Striato-Kapsüler Enfarkta Bağlı Frontal Sendrom

Frontal Syndrome due to Striato-Capsular Infarction

Short title: Striatum and cognition

Türkçe Kısa Başlık: Striatum ve kognisyon

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Abstract

The frontal lobes have an important role in human cognition, including executive functions and social cognition. These domains are broadly subsumed under the rubric of frontal functions. Human cognition is subserved by large-scale neural networks, which have subcortical as well as cortical components. Therefore, the frontal syndrome should be understood as the clinical consequence of the damaged parallel frontostriatal circuits residing in the frontal lobes. While these manifestations may evolve progressively during neurodegenerative processes (e.g., frontotemporal dementia), they may appear acutely, full-blown after a strategically located infarction within a specific neural network, be it a cortical or subcortical hub. Here I report a case of a 70-year-old woman with acute onset of apathy, restlessness, and hyperorality. Mental status examination showed perseverations, decreased resistance to interference, and a left-sided hemineglect. Magnetic resonance imaging revealed a right striato-capsular infarction. An FDG-PET one year later showed large ipsilateral frontal and contralateral cerebellar hypometabolism compatible with diaschisis. Acute onset of a complex clinical presentation, including the majority of the functions of a single hemisphere, may be seen after a strategically located single cerebral infarction. Basal ganglia structures such as right-sided caudate and anterior putamen may host the hubs for the large-scale networks for executive functions, social cognition, and directed attention. Behavioral-cognitive syndromes should be evaluated as a manifestation of network damage.

Keywords: Frontal syndrome, basal ganglia, infarction, caudate nucleus, hyperorality

Özet

Frontal loblar yürütücü işlevler ve sosyal kognisyon gibi alanlar da dahil olmak üzere insan kognisyonunda önemli bir role sahiptir. Bu alanlar genel olarak frontal işlevler başlığı altında

toplanır. İnsan kognisyonu, kortikal bileşenlerin yanı sıra subkortikal bileşenlere de sahip olan geniş boyutlu nöral ağlar tarafından yürütülmektedir. Bu nedenle frontal sendrom olarak adlandırılan frontal işlev bozukluğu, frontal loblarda yerleşik paralel frontostriatal devrelerin hasar görmesinden kaynaklanabilir. Bu tezahürler nörodejeneratif süreçler (örneğin, frontotemporal demans) sırasında progresif olarak gelişirken, belirli bir sinir ağı içinde kortikal veya subkortikal bir bileşende stratejik olarak konumlandırılmış bir enfarktüsün ardından akut olarak da ortaya çıkabilirler. Bu makalede akut başlangıçlı apati, huzursuzluk ve hiperoralite nedeniyle değerlendirilen 70 yaşında bir kadın hasta sunulmaktadır. Mental durum muayenesinde perseverasyonlar, çeldiricilere azalmış direnç ve sol yarı mekan ihmali saptanan hastanın manyetik rezonans görüntülemesinde sağ striato-kapsüler enfarktüsü mevcuttu. Bir yıl sonra yapılan FDG-PET görüntülemesinde, diaşizis ile uyumlu büyük ipsilateral frontal ve kontralateral serebellar hipometabolizma gözlemlendi. Tek bir hemisferin fonksiyonlarının çoğunda bozulmayı içeren akut başlangıçlı bir hasar stratejik yerleşimli bir serebral enfarktüs sonrasında görülebilir. Sağ tarafta kaudat ve anterior putamen gibi bazal ganglia yapıları, yürütücü işlevler, sosyal kognisyon ve mekansal dikkat için büyük ölçekli ağların merkezlerini barındırabilir. Davranışsal-kognitif sendromlar, geniş boyutlu kognitif ağ hasarının bir belirtisi olarak değerlendirilmelidir.

Anahtar Kelimeler: Frontal sendrom, bazal ganglia, enfarktüs, kaudat çekirdek, hiperoralite

1. Introduction

The unique personality structure of a human individual that is subjectivity is determined by the frontal lobes. Personality change is a well-known consequence of frontal lobe damage, as taught by the inaugural case, Phineas Gage. Behavioral changes such as apathy, impulsivity, and cognitive changes in the executive functions observed in Gage and the following reported cases, were collectively coined as the "frontal syndrome." This term is used as a descriptor of the clinical presentation rather than strictly denoting the underlying anatomic structure. After the advent of computerized tomography, it was seen that some lesions outside the frontal lobes, mostly confined to the subcortical structures, such as the thalamus and basal ganglia, could also result in frontal syndrome. A paradigm shift occurred in understanding the brain-behavior relationship within the last quarter of the 20th century. The centrist-localizationist approach gave way to the network approach. This new approach enabled the conception of discrete large-scale neurocognitive networks composed of both cortical and subcortical components (1). At least two such networks subserving distinct executive and social cognitive functions are hosted by the frontal lobes (2). Based on current understanding, clinical neurology of the frontal lobes is parsed out as two sub-syndromes: A dysexecutive syndrome associated with the dorsolateral prefrontal cortex and a disinhibited-social cognitive syndrome associated with the orbito-medial prefrontal cortex (3). Hereby, I would like to report a case who not only presents two frontal subsyndromes concurrently but also a left-sided hemineglect after a right-sided striato-capsular infarction, thus illustrating how a relatively small subcortical area behaves as a bottleneck for entire hemispheric cognitive functions.

2. Case Report

A 70-year-old, right-handed woman with an elementary school education was brought to my attention in the Neurology outpatient clinic with a two-week history of behavioral change. Her granddaughter reported a flu infection two weeks earlier with daytime sleepiness and a concurrent acute onset of behavioral change. She saw her family physician, and the doctor prescribed her an antihistamine and a non-steroidal anti-inflammatory drug for 5 days. Flu infection had recovered in a week, but behavioral change and daytime sleepiness persisted.

Loss of spontaneity, admixed with restlessness, and an increase in appetite were the salient features of the behavioral change. She became reticent, almost unresponsive. The increase in appetite was particularly for sweets and manifested itself as late-night cravings. However, one morning she was found trying to eat a small plastic ball. When questioned, she replied: “these candies are not tasty anymore.”

She had no other cognitive-somatic neurologic symptoms. Her previous medical history included essential hypertension and idiopathic generalized epilepsy, which was present since her childhood. Reportedly, the seizure frequency had gradually subsided, decreasing to once in two years within the last 20 years. She did not have a seizure for at least one year. The drugs she used were listed as amlodipine, candesartan, hydrochlorothiazide, and carbamazepine 400 mg twice a day. She had no history of cognitive impairment and was independent in the activities of daily living.

In the neurological examination, she was awake. Her apathy and perseverative behaviors were readily observable. She was indifferent, and her affect was blunted. She could not sit still on the chair, repeatedly stood up and wandered around the room, or displayed utilization behavior manipulating various objects on the table. She had no sensory-motor neurologic signs. Mental status examination (MSE) consisted of a short battery of bed-side tests. The Mini-Mental State Examination (MMSE) was used as a general cognitive screening test. The patient’s score was 22/30, with a marked impairment in orientation to time and space. Luria’s Alternating Sequences test, a bed-side assessment of mental flexibility that consists of drawing alternating incomplete squares and triangles, revealed marked perseverations. The Clock Drawing Test (CDT), which assesses several cognitive skills, including visuospatial functions, abstract thinking, and planning, revealed left-sided unilateral neglect (Figure 1). MSE was concluded with the Frontal Assessment Battery (FAB). The FAB includes six bedside tests for executive functions. In FAB, she had difficulty comprehending similarities, reflecting impaired abstraction. Despite the repeated instructions reminding her of the rules, she kept recounting proper names in lexical verbal fluency (the second subtest). She was unable to perform Luria’s alternating hand series, another bedside test for mental flexibility (the third subtest). She showed complete insensitivity to interference by “conflicting instructions,” which is the fourth subtest (i.e., “Tap twice when I tap once.”). She had no inhibitory control in the fifth subtest, which is the Go-No Go task (i.e., “Tap twice when I tap once, do nothing when I tap once.”). Finally, she displayed environmental dependency in the sixth subtest, which is the prehension behavior (i.e., failure not to shake the extended hand of the examiner despite the explicit instruction: “Do not take my hands.”). Accordingly, she scored zero for FAB. Total Frontal Behavioral Inventory (FBI) is a 24-item questionnaire that assesses behavioral and personality changes via caregiver reports. It comprises a negative behavioral score (NBS) and a disinhibition score (DS), with higher scores indicating frontal lobe dysfunction. The patient’s score was 31 (NBS: 23, DS: 8).

Figure 1. Clock drawing revealed unilateral neglect.

Routine laboratory investigations included complete blood count, biochemistry, thyroid function tests, ferritin, folate, vitamin B12, hepatitis markers, syphilis markers, anti-HIV, chest x-ray, electrocardiogram. They were all within the normal range.

A magnetic resonance imaging (MRI) showed a large right striato-capsular infarction, which included the head of the caudate nucleus, anterior limb of the internal capsule (ALIC), and anterior putamen (Figure 2).

Figure 2. Magnetic resonance imaging shows an acute right striato-capsular infarction. A. Diffusion-weighted image, B. Apparent diffusion coefficient image, C. T2-weighted image.

She was diagnosed with probable vascular dementia (VaD) (the AHA/ASA criteria) or major vascular cognitive disorder (the VASCOG criteria) due to a strategically located cerebral infarction (4,5).

To evaluate the etiology of ischemic cerebrovascular disease, transthoracic echocardiogram and Doppler ultrasound imaging of the carotid and vertebral arteries were performed. Her echocardiogram was normal. Doppler ultrasound imaging showed atherosclerotic changes in carotid arteries that did not cause significant stenosis. Later, a computed tomography angiography (CTA) of cerebral arteries was performed, which showed atherosclerotic plaques without significant stenosis. I prescribed 300 mg of acetylsalicylic acid once a day. The family was instructed for the possible relative recovery in the following year and asked for follow-up visits.

She was brought back to the outpatient clinic ten months after the stroke. A family member noted that she had a daily intake of 7-8 liters of water. The polydipsia-associated low urine osmolality increased after fluid deprivation treatment. Serum Na⁺ level was 131 mg/dL. Polydipsia spontaneously recovered within a few weeks.

After one year in the routine follow-up examination, she was reportedly better. Her spontaneity had improved somewhat. She was calmer and displaying no bizarre eating behavior. Although still needing some prompting and instructions, she had become able to manage some domestic chores. In MSE, both scales sensitive to frontal lobe damage improved: the FAB score had increased to 10, and the total FBI score had decreased to 7 (NBS 7, DS 0), which indicated an obvious clinical improvement but not the complete recovery of frontal symptoms. Therefore, I retained her previous diagnosis (VaD). I ordered an 18C-Fluorodeoxyglucose (FDG)-PET scan, which revealed large prefrontal hypometabolism, including all its subsectors (dorsolateral and orbitofrontal) and hypometabolism in the left cerebellar hemisphere (Figure 3).

Figure 3. FDG-PET images showing right prefrontal and left cerebellar hypometabolism. Note asymmetric metabolism pattern in prefrontal subsectors and cerebellum: A. frontopolar, B. dorsomedial, C. and D. dorsolateral, E. ventrolateral, F. and G. Cerebellar.

3. Discussion

This is a case report of a lady with an acute onset of frontal lobe syndrome and a left-sided hemineglect due to a right-sided striato-capsular infarction. I used MMSE, Luria's Alternating Sequences test, and CDT as general screening tools and FAB and FBI for evaluating the frontal findings in detail. FBI is a 24-item questionnaire that assesses behavioral and personality changes via caregiver reports, and FAB is a group of bedside tests for executive functions.

Her cognitive status before the stroke was normal as her relative stated that she had no history of cognitive impairment and was independent in the activities of daily living. The significance of the accompanying idiopathic epilepsy had apparently decreased over the years.

The patient had no pyramidal findings as the posterior limb of the internal capsule was spared being outside the vascular territory of the striatocapsular artery, which pyramidal tracts travel from the cortex through.

The disconnection approach to the brain-behavior relationship was introduced by Norman Geschwind, who was the founding father of behavioral neurology (6,7). This approach was the culmination of the observations that the impairment of higher mental functions arises not only due to damage to the critical centers of the brain but also by damage to the conduction pathways that interconnect these critical centers. The disconnection approach resulted in a paradigm shift in the conception of brain-behavior relationship; the centrist approach became outmoded and gradually gave way to the new paradigm that is the large-scale neurocognitive networks that comprise not only cortical hubs but also subcortical components, such as association nuclei of the thalamus and different sectors of the dorsal and ventral striatal structures (1,8).

Five major frontal-subcortical circuits defined by Alexander et al. in the primate brain revolutionized the conception of basal ganglia (9). After that historical paper, striatal structures other than putamen, which are caudate with its dorsolateral and ventromedial sectors, and ventral striatum were associated with non-motor complex mental functions, such as executive control, social cognition, and reward-seeking. The defined five parallel circuits link specific regions of the frontal cortex with a posterior to the anterior gradient to the specific regions in the basal ganglia and the thalamus and constitute a cortico-striato-pallido-thalamo-cortical closed-loop (2).

Recently Graff-Radford et al. discussed in detail the cognitive and behavioral consequences of striatal lesions such as apathy, loss of empathy, and hypersexuality with two cases (10). Similar to the present case, the authors reported hypometabolism in the prefrontal cortex and contralateral cerebellum. The finding of ipsilateral frontal and contralateral cerebellar hypometabolism in FDG-PET demonstrates the widespread functional network disruption due to relatively small-scale subcortical damage. Functional MRI studies have shown that the cerebellum contributes to the executive control, salience network, default mode network, and a lesser degree to the left fronto-parietal network (11).

Mesulam et al. suggested two models for the lesion-symptom relationship: one based on disconnection and the other on diaschisis. According to the disconnection model, a stroke lesion includes not only the cortex but also deep white matter tracts and causes more deficits than the cortical lesion by itself may cause. On the other hand, diaschisis refers to a change of function in a brain region that is not primarily damaged but lost or decreased its function because it is critically connected to the distant and damaged brain area for functioning. Loss of function is not caused by simple disconnection (*i.e.*, damage to the connecting pathway) but a postsynaptic depression of neuronal activity due to loss of input (12). The most likely candidate for the underlying mechanism could be the diaschisis in our patient.

The patient had a right striato-capsular infarct, which includes the ventral and dorsal caudate nucleus and the anterior putamen. While the ventral caudate participates in emotional and affective aspects of behavior such as reward processing, the dorsal caudate participates in cognitive and executive functions, such as spatial working memory. The anterior putamen has been attributed to social and language function, while the posterior putamen that receives projections from the sensorimotor cortex has been attributed to sensorimotor processing (10). This patient had no sensory-motor signs, and the posterior putamen was intact. Having had a right-sided striatal infarction, including the anterior putamen, the patient had no aphasia as expected from a left-sided striatal infarction but displayed hemispatial neglect. The subcortical structures that partake in Mesulam's definition of the large-scale distributed network for spatial attention are the medial pulvinar nucleus of the thalamus, striatum, and superior colliculus (1). Later Karnath et al. reported

that the putamen, the pulvinar, and to a lesser degree, the caudate nucleus are associated with spatial neglect (13). It may be suggested that the right anterior putamen and probably dorsolateral caudate nucleus may involve in spatial attention.

Acute confusion, abulia, loss of spontaneity, apathy, impulsivity, amnesia, aphasia, memory impairment, contralateral neglect, agitation, hyperactivity, depression, and hallucinations were reported to be the clinical findings in acute caudate lesions (14,15). Although abnormally increased craving for sweets has been reported before for caudate nucleus lesions (10), to my knowledge, there was no report of mouthing of inedible objects, which was apparent in this case in a very colorful way, almost similar to a Kluver-Bucy-like hyperorality.

The major limitation of this case report is the lack of resting-state imaging (rs-MRI) data, which would directly support the above-mentioned network approach revealing dysfunctional intrinsic connectivity networks. Yet, one must remember that rs-MRI is still essentially a group comparison tool, which is not undisputedly adapted for single-patient interpretation.

Conclusion

A partial hemineglect and apathetic-dysexecutive subsyndrome were evident in this case. Although she was not overtly disinhibited despite some purposeless hyperactivity and utilization behavior, I think that hyperorality could be taken as evidence of the disinhibited-social cognitive subsyndrome. I suggest that the relatively small subcortical striato-capsular territory infarction, damaging the striatal structures and ALIC, which carries the interconnecting and intersecting neural fibers of the said neural circuits, thus behaving as a bottleneck, could explain the full-blown right-hemispheric cognitive syndrome.

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