Osmotic demyelination syndrome: central pontine and extrapontine myelinolysis in a patient in the early postpartum period. Clinical observation

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The article presents a review of the literature and a description of a clinical case of osmotic demyelination syndrome manifested by pontine and extrapontine myelinolysis in a 36-year-old woman after her third surgical preterm delivery. The reasons for the development of a demyelinating lesion of the central nervous system are discussed, and clinical cases described in world literature sources are presented. An analysis of the pathogenesis of the development of this disease in women during pregnancy, childbirth, and lactation is provided. The importance of this period in a woman's life as an independent significant risk factor for the development of osmotic demyelination syndrome is discussed.

Keywords: *central pontine and extrapontine myelinolysis; osmotic demyelination syndrome; pregnancy; childbirth.*
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Central pontine myelinolysis (CPM) is characterized by a demyelinating lesion of the structures of the central nervous system against the background of electrolyte and metabolic disorders. It was first mentioned in the work of R.D. Adams et al. [1], who described in 1959 the "osmotic demyelinating syndrome" in patients with chronic alcoholism. The name "central pontine myelinolysis" appeared much later, when pathomorphology of the process was described, and destruction of the myelin sheath of oligodendrocytes was revealed, caused by a rapid increase in serum osmolarity in other very different pathological conditions, including renal and hepatic insufficiency, diabetes mellitus, pituitary adenoma, Sheehan syndrome, systemic lupus erythematosus, gastroenteritis, urea metabolism disorders, acute viral infections, immunodeficiency syndrome, long-term diuretic therapy, bulimia, malnutrition, etc. [2]. The term "myelinolysis" was used intentionally to emphasize the predominance of non-inflammatory myelin lesions compared to other neural structures.

The pathological process usually begins in the area of the pons Varolii and the white substance of the cerebral hemispheres. At the same time, involvement of the brain structures of extrapontine localization, such as the inner capsule, visual tubercle, corpus callosum, basal ganglia, cerebellum, and cerebral peduncles is possible. Due to the more extensive localization of disorders noted in the description of cases of "pontine myelinolysis" associated not only with the involvement of the pons Varolii, the term "osmotic demyelination syndrome" (ODS) was adopted, combining CPM and extrapontine myelinolysis (EM) [3]. There are cases of description of central EM without pontine myelinolysis [4].

To date, there are no accurate epidemiological data on the prevalence of ODS. One of the retrospective studies which most researchers refer to, included an analysis of data from 665 patients over a five-year follow-up period who were admitted to the intensive care unit with the diagnosis of ODS. This study showed that the frequency of its detection in the selected population is about 2.5% [5]. At the same time, it should be noted that the actual prevalence of this pathology is probably much higher, since in clinical practice ODS is not often indicated as an independent diagnosis, as there is not always a clear distinction between ODS and the underlying disease. In addition, it is difficult to establish an accurate diagnosis in the absence of magnetic resonance imaging (MRI), the introduction of which has led to a significant increase in diagnosed cases of ODS with the demonstration of both symptomatic and asymptomatic manifestations.

Previously, it was believed that the disease led to death in 90–100% of cases. Currently, the prognosis has improved as a result of the introduction of timely diagnostics based on MRI technologies. The work of A. Danyalian and D. Heller [6] showed 94% survival, but 25–30% of patients remain incapacitated after the disease. P.B. Rao et al. [5] wrote about the development of a vegetative state in 18% of patients and a mortality rate of 12%. According to R.J. Martin [7], mortality in CPM reaches 40–50%. However, most researchers currently agree that the demyelinating process in CPM can be reversible, accompanied by the restoration of functions even in patients with a severe course of the disease [8]. The risk group for adverse prognostic outcomes includes patients with serum sodium levels <120 mmol/L, hypokalemia and low values of the Glasgow Coma Scale during hospitalization. Improvement of prognostic outcomes is focused on early recognition of those patients who have an increased risk of developing ODS, avoiding rapid correction of sodium levels, and timely diagnosis of

the patient's condition. Favorable prognostic outcomes also include the prevention of secondary complications, such as aspiration pneumonia, urinary tract infections or deep vein thrombosis [6].

The pathogenesis of CPM, despite considerable interest in this problem, has not been studied enough. Common to all publications is a description of the development of CPM as a result of a severe illness and/or its treatment. In most studies covering the period up to the mid-1980s, chronic alcohol abuse was considered a leading etiology (40% of cases). In later publications, it was indicated that the cause of the development of this pathology may also be electrolyte imbalance [3]. Hyponatremia associated with a rapid shift in the osmolarity gradient, occurring in 30–78% of cases, as well as hypokalemia and hyperglycemia are most often considered to be a factor triggering the pathological process in the cascade of electrolyte disorders [3, 9]. D.O. Beraldo et al. [10] published a description of a case of CPM which developed in a patient against the background of prolonged treatment with diuretics with hypophosphatemia, hypokalemia and hypomagnesemia.

Thus, the spectrum of diseases and conditions that can be a direct cause of the development of ODS is currently quite wide, so S.U. Khan et al. [11] who studied this problem conclude that it can result from "stressful" situations for the body, including metabolic disorders, alimentary disorders, severe burn disease, malignant neoplasms, surgical interventions, pregnancy and childbirth.

The last cause on this list is given special attention today. The publications actively discuss cases of CPM in pregnancy and postpartum period, assess the risk of developing CPM in the presence of electrolyte disorders, such as hypo- and hypernatremia. Most of the observations are associated with the development of CPM in pregnant women in the first trimester, in particular, in the context of hyperemesis gravidarum ("indomitable vomiting of pregnant women"), when, in addition to the symptom of morning sickness, pronounced disorders occur in the woman's body, including significant dehydration, a sharp loss of body weight, which is accompanied by fluctuations in blood osmolarity due to acute hyponatremia and/or its rapid correction. Of course, an important contribution is also made by changing a woman's lifestyle during pregnancy, when there is a change in nutrition, including the need to reduce salt intake up to its complete elimination from the diet [12].

It should be noted that to date cases of CPM have also been described in pregnant women and new mothers with acute hypernatremia. G. Choudhary et al. [13] presented data on EM in a patient in the early postpartum period with hypernatremia 182 mmol/L. S. Bhatia et al. [14] reported a case of postpartum CPM associated with hypernatremia up to 200 mmol/L.

In earlier publications, K.R. Naik and A.O. Saroja [15] presented the results of the observation of a group of patients with the development of CPM, including 11 pregnant women with hypernatremia ranging from 158 to 199 mmol/L, a change in the level of consciousness from confusion to deep coma. Nine patients had tetraparesis, eight had bulbar disorders, six had ataxia, and four had convulsive seizures. MRI scans of the brain in all cases showed symmetrical lesions in the inner capsule, the radiant crown, the cerebellar peduncles and the hippocampus.

In the literature, there are cases of observation of the development of ODS in pregnant women with normal indicators of natriemia. In addition, sodium metabolism disorders are often combined with hypokalemia associated with vomiting, as a rule, in the first trimester. S.V. Patel et al. [16] described a case of the development of ODS in a 20-year-old African-American woman hospitalized for hyperemesis gravidarum, with hypokalemia and normonatremia.

The presented publications demonstrate that electrolyte disturbances that may accompany a special physiological period of a woman's body associated with pregnancy, delivery, breastfeeding, cause the development of ODS. At the same time, an increasing number of experts all over the world are coming to the conclusion that pregnancy and childbirth should be considered as an independent, significant risk factor for the possible development of ODS. S.U. Khan et al. [11], presenting a case of a 25-year-old woman 12 days after the childbirth without any previous pathological changes and in the absence of obvious triggers, suggest "direct influence" of pregnancy and childbirth on ODS genesis. T.D. Gosavi and S.J. See [12] in their publication give a description of a case of a pregnant woman at 38 weeks, who did not have any complications during the entire follow-up period before the delivery. The authors also express the opinion that pregnancy itself contributed to the development of CPM due to changes in the body characteristic in this period of a woman's life.

We present our own clinical observation of a patient who was treated at Moscow Regional Research Clinical Institute named after M.F. Vladimirsky.

***Patient O.**, 36 years old, was being treated with a diagnosis of G37.2 -pontine and extrapontine myelinolysis. Mixed tetraparesis to the level of plegia in the lower extremities. Complications: severe preeclampsia, hematoma of the soft tissues of the anterior abdominal wall in the area of the postoperative wound. Concomitant: on the 16th day after the third premature operative delivery at 34 weeks of pregnancy in the head presentation, hypertension stage II, medically uncontrolled, risk of cardiovascular complications 3. Chronic kidney disease stage 2 (GFR – 88.35 ml/min/1.73m^2). Operation: 08.10.2022. Pfannenstiel's incision, Caesarean section in the lower uterine segment.*

From the history of the disease: according to the medical record, the patient was admitted to Moscow Regional Perinatal Center on 08.10.2022 with complaints of an increase in blood pressure (BP) to 200/130 mm Hg. Diagnosis upon admission: pregnancy 34 weeks, head presentation, severe preeclampsia against the background of hypertension. Chronic pyelonephritis, remission. On 08.10.2022 an emergency delivery was performed, a live premature baby girl weighing 950 g, 39 cm long was born. Apgar score of the newborn was 5/6 points. The total volume of blood loss was 2500 ml. In the postpartum period, the patient's condition was assessed as severe; sopor, dysarthria, visual impairment in the form of blurred vision of objects, central tetraparesis to the level of plegia in the legs. MRI of the brain: multiple diffuse changes in the brain substance, cerebellar structures, stem structures – CPM and EM. She was transferred to the intensive care unit No. 2 of Moscow Regional Research Clinical Institute named after M.F. Vladimirsky on the 2nd day after the operative delivery. The informed consent was signed by the patient's legal representative.

Objectively: upon admission, the general condition was assessed as severe. Verbal contact was available, simple commands were executed. The patient was conscious, euphoric, irritable,

answered questions in monosyllables, after a pause, a repetition of the question was required. She was correctly oriented in place, time, her own personality, breathing on her own. However, the patient did not realize the severity of her condition; she was emotionally labile, considering herself "healthy", was not in the mood for treatment, demanding urgent discharge home, believing that at home " the walls will help to recover." At the same time, she reported that she was not at all concerned about the lack of active movements in her legs, claiming that "everything will be fine at home at once."

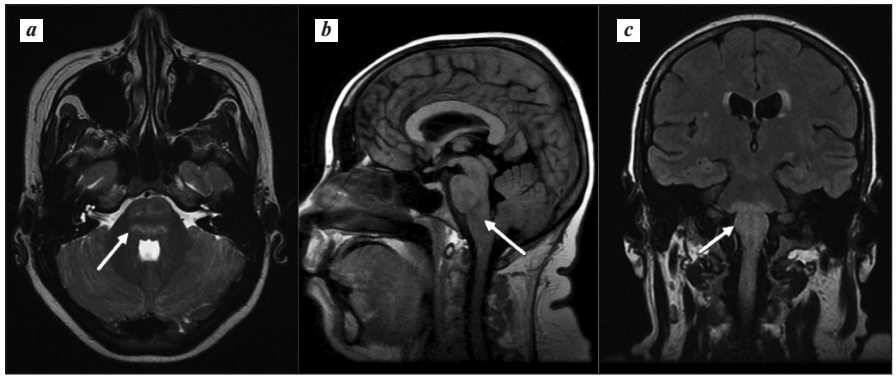

Fig. 1. *The result of an MRI scan of the brain of patient O. in the axial section in T2 mode (a), in the sagittal section in T1 mode (b), and in the coronal projection in FLAIR mode (c). In the central parts of the pons and medulla oblongata, the arrows indicate a "pig nose"-shaped area characteristic of central pontine myelinolysis on axial sections, with increased signal in the T2 and FLAIR modes and slightly reduced signal in the T1 mode*

The patient was not active within the bed, could not turn on her side on her own. Breathing through the nose was free. Auxiliary muscles did not participate in the act of breathing. Auscultation showed breathing conduction on both sides, in the lower parts somewhat weakened. There was no wheezing. Respiratory rate – 16 in 1 min. The heart tones were muted, rhythmic. Blood pressure on admission – 145/95 mmHg, pulse – 60/min. The tongue was clean, moist. The abdomen was soft during palpation, not swollen. There were no peritoneal symptoms. Peristaltic single noises were noted. The postoperative scar was without specific features, the aseptic dressing was dry. The stool was monitored, a cleansing enema was performed once in 3 days. Urination with a catheter.

Neurological status: there were no cerebral and meningeal symptoms. The eye slits were D=S, full movements of the eyeballs preserved, the pupils were round, D= S. There was no nystagmus. Photoreactions were direct and consensual, D=S, live. The reaction to convergence and accommodation was preserved. The exit points of the trigeminal nerve on the face were not painless. Sensitive disorders on the face were not detected. The face was symmetrical. Phonation of the soft palate, undisturbed swallowing, uvula along the midline. The reflex from the soft palate and the posterior wall of the pharynx was preserved, D= S. The tongue in the middle line, tongue movements were not limited. Speech was dysarthric. Reflex-motor sphere: the volume of passive movements in the limbs was full, the volume of active movements in the limbs reduced (muscle strength in the distal parts in the arms – 3 points, in the proximal parts – 3 points, in the legs – 0 points). The muscle tone of the extremities was diffusely low. There were no atrophy, fasciculations. Hyperkinesis was not detected. Periosteal and tendon reflexes: from the hands D = S, reduced, from the legs (knee, Achilles) – absent. Pathological reflexes: Babinsky's symptom on both sides. It was not possible to assess coordination disorders due to the severity of the condition. Sensitivity disorders were not detected.

Examination results: Hb – 88 g/L, red blood cells – $3.02 \cdot 10^{12}$/L, white blood cells – $29.12 \cdot 10^{9}$/L; total protein – 49 g/L, albumin – 28 g/L; glucose – 4.6 mmol/L; potassium – 4.2 mmol/L (norm 3.5–5.0 mmol/L); alanine aminotransferase – 24 mmol/L; aspartate aminotransferase – 29 mmol/L; alkaline phosphatase – 81 mmol/L; gamma-glutamyltranspeptidase – 21 mmol/L. An increase in the level of creatinine in the blood to 151 mmol /L, urea – up to 17 mmol /L, uric acid – up to 781 mmol /L, C-reactive protein – up to 65 mg /L. Decrease in the level of sodium in the blood on admission to 128 mmol /L (norm 136.0–146.0 mmol/L). Examination was carried out: ultrasound of the pleural cavity, ultrasound of the abdominal cavity and retroperitoneal space, computed tomography of the chest, MRI of the brain; color duplex scanning with color mapping of the veins of the lower extremities, kidney vessels, electrocardiography, echocardiography, daily monitoring of blood pressure; the patient was consulted in dynamics by a cardiologist, obstetrician-gynecologist.

MRI scans of the brain from 09.10.2022 showed a typical picture of symmetrical signs of aseptic inflammation (and astrogliosis): a diffuse anomaly of the signal from the pons and rather symmetrical spotty hyperintensive changes in the T2 signal on both sides in the extrapontine area. (Fig. 1, 2).

During the control MRI examination of the brain, regression of changes in the signal from the cerebellum, pons and medulla oblongata was noted. Symmetrical zones in the insular lobes were preserved in a smaller volume. There are no foci of ischemia. After intravenous contrasting, no foci of pathological MR signal were detected in the hemispheres of the brain, in the cerebellum and the brain stem. The contrast of the meninges was uniform,

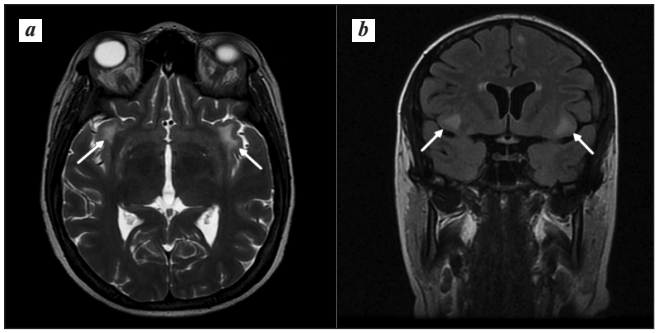

Fig. 2. *The result of an MRI scan of the brain of patient O. in the axial projection in T2 mode (a) and in the coronal projection in FLAIR mode (b). The arrows indicate symmetrical areas of increased signal at the level of the insular regions on both sides, specific for extrapontine myelinolysis*

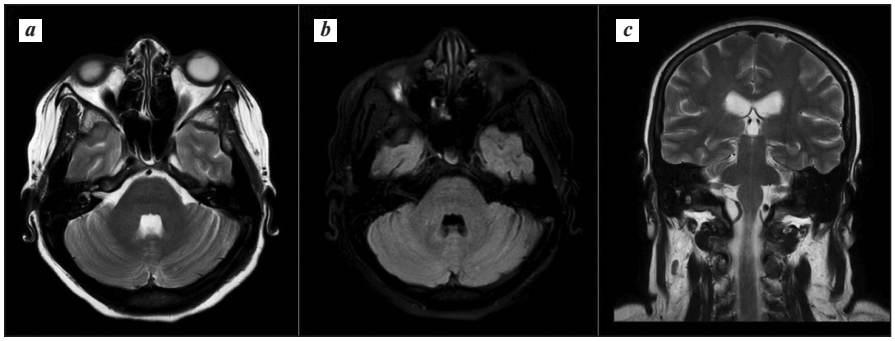

Fig. 3. *The result of an MRI scan of the brain of patient O. in the axial projection in T2 and FLAIR mode (a, b) and in the coronal projection in T2 mode (c) after 8 days. In a control examination after treatment, complete regression of the previously described pathological zone in the pons and medulla oblongata was observed*

without thickening. Venous sinuses were contrasted without filling defects (Fig. 3, 4).

Treatment: magnesium sulfate 25% 4 ml/h (via infusomat); methylprednisolone 1000 mg intravenously drip No. 5; antihypertensive; antibacterial therapy, plasma replacement drugs; rehydration and detoxification therapy. In order to prevent the progression of ODS during the correction of hyponatremia, therapeutic restrictions were observed, according to European recommendations, including the limit of sodium correction at the level of 8 mmol/L for each subsequent 24 hours [17, 18]. Drug therapy was supplemented by a program of medical rehabilitation: physiotherapy, inhalation. An individual complex of therapeutic gymnastics was carried out in combination with breathing exercises.

Positive dynamics was noted against the background of treatment. The patient became critical, oriented, adequate. There was an increase in the volume of active movements in the lower extremities, the patient was able to move within the ward with a two-sided support and to control the pelvic functions. The dynamics of laboratory parameters was noted, the sodium level was within the reference values; the level of uric acid decreased to 208.9 mmol/L, creatinine – to 63 mmol/L; the complete blood count (CBC) showed normalization of the leucocyte formula and the levels of erythrocytes, hemoglobin, albumin.

On the 16th day after the operative delivery, the patient was transferred to the place of residence in a satisfactory condition to be followed up by a neurologist, a gynecologist, and a primary care physician.

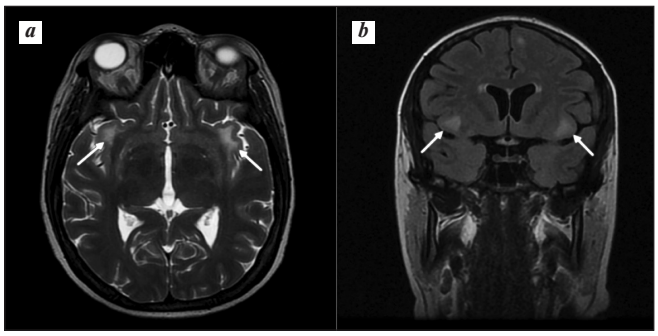

Fig. 4. *The result of an MRI scan of the brain of patient O. in the axial projection in T2 (a) and FLAIR (b) mode after 8 days. The control examination showed partial regression of the changes in the insular zones (arrows)*

Discussion

In the presented clinical case, a patient at 34 weeks of pregnancy, with preeclampsia, arterial hypertension, chronic pyelonephritis, after the emergency delivery by caesarean section and total blood loss during childbirth up to 2500 ml, developed CMP and EM manifested in neurological symptoms such as sopor, dysarthria, visual impairment, central tetraparesis with a predominant lesion of the lower extremities to the level of plegias and characteristic changes noted on the brain MRI.

The accompanying medical documentation from the health care facility at the place of residence showed the following changes in laboratory parameters: anemia, an increase in creatinine and urea levels, a decrease in blood levels of total protein and albumin, an increase in uric acid, C-reactive protein, pronounced inflammatory changes in the CBC. The patient's electrolyte balance indicators were within the reference values.

Upon admission to M.F. Vladimirsky Moscow Regional Research Clinical Institute, a slight decrease in the level of sodium in the blood to 128 mmol/L (the laboratory norm is 136.0–146.0 mmol/L) was noticed when evaluating laboratory parameters, while the indicators of potassium and glucose levels were within the reference values.

Thus, all of the above represented a complex of significant risk factors for the development of ODS during pregnancy and after delivery. Numerous diseases and conditions leading to the development of ODS are described in the literature, the list of which can vary significantly from patient to patient; in our opinion, pregnancy with a burdened background of somatic diseases, the development of preeclampsia, electrolyte disorders was the determining factor in this patient.

The connection between pregnancy and ODS is emphasized in the works of many researchers [11, 12]. Pregnancy and childbirth are a burden for a woman's body, in which complex physiological mechanisms come into force that determine significant changes in homeostasis aimed at preserving and developing the fetus: the placenta which produces anabolic hormones has pronounced hormonal activity; estrogen and progesterone are excreted in the ovaries, contributing to the development of the decidual lining of the uterus, muscle hyperplasia, reducing the contractile function of the uterus and providing favorable conditions for the development of the child.

The characteristics of mineral metabolism during this period also differ, having a tendency to retention of sodium, potassium, and chloride salts, and changes in the concentrations of magnesium salts. Steroid hormones, in turn, affect the content of electrolytes in the blood plasma. There is a decrease in the excretion and clearance of electrolytes as substances with pronounced osmotic activity, which is important under conditions of a drop in the overall level of osmolarity as a result of an increase in the volume of circulating blood. At the same time, even minor fluctuations in these indicators can be sensitive, triggering a cascade of complex pathological reactions. Research results show that not only hyponatremia in the first

trimester of pregnancy is dangerous, but also hypernatremia, the occurrence of which is associated with the possible development of rhabdomyolysis, osmotic demyelination [12, 15]. Hypernatremia in pregnant women is associated with active metabolic clearance of arginine-vasopressin, determining not only an increase in plasma osmolarity and fluid movement into the extracellular space, but also a disruption of the ratio between intra- and extracellular sodium content with a change in membrane potential, stimulation of sympathetic activity, increased sensitivity of cells to catecholamines and other vasopressor mediators.

In our observation the attention is clearly drawn to a good therapeutic effect, which can be defined as a "dramatic improvement" achieved in a short time in a patient with several comorbid risk factors that caused the development of the process, which in any other situation could be a predictor of a severe, prolonged course of the disease with a possible fatal outcome. In this case, however, in less than 2 weeks, the patient's level of consciousness was restored, she was activated, was able to move independently with bilateral support within the ward as a result of regression of motor disorders in the legs which reached the degree of plegia at the onset of the disease; she had a complete recovery of pelvic functions.

In our opinion, it is possible that it was the features of the patient's condition associated with pregnancy, childbirth, lactation, with complex humoral and cellular immunological reactions during this period that determined the outcome of the disease in this clinical case. For example, the fact of "immunological tolerance" of the maternal organism to fetal antigens is widely known, when the pregnant woman's body not only ceases to respond to antigenic stimulation of the fetus, but also produces antibodies binding antigens of paternal origin, determining the zone of biological protection of the fetoplacental complex from the action of components of the immune system.

Currently, there are more and more works aimed at studying the development of demyelination in ODS, as well as subsequent remyelination, where attention is paid to the special role of protein molecules produced by astrocytes, such as aquaporin-1 and aquaporin-4 (AQP1 and AQP4). As "key players" in myelination, oligodendrocytes are in close contact with other glial cells, in particular with astrocytes. Osmotic disorders in the body are associated with the primary loss of astrocytes, which leads to ODS, and brain damage in ODS is currently defined as astrocytopathy.

It is assumed that in the pathogenesis of ODS, in addition to osmotic disorders, an important role is assigned to complex autoimmune mechanisms accompanied by the loss of aquaporin proteins by astrocytes, which leads to the development of ODS. All processes necessary for myelination, such as recruitment, proliferation, differentiation and maturation of oligodendrocytes, are regulated by factors secreted by astrocytes. Astrocytes, which are five times more numerous in the central nervous system than neurons, are involved in maintaining the blood-brain barrier. With the development of ODS, a decrease in the level of expression of AQP1 and AQP4, which are "key regulators" of maintaining the brain homeostasis necessary for normal functioning, was noted. The immunoreactivity of AQP1, AQP4 and related pathology detected on microscopic cross-sections of autopsy brain tissues in patients with pathoanatomically confirmed ODS was evaluated. The loss of both AQP1 and AQP4 was evident in demyelinating lesions. The authors indicate that the loss of aquaporins observed in ODS not only disrupts the bidirectional flow of water in astrocytes but can also disrupt the transport of ions and organic osmolytes and possibly exacerbate osmotic stress and glutamate excitotoxicity. Moreover, it has been shown that protein molecules secreted by astrocytes affect oligodendrocyte progenitor cells capable of differentiating into new oligodendrocytes, thereby "covering axons with myelin", which determines the subsequent possibility of remyelination.

To date, data have also been obtained indicating that sex hormones under osmotic stress can have a multidirectional effect on the expression of AQP1 and AQP4, thereby increasing or decreasing the adaptation of the brain to hyponatremia. There are facts indicating increased immunoreactivity of AQP1 and AQP4 in the female population, in contrast to male patients, who, on the contrary, had a loss of immunoreactivity of AQP1 and AQP4. The study of this issue continues; it is necessary to clarify whether this occurs secondary to the destructive process of the disease or is a compensatory mechanism protecting the astrocyte from apoptosis [19]. In addition, very little is still known about remyelination in an osmolyte-induced demyelinating process with primary astrocyte loss. There are isolated studies where histological signs of remyelination found in the lesion are presented. Therefore, the active recovery processes that we observed in the patient against the background of the developed ODS probably obey their own specific laws, the study of which requires further research, observations, and future in-depth analysis.

Conclusion

It should be noted that the development of ODS is possible in any pregnant woman or a woman in the postpartum period, so clinicians should remember about this pathology. The development of ODS in this category has its own characteristics; the clinical signs of ODS in pregnant women and new mothers may not be as acute as in other diseases and conditions, characterized by a gradual onset. For effective management of such patients, monitoring of electrolyte levels, timely diagnosis based on MRI, and adequate treatment are crucial.

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