of caudate nucleus were taken as parallel with axial plane to observe neuronal numbers. Twenty sections (5µm) of subthalamic nucleus examined to estimate degenerated neurons with stereological methods. The specimens were stained with hematoxylene-eozine (H&E) and glial fibrillary acidic protein (GFAP). Stereological methods were performed as described in our previous manuscripts.

All values are expressed as the mean±SD. The differences between the degenerated neuron densities of subthalamic nucleus each groups were compared statistically. A one-way analysis of variance (ANOVA) followed by Boneferroni's Post Hoc Test was used to determine significant differences between the groups for Differences were considered to be significant at $p< 0.05$.

Clinical Results

Two of the test subjects died in study group with a clinic of by meningeal irritation signs and unconsciousness. Prolonged QT intervals, ST depressions, and low voltage QRSs were noticed in GIII animals. Numerical documents of heart-respiratory rates (n/min), degenerated neuron densities of subthalamic nucleus (n/mm3) as follows: 219±324/21±4/8±3 in GI; 209±14/15±4/16±4 in GII; and 175±19/19±5/123±21 GIII. P values: $p<0.005$ in GI/GII; $p<0.0005$ in GII/GIII and $p<0.00001$ in GI/GIII.

Histopathological Results

Histologically, cellular angulation, nuclear shrinkage, cytoplasmic condensation and cellular darkening were accepted as criteria for neuronal degeneration. Severe vasospasm has been studied in ethers feeding the subthalamic nucleus, and subthalamic nucleus destruction has also been associated with spasm developing in this vessels arc. Blood brain barrier destruction fndings such as capillary vasospasm, endothelial injury, astrocytic foot fragmentation, narrowed perivasculary spaces and perivasculary inflammation was moderately in SHAM animals and seriously study animals (**Figure 1-3**).

Numerical Results

Three rabbits dead in study group represented by meningeal irritation signs and unconsciousness. Numerical documents about degenerated neuron densities of subthalamic nucleus (n/mm3) as follows: 8±3 in GI; 18±4 in GII; and 123±21 GIII.

Statistical Results

P values: $p<0.005$ in GI/GII; $p<0.0005$ in GII/GIII and $p<0.00001$ in GI/GIII.

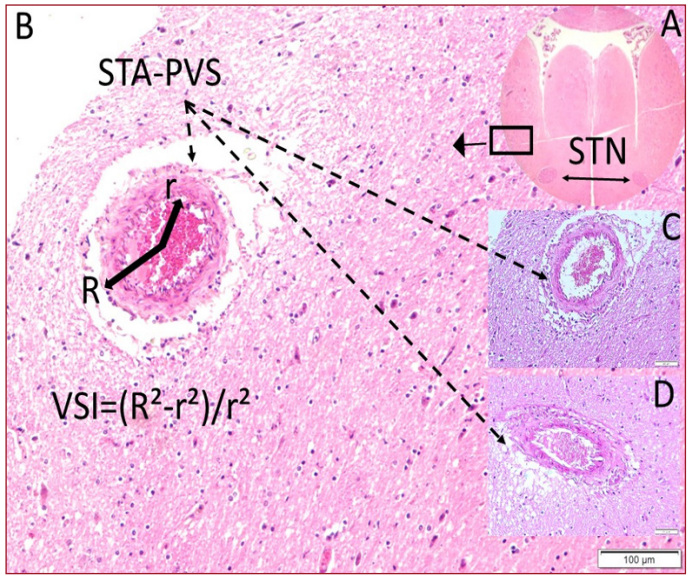

Figure 1: In a normal subject, subthalamic nucleus (STN) and the arterioles (STA) location (Square) feeding the subthalamic nucleus and the perivascular space (PVS) filled with cerebrospinal fluid are observed around it (A,B). A subject (C) belonging to the SHAM group has a moderately contracted arteriole with few blood elements and pial adhesions in its perivascular area. In a subject (D) belonging to the study group, an arteriole is significantly contracted and has many blood elements in its perivascular area and adhesions with pial thickening. At the same time, sponging and fluid increase in the brain parenchyma around the arteriole are clearly observed. Also, vasospasm index calculation method (VSI) is seen in figure B (LM, H&E; x4/A; x10/B-D).

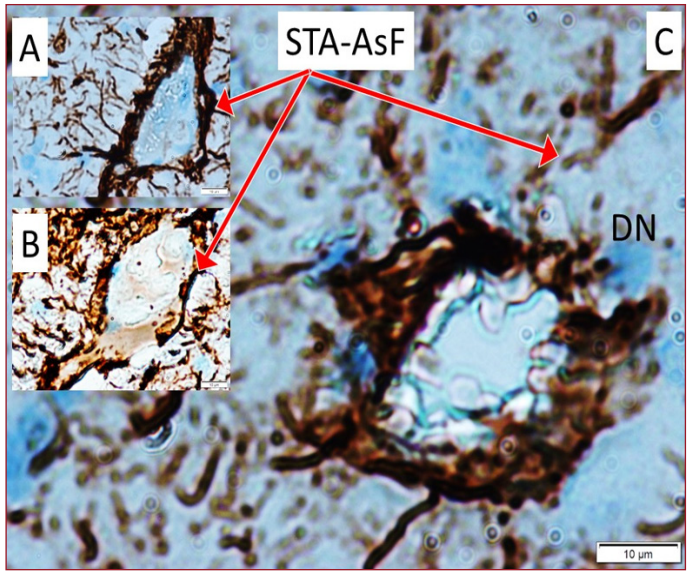

Figure 2: In a normal subject, arteriole (STA) feeding the subthalamic nucleus, astrocyte and astrocyte footplates (AsF) concentrated around the artery and perivascular space filled with cerebrospinal fluid are observed around it (A). In a subject (B) belonging to the SHAM group, a small number of astrocytes with reduced density around the artery and a narrowed perivascular space are observed alongside partially fragmented astrocyte astrocyte footpads (AsF). In a study subject (C), an arteriole is significantly contracted and has many blood elements and pial thickening and adhesions in its perivascular area. At the same time, degenerated neurons (DN) are clearly observed in addition to sponging and fluid increase in the brain parenchyma around the arteriole (LM, GFAP, x100/A-C).

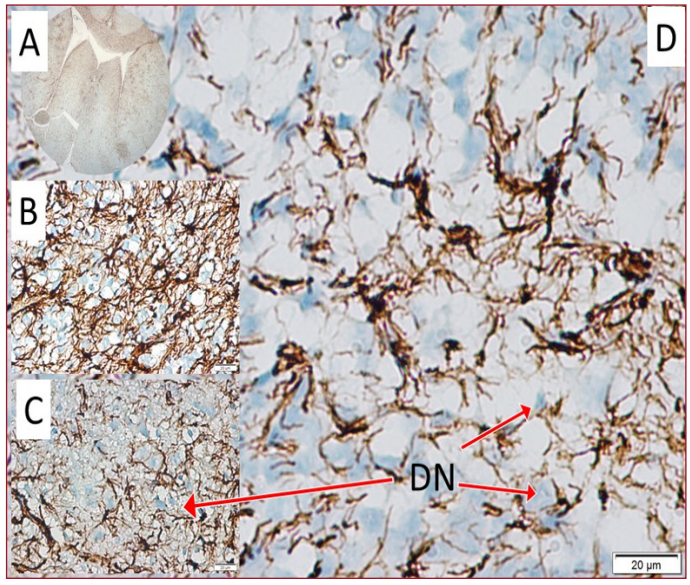

Figure 3: Localization of the subthalamic nucleus (STN) in a normal subject (A); Normal light blue neurons contained in the subthalamic nucleus and a large number of astrocytes with abundant pedicles surrounding them are observed (B). In a subject belonging to the SHAM group, a large number of slightly dark colored neurons and slightly dark blue neurons in slightly deformed condition and partially reduced branch and number astrocytes (C). In a subject belonging to the study group, in addition to the dark blue colored neurons (DN), which are considerably reduced and deformed, astrocytes with significantly reduced number and branches are observed.

DISCUSSION

The safest abstract findings such as anosmia and ageusia are considered as the most common and frequent nonmotor feature of Parkinson's disease.[4] However, the pathologies that are the cause of these findings are now on the list of causes.[5] As new studies on the etiology of Parkinson's disease imply that olfactory and taste disorders may be the initiating cause, not the finding; It will also reveal the responsibility of asymptomatic microischemic pathologies that disrupt the blood brain barrier. Although cerebral ischemic pathologies have not been taken into account sufficiently in the etiology of Parkinson's disease, recent studies have begun to focus on these pathologies. It has recently become clear that cerebral ischemic insults and subarachnoid hemorrhage should be considered as important etiological factors in the etiology of Alzheimer's and Parkinson's disease. It is well known that traumatic or spontaneous deep brain centers hematomas or ischemia can cause extrapyramidal sypmtoms.[1-3] It is very interesting that the subthalamic nucleus has not been adequately studied in subarachnoid hemorrhages. Anosmia and ageusia have been recognized as the earliest, most common, and most frequent non-motor symptoms of Parkinson's disease, and all theories are based on this idea.[4] However, it is observed that the views in the form of fault lines, which form the basis of these theories, are beginning to be shaken. Indeed, the pathologies that are the cause

of the findings are now included in the list of causes.[5] In the future, ischemic pathologies of the basal ganglia, which will be explained more effectively, will also take their deserved place in the etiology of Parkinson's disease. Indeed, disruption of the blood-brain barrier in the basal ganglia is an important initiating cause, which strengthens this theory.

Parkinson's disease is accompanied by neurodegeneration, neuronal loss, reactive gliosis and synuclein (Lewy bodies) accumulation in the substantia nigra. Dying neurons undergo phagocytosis by microglia or neuronophagia.[6] Blood brain barrier disruption is an important stimulator on the development of Parkinson disease.[7] Magnetic resonance images detected gray matter, hippocampus, amygdala and basal ganglia atrophy.[8] The subthalamic nucleus is anatomically and functionally connected with important regions of brain such as cerebral cortex, basal ganglia, brainstem, limbic system and also spinal cord.[9-11] For the functonal cönnectivity of subtahalamic nucleus, deep brain stimulation and focused ultrasound applications directed to that nucleus are becoming widely accepted as a therapeutic option in Parkinson's disease. Because they allows closed focal blood-brain barrier opening.[12]

The blood flow of subthalamic nucleus can be constructed because of subarachnoid hemorrhage induced various mechanisms and obliged to ishemic insult.[13,14] Because we think that the subthalamic nucleus is exposed to neurodegeneration in such events and loses its ability to work like the battery of the brain. Indeed, in a neurophysical sense, deep brain stimulation is actually nothing more than an electrical charge of the subthalamic nucleus. In this study, we discuss whether the subthalamic nucleus is exposed to any neurodegeneration in subarachnoid hemorrhages, which are important causes of movement disorders.

As well as considering the inability to smell and taste in the etiology of Parkinson's disease as a symptom rather than a cause; it is also very surprising that the ischemic damage of the basal ganglia, which we think has a serious role in the etiology, has not been adequately examined. As a team, we decided to illuminate this darkness as much as we could, and one of our first articles is this study. Although cerebral ischemic pathologies have not been taken into account sufficiently in the etiology of Parkinson's disease, recent studies have begun to focus on these pathologies. It has recently become clear that cerebral ischemic insults and subarachnoid hemorrhage should be considered as important etiological factors in the etiology of Alzheimer's and Parkinson's disease.[1] It is well known that traumatic or spontaneous deep brain centers hematomas or ischemia can cause extrapyramidal sypmtoms.[2,3] Parkinson's disease is accompanied by neurodegeneration, neuronal loss, reactive gliosis and synuclein (Lewy bodies) accumulation occurs in the substantia nigra. Dying neurons undergo phagocytosis by microglia or neuronophagia.[6] Blood barrier disruption is an important stimulator on the development of Parkinson disease.[7] Blood brain barrier dysruptions vascular inflammation are observed in the basal ganglia in Parkinson's disease.[16,17] Magnetic resonance images detected atrophy in gray matter, amygdala, hippocampus and basal ganglia.[8] Microscopic iron crystals which 3 to 8 nm in diameter can be found in degenerated brain regions. These electromagnetic field generator DADA-Black Holes, described for the first time in the literature, can delete neuronal information that has not been mentioned in the literature.[18] In this study, it was observed that subarachnoid hemorrhage caused both neuronal and glial cell loss in the subthalamic nucleus which hasnot been adequately investigated so far.

Iron mapping shows blood brain barrier dysruption in the basal ganglia in Parkinson's disease.[19] With age, iron accumulation in the basal ganglia increases and may contribute to the pathology of neurodegenerative diseases. Deterioration of the blood-brain barrier leads to iron accumulation, and an increase in iron in the basal ganglia increases the damage of the blood-brain barrier.[20]

Great goal in Parkinson's disease slowing down neurodegeneration. The goal of thermal lesions with focused ultrasound is to renormalize dopamine-driven basal ganglia abnormalities and temporarily open the blood-brain barrier.[21] The subthalamic nucleus is anatomically and functionally connected with some important regions such as zona incerta, brainstem reticular formation, cerebral cortex, substantia nigra, globus pallidus, amygdala, habenular nucleus, tegmental regions, limbic system, preoptic and periventricular area, stria terminalis, arcuate nucleus, mammillary nucleus, central gray, raphe and parabrachial nucleus, solitary tract nucleus cuneiform nucleus and nucleus locus ceruleus.[9-11] Focused ultrasound applications in low-intensity modality and neuromodulation, is becoming widely accepted as a therapeutic option, allows closed focal blood-brain barrier opening.[12] Buy, the peri-lead edema after bilateral deep brain stimulation is the result of severe microtrauma with blood-brain barrier disruption is an unwanted complication of deep brain stimulation.[22] On the other hand; mostly levodapa is used in the treatment of Parkinson's disease on behalf of dopamine because dopamine cannot cross the blood-brain barrier.[23] In patients using levodopa, the drug's lack of facility over time and the progression of the disease may be due to the fact that levodopa disrupts the blood-brain barrier. Because, it has been suggested that levodopa induced dyskinesia is associated with a disrupted blood-brain barrier.[24]

What Our Study Suggests About the Etiology of Parkinson's Disease

It is now certain that cerebral icemias disrupt the blood-brain barrier.[7] If so; disruption of the blood-brain barrier as well as the collapse of the intelligence, military and civil defense systems of the brain; it means that it has become vulnerable to internal and external attacks. The blood flow

of subthalamic nucleus is maintained by the perforforant branches of middle cerebral artery, posterior cerebral artery and anterior cerebral arteries in rats in order from most to least.[13,25,26] In this case, subthalamic nucleus ischemia due to subarachnoid hemorrhages also disrupts the blood-brain barrier in these structures. Because we have determined by immunohistochemical methods that structures similar to the blood-brain region in the subthalamic nuclei of the stones are damaged after subarachnoid hemorrhage. Subthalamic nucleus degeneration may be the source of psychological, psychiatric, mental disability, speech and comprehension disorders, as well as severe mental destructions and movement disorders that will soon be enlightened.

Limitations

This study does not include clinical data.

CONCLUSION

When we think of the subthalamic nucleus in terms of neurophysics, we conclude that this nucleus is an accumulator that specifically charges the basal ganglia. Because stimulating this core with a battery is actually a process to increase its weakened electrical potential. When we think of the subthalamic nucleus in terms of neurophysics, we conclude that this nucleus is an accumulator that specifically charges the basal ganglia. Because stimulating this core with a battery is actually a process to increase its weakened electrical potential. However, the fact that this procedure destroys the subthalamic nucleus over time weakens the popularity of the procedure.

Future Insights

By making more digital approaches to the software and hardware of the subthalamic nucleus in the initiation, continuation and termination of movements, more effective, easier and cheaper treatment methods will be developed with wirelwees signals.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval for this study was given by Atatürk University Faculty of Medicine, HAYDEK Ethics Committee (Date: 09/11/2022, Decision No: E-42190979-050.01.04-2200370519).

Informed Consent: All participants 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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