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When A Stroke Is Not A Stroke –Reversible Splenial Lesion Syndrome - RESLES – Case Report

Dominika Tatar[1]*, Bogusława Bocian[2], Krzysztof Świerzy[1], Karina Badura Brzoza[1]

[1]Clinical Department of Psychiatry, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice

[2]Clinical Department of Psychiatry, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Research Circle

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***Corresponding author:** Dominika Tatar, Clinical Department of Psychiatry, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice.

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The corpus callosum plays an important role in the brain function. The trunk is the part of the corpus callosum, in which, in the course of various diseases, there may be temporary, reversible (RESLES), as well as partially reversible and irreversible changes. This article discusses the differentiation of RESLES and other conditions that proceed with changes in the corpus callosum accompanied by the clinical symptoms. Moreover, this article is also a case report of a patient in whom the above changes appeared in the NMR. 20-year-old patient with the diagnosis of Ehlers-Danlos syndrome type VI was admitted to the psychiatric hospital in an emergency procedure due to psychomotor agitation, refusal of food and fluids intake, with delusional statements of a grandiose nature as well as ideas of self-reference and missionary ones and auditory hallucinations. The brain MRI revealed an non-specific hyperintense area in T2-weighted images in the corpus callosum lobe, which was significantly hyperintense in DWI sequences, and in APC sequences had a reduced signal intensity, without bleeding features. After those test results the hypothesis of a subacute ischemic stroke of the corpus callosum was made. In the control MRI, changes in the corpus callosum completely regressed, thus excluding ischemic etiology and favoring the diagnosis of RESLES. During hospitalization, the patient experienced significant fluctuations in his mental state with the typical symptoms of schizophrenia. Clear and stable improvement was obtained after using olanzapine in the form of intramuscular injections with prolonged action. Finally the patient was diagnosed with paranoid schizophrenia.

Keywords: RESLES stroke corpus callosum schizophrenia

Introduction

The corpus callosum (Latin corpus callosum) is the largest subcortical commissural fiber. It includes the trunk of the corpus callosum (Latin truncus corporis callosi), the rostrum (Latin genu corporis callosi), genu (Latin rostrum corporis callosi), isthmus (Latin lamina rostralis) and the most posterior and thickened part - splenium (Latin splenium corporis callosi) [1] It has an important role in the functions of the brain. It creates a bridge between both hemispheres of the brain containing intersecting axonal fibers, which in the lobe of the corpus callosum are projections from the occipital-parietal and temporal cortex [2,3]. So far, the function of the corpus callosum has not been fully understood, but studies have shown that its damage may result in the disconnection of the cerebral hemispheres with disruption of higher cortical functions and disturbances in the stream of consciousness [3].

Changes in splenium are described in many diseases - irreversible or partially reversible are related, among others, to isolated corpus callosum infarction (ICCI), head region injuries, congenital malformations (agenesis / dysgenesis of the corpus callosum, lipoma), metabolic disorders (Wilson's disease, X-linked adrenoleukodystrophy, Krabbe's disease), neoplastic tumors (glioblastoma, lymphoma). Transient, reversible changes occur in viral, bacterial and parasitic infections, during therapy with the use of metronidazole or 5-fluoro-uracil, in the case of toxicity or discontinuation of antiepileptic drugs treatment, especially levetiracetam, carbamazepine and valproates, as well as in states of hypoglycaemia, hyper- or hyponatremia and in high-mountain

cerebral edema or in patients with Wernicki's syndrome [2,4,5-7]. The clinical and radiological condition associated with these changes was defined as "Reversible splenial lesion syndrome" (RESLES) [2,3]. The literature also includes the terms "mild encephalitis / encephalopathy with reversible splenium lesion" (MERS), "boomerang lesions" and "corpus callosum diffusion limited cytotoxic lesions" (CLOCC). The term RESLES seems to be the most appropriate one because it emphasizes the reversibility of changes and their localization [3]. Performing brain imaging with the use of magnetic resonance imaging is an important diagnostic tool visualizing the extent of changes within the corpus callosum. Imaging of the CNS together with the data obtained from the patient's medical history and physical examination are important for the diagnostic and therapeutic process, and also allow to establish the final diagnosis and select the appropriate treatment [Tab. 1.].

Table 1. MRI imaging of lesions with localization in the corpus callosum [3-9]

CNS pathology	Characteristic of lesions in CNS	Location	Signal intensity	Clinical symptoms
RESLES	round, ellipsoidal, fusiform	bilateral, symmetrical in splenium	hyperintense T2, FLAIR, hypointense T1, diffusion limitation DWI / ADC	depending on the cause
Ischemic stroke	irregular, patchy	lateral, asymmetrical in splenium	T2 hyperintense, FLAIR, DWI, DWI / ADC cytotoxic edema	depending on the ischemic area of the brain
Swelling of the corpus callosum lobe	rim	central, ventral in splenium	hyperintense DWI	changes in mood, behavior, and decline of cognitive abilities
Wilson's disease	various	bilateral, symmetrical in splenium; nuclei basales, thalamus, mesencephalon, most Varola, dentate gyrus	hyperintense DWI, FLAIR, no hypointense ADC, white matter edema	psychiatric, neurological, hepatic, renal, Kayser-Fleischer rings in the cornea
X-linked adrenoleukodystrophy	various	Splenium, may pass to the white matter of the parieto-occipital area	hyperintense T2, FLAIR or variable contrast enhancement	visual disturbances, behavioral disturbances, emotional instability, occurring from childhood
Krabbe disease	Globoid cells	Splenium, cortico-spinal pathways and white matter of parietal lobes	T2 hyperintense axial, T1 hypointense sagittal, FLAIR, DWI, ADC	in early childhood in the form of irritability, psychomotor regression, loss of contact with the environment
Glioblastoma multiforme	irregular large mass with infiltration and necrosis	Splenium, supratentorial white matter	hyperintense sagittal T1 and axial T2	depending on the location of the tumor; additionally headache and dizziness, visual disturbances
B cell lymphoma	irregular mass	along the perivascular spaces, splenium	hyperintense center and hypointense rim in axial FLAIR, isointense T2, iso- or hypointense T1, DWI, ADC	Depending on the location of the tumor, symptoms typical of lymphoid neoplasms
Lipoma	often accompanied by agenesis or dysgenesis of the corpus callosum	mostly in the midline of the splenium	hyperintense T1 with slight diffusion limitation in DWI and ADC	usually asymptomatic; accidentally discovered on imaging
Post-traumatic lesions	various	Asymmetrical with a midline shift	DWI and ADC diffusion's limitation	Hematoma, swelling of the brain and complications associated with it
Intracranial hypotension	various	stump-shifted downward splenium, displacement of the brain, expansion of the veins and sinuses of the dura mater and its strengthening	isointense FLAIR	headache that decreases on tilting, short-term memory impairment, dementia, somnolence and coma

In the acute phase RESLES, a local increase in signal intensity is seen in the DWI sequence, with a decreased signal on the ADC map, consistent with cytotoxic edema. The abnormal area is hyperintense in the T2 and FLAIR sequences and hypointense in T1, surrounded by normal axon junction. The time of development and disappearance of changes in RESLES varies - in the case of infections, they are most often visible from the first day and gradually disappear within 1-2 weeks, while in the case of the toxic effect of an antiepileptic drug, they may persist for up to three weeks [3,7].

The most common prodromal symptom of RESLES is fever, and the most frequently observed clinical picture is disturbance of consciousness with subsequent full-blown delirium and seizure which disappear within a month [3, 11, 12].Other symptoms include: headache, disorientation, confusion, hallucinations and other psychotic symptoms, ataxia, dysarthria, disconnection syndrome, coma [6, 12-15].Particular attention should be paid to the disconnection syndrome, also known as split-brain syndrome or dyscirculation syndrome, which is known e.g. as a complication of calosotomy (a neurosurgical procedure involving cutting the corpus callosum, used mainly in severe forms of drug-resistant epilepsy) [16], however, it may also be present in RESLES. In its course, the coexistence of several independent consciousnesses in one brain was observed, visual integration disorders (each hemisphere independently perceives the contralateral field of view, however, proper functioning of the corpus callosum is necessary for integration. In the case of disturbance of its functions, the patient is not able to compare two objects when each of them is presented in a different field of vision - right and left), limited reception of stimuli from the non-dominant hemisphere, tactile and / or visual anomy (inability to identify previously known objects, concepts), alien limb syndrome, confusion, hallucinations, psychosis, motor aphasia, mutism, akinesia and hemiplegia [3,6,12-16].

As mentioned above, these symptoms are non-specific and may appear in many other diseases. At the same time, not always in the case of their occurrence, MRI of the brain is performed, especially in cases where the result of the CT scan of the head is normal. Meanwhile, the available clinical trials have shown, among others, that in 5.71% of hypoglycemic patients and in 1.35% of patients with influenza experiencing intermittent episodes of disturbances of consciousness, there are changes characteristic of RESLES [3, 13-15].

The aim of the study is to present the difficulties related to the diagnostic and therapeutic management of patients with impaired consciousness and to emphasize the role of brain imaging using magnetic resonance imaging.

Case Report

Man, 20 years old, BMI = 13.88, under the care of the Genetic, Cardiology and Orthopedic Clinic due to the suspicion of Marfan syndrome, and then Ehlers Danlos syndrome type VI caused by a homozygous mutation in the PLOD1 gene, from pregnancy I, delivery I with uncomplicated course . At birth, length 58 cm, body weight 2800 g, APGAR 6/9; physical examination revealed high articular laxity and clubfoot. Motor development was delayed; at the age of 10 months, MRI of the brain was performed, which revealed hypoxic-ischemic changes. Chest deformity was also observed, which worsened with age, while in EMG examination, primary myopathy was excluded. In the following years, he was diagnosed with bilateral hyperopia with hyperopic astigmatism, and when he was 13 years old the patient underwent amputation of the left lower limb at the level of the left thigh due to a rupture of the left popliteal artery aneurysm. The patient also had two spontaneous pneumothoraxes - for this reason, surgery was performed to remove the apex of the lung.

The patient was brought to the Hospital Emergency Department (HED) by the Medical Rescue Team accompanied by his mother. According to the family reports, during the one-week period the patient had persisted bizarre behavior, significant psychomotor agitation, religiously motivated refusal to drink and eat, delusional statements with the content of a mission, grandiose fantasies, ideas of self-reference, and auditory hallucinations. The symptoms were preceded by a two-week period of anxiety and insomnia, which the family associated with his difficult personal situation (a friend's suicide attempt), simultaneously denying the use of psychoactive substances and recent head injuries. The day before the admission, the patient attacked a paramedic in HED.

Due to the condition that did not allow the patient to express his / her informed consent, he was admitted to the ward under Art. 22 sec. 2a UoOZP [17]. On admission: conscious, without logical contact, disoriented about the place and time, with psychomotor agitation, in an accelerated drive, unstable mood, with disturbed form and content of thinking in the form of disorganization, paralogy, delusional statements of a grandiose nature as well as religious and missionary ones without structured content. Additionally echolalia, auditory and visual hallucinations were observed. A complete physical examination was impossible due to the patient's lack of cooperation; the aberrations from the normal state revealed features of dehydration (drying up mucous membranes), deformation of the chest, condition after amputation of the left lower limb at the thigh level. A preliminary diagnosis of consciousness disorders of unknown etiology was made for differentiation from acute paranoid syndrome on the basis of schizophrenia.

The results of the obtained laboratory tests are presented in the table below.

Table 2. Laboratory tests performed on a patient

Hospitalization day	1	2	3	7	Reference values
WBC [x10^3/µL]	17,81	17,29	10,10	12,42	4,00 – 10,00
RBC [x10^6/µL]	5,83	5,04	4,67	4,87	4,50 – 5,90
HGB [g/dl]	18,6	16,4	15,3	15,8	13,5 – 17,5
HCT [%]	53,1	46,5	42,6	43,8	40,0 – 51,0
PLT [x10^3/µL]	306	257	201	254	150 – 400
Na+ [mmol/l]	150,1	151,1	143,1	142,9	136 – 146
K+ [mmol/l]	4,31	3,66	3,50	3,68	3,5 – 5,1
Glucose [mg/dl]	90	79	-	-	70 – 100
Creatinine [mg/dl]	0,7	0,73	0,34	0,54	0,67 – 1,17
ALT [U/l]	38,6	-	-	27,9	10,0 – 37,0
AST [U/l]	154,5	-	-	31,1	10,0 – 37,0
CK-NAC [U/l]	7391	8928	6121	305	25 – 175
CRP [mg/l]	17,40	-	9,8	29,90	0,00 – 5,00

On the first day of hospitalization, the use of the direct means of the physical coercion was performed in the form of immobilization with magnetic belts and the patient was placed in an observation room, catheterized and vital parameters were monitored. The treatment included haloperidol (5 mg / ml / d) and lorazepam (4 mg / d) in the form of i.m injections and parenteral hydration. Control tests were performed, the results of which indicated a further increase in leukocytosis, hypernatremia and an increase in creatine kinase levels. The concentration of troponin I was 21.30 [mg / L], CK-MB 64 [U / L], D-dimers 1801.37 [ng / ml]. The consulting internist excluded acute coronary syndrome and pulmonary embolism. No signs of bacterial or viral infection were observed. Computed tomography of the head showed no abnormalities, chest tomography showed a large deformation of the chest with a significant reduction in the sagittal dimension and the wedge flattening of the L1 vertebrae with probable post-traumatic etiology. Enoxaparin 40 mg / 0.4 ml s.c. was included in the treatment, parenteral hydration with 5% glucose solution was applied. From the third day of stay, these parameters were gradually stabilizing. Slow resolution of disturbances of consciousness and the presence of persecutory statements and delusional behavior, influence and revealing thoughts, as well as magical thinking and associative association, resulted in the decision of modifying the treatment. Olanzapine was used in the form of i.m injection. The intensity and fierceness of the above-mentioned symptoms in the clinical picture and the appearance of disturbances of consciousness, despite the correct result of the CT scan of the head, did not allow for the complete exclusion of the stroke process. MRI of the brain was performed with intravenous administration of a contrast agent, showing streaked, bilateral, T2-intense paraventricular areas with a predominance of changes on the left side with a significant reduction in the volume of the left paraventricular white matter and distortion of the outline of the lateral ventricles - mainly the left - with possible hypoxic-ischemic etiology and in lobe of the corpus callosum, a hyperintense area uncharacteristic in T2-weighted images, which was significantly hyperintense in DWI sequences and had reduced signal intensity in APC sequences.

No bleeding features were visualized in this area and a hypothesis of subacute ischemia within the 12x4 mm corpus callosum in the transverse plane was put forward. In view of the obtained results, the patient was consulted neurologically and an angio-CT examination of the intracranial arteries was performed, which revealed asymmetry of vertebral arteries with the dominant right artery, but no signs of vascular malformation were found. Due to the patient's lack of cooperation, as well as unambiguous indications to be performed, the lumbar puncture was abandoned. In the course of further diagnostics, the patient was diagnosed with hypovitaminosis D3 (14.6 ng / ml), while the antiphospholipid syndrome was excluded (the level of p / cardiolipin antibodies in IgM and IgG classes <2.00 U / ml, the level of p / β -2-glycoprotein antibodies) in IgM and IgG <2.00 U / ml). The patient's stay in the ward was complicated by an infection of the urinary tract with Escherichia coli ESβL on the 14th day of hospitalization. Pharmacotherapy was carried out in accordance with the antibiogram, improving the physical condition.

During the patient's stay in the ward, due to the lack of cooperation, the treatment was carried out with olanzapine in the form of intramuscular injections (up to 20 mg / day), and then after the reduction of acute productive symptoms, in the oral form (up to 20 mg / day). After a few days, a significant deterioration of the mental state was observed (probably resulting from not taking medication by the patient), in the form of intensified delusional content, mainly of a religious nature, hallucinations and psychomotor agitation. The patient refused to take medication; auto- and allo-aggressive behaviors were present, therefore, the use of the direct means of the physical coercion was performed again in the form of immobilization with magnetic belts. Pharmacotherapy was continued with reintroduction of olanzapine (up to 20 mg / day) in the i.m. form, together with haloperidol (4 mg / day) in the form of an oral solution and lorazepam (2 mg / day) p.o. Eventually, a marked improvement in the mental state was achieved and it was decided to continue the treatment with intramuscular olanzapine injections with extended release (300 mg every 14 days). After 6 weeks of hospitalization, the patient underwent another MRI of the brain, which showed complete regression of changes in the corpus callosum, thus excluding ischemic aetiology and favoring the diagnosis of RESLES. In addition, the MRI image of the brain was comparable to the previous examination.

The patient was discharged home with improvement in the intensity of psychotic symptoms and accompanying behavioral disorders. On the day of discharge, the patient was clearly aware, comprehensively oriented, calm and adjusted in behavior, did not seem hallucinating, and did not spontaneously express delusional content. Taking into account the entire clinical picture (with the dominant productive symptoms characteristic of the endogenous process) and the results of the research, the diagnosis of paranoid schizophrenia was made and it was recommended to continue pharmacotherapy on an outpatient basis under ambulatory care.

Discussing

RESLES is a rare unit with a wide clinical and radiological spectrum occurring in the course of many diseases, metabolic disorders and other disease states [3-7,12,18]. In most cases, clinical symptoms tend to improve or even completely resolve, however, in patients with severely disturbed consciousness, the prognosis is unfavorable [13-15,18].In the case presented above, in the performed CT scan of the head, no deviations were found. Due to the data obtained from the history of the sudden onset of symptoms and their duration, nonspecific laboratory test results and severe clinical course with the presence of disturbed consciousness, it was decided to perform a head MRI, which showed changes in the corpus callosum characteristic for a previous ischemic stroke [2,4,8]. Previous studies were not available for comparison, therefore, based on the morphology, distribution and coexistence of changes in the paraventricular white matter and the clinical picture, a hypothesis about a history of ischemic stroke was made [4, 18]. On the other hand, the control MRI showed complete regression of changes in the corpus callosum, which gave grounds for the diagnosis of RESLES. [3-5,7-9,11,18]. In the clinical picture, at the same time, there was no complete withdrawal of positive symptoms typical for schizophrenia. There were logical thinking disorders with additional distraction, the occurrence of hallucinations and delusions, disorganization and bizarre behavior, psychomotor agitation, and lack of criticism towards one's own judgments. The above-mentioned symptoms began to improve only after intensive antispychotic treatment.

Taking into account all the available information, it seems that in the described case typical symptoms of the schizophrenia picture and symptoms related to the reversible changes in the corpus

callosum (RESLES) could coexist. It is difficult to determine what could have been the cause of the above-mentioned changes and whether they could have influenced the clinical condition of the patient, which in the initial period of hospitalization seemed to indicate an acute cerebral cause, despite patient's medical history suggesting a prodrome of the schizophrenic process [15]. The complete withdrawal of changes in the NMR image, the presence of typical symptoms of the schizophrenia image, the patient's age of the episode onset, the rapidity of the disease development and the improvement of the clinical condition after the initiation of antipsychotic drugs made the final diagnosis of paranoid schizophrenia [15,19].

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