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Postinfectious autoimmune encephalitis with opsoclonus-myoclonus syndrome

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Abstract

Opsoclonus is irregular chaotic eye movements, accompanied by impaired gaze fixation, oscillopsia and associated visual impairment. It is combined with myoclonus of the extremities, trunk, change in gait. It occurs in many pathological conditions, most often in oncological and post-infectious diseases. The rarity and uncommonness of the clinical manifestations of the opsoclonus-myoclonus syndrome, as well as the poor awareness of doctors about this pathology, cause diagnostic difficulties and errors. This report presents the case of a 49-year-old patient, who developed unsteadiness when walking, opsoclonus, myoclonus, startle syndrome, exaggerated startle response 3 weeks after an acute intestinal infection. The diagnostic errors made were analyzed. The diagnosis "Post-infection autoimmune encephalitis" was proposed and substantiated. Paraneoplastic opsoclonus-myoclonus syndrome was excluded by prospective observation of the patient for 6 years. High efficiency of glucocorticoid treatment was noted.
Keywords: opsoclonus-myoclonus, myoclonus.

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Opsoclonus–myoclonus syndrome (OMS; synonyms are opsoclonus-myoclonus-ataxia syndrome, Kinsbourne encephalopathy, etc.) is a rare neuro-ophthalmological disorder. It was described in 1913 by the Polish neurologist K. Orzechowski. It is characterized by sharp, involuntary movements of the eyeballs in various directions, which increase with gaze fixation, tracking, and convergence, persists during sleep and with eyes closed, and is accompanied by oscillopsia (i.e., illusion of the movement of the surrounding world). Myoclonic hyperkinesis in the extremities, trunk muscles, cerebellar ataxia, postural tremor, encephalopathy, and behavioral disorders are quite common in this pathology [1, 2].

OMS is an internationally recognized neurological manifestation of oncological, infectious, degenerative diseases, as well as toxic and metabolic disorders [1–5]. The disease is rare, as the largest review with the onset of OMS in adulthood only presented 116 cases [3]. The prevalence is 1 case per 10 million inhabitants in adults and two times higher in children [2].

The etiology and pathogenesis of OMS are under-investigated. The detection of neuronal nuclear antibodies based on data obtained in the study of the immune status of patients with OMS [2], symptom reversibility, and good response to immunotherapy (immunoglobulins and glucocorticoids) [1, 3] led to the conclusion that immune mechanisms are involved in the pathogenesis of OMS. In many pathological conditions associated with OMS, autoantigens are formed, followed by the development of the same type of autoimmune aggression against certain structures of the nervous system [2].

Evidence of an autoimmune process in OMS is the B-cell activating factor detected in the blood serum and cerebrospinal fluid of patients, increased levels of cytokines associated with B-lymphocytes, positive correlation between the levels of B-cell activating factor in the cerebrospinal fluid, and presence of anti-inflammatory granular neuronal antibodies [2, 6]. Neuronal degeneration does not occur in OMS [1, 2]; however, damage to synapses and death of small but functionally significant populations of cells related to the synthesis of serotonin, which entails brain dysfunction, are possible.

The most probable pathophysiological mechanism for the occurrence of OMS is the disinhibition of the nuclei of the fastigium (*n. fastigii*) of the cerebellum (damage to afferent projections to the fastigial nuclei is also possible), which control omnipause neurons, and its activation stops the saccadic movements of the eyeballs [7]. This assumption is consistent with the results of functional magnetic resonance imaging [1] and is con-

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firmed by histological findings. In OMS, changes in Purkinje cells, infiltration with lymphocytes, gliosis, edema, and demyelination in the zone of the dentate nuclei of the cerebellum are observed [6]. A study using immunoreactive labels showed that afferent projections to omnipause neurons are predominantly GABA[1]-, glycine-, and glutaminergic and, to a lesser extent, monoaminergic [4].

Most patients with OMS are seronegative for all-known neuronal antibodies [1, 2]. However, the absence of autoantibodies does not rule out neuroimmunological disorders [5].

Distinguishing paraneoplastic forms from other forms of OMS is clinically important because they have a more severe course. If the tumor is not treated, the majority of the patients die [2, 3]. Given the rarity of OMS, the standard treatment has not yet been established. Symptomatic treatment with clonazepam, valproic acid, and piracetam is used. The treatment of choice includes immunoglobulins, glucocorticoids, and plasmapheresis. Therapy with monoclonal antibodies (rituximab) has demonstrated efficiency in paraneoplastic OMS [3].

Clinical case

A clinical case of a 49-year-old man with OMS, whose medical history was followed for >6 years, which is a significant period to rule out a paraneoplastic process, is presented below [8].

The patient was admitted to the neurological department of Kazan Emergency Hospital No. 2 on November 19, 2014, with complaints of blurred vision aggravated by movement, gaze fixation ("I see only silhouettes"), and shuddering at sharp sounds. In the prone position, in an attempt to roll over on his side, he had an unpleasant sensation of "sharp compression inside" and "everything goes down as if on a rollercoaster." There was instability when walking and a feeling of "sinusoidal rocking" of the body that spread to the legs. With any movement, the patient experiences shuddering of the head "as when working with a jackhammer" and twitching of the limbs.

The event preceding the disease was the bankruptcy of an enterprise organized and headed by the patient (May–June 2014). He lost 10–13 kg of body mass.

On August 15, 2014, the next day after consumption of alcohol (0.3 L of vodka) at a company event, he experienced nausea, and his body temperature increased to 37.8°C. He associated his condition with poisoning. However, the rest of the participants of the event, who consumed the same amount of alcohol, did not have these signs. In some villagers in the settlement where the patient lived, diseases with similar symptoms were recorded at the same time. The epidemiological situation, according to the sanitary and epidemiological service in the area, was characterized by a seasonal increase in the incidence of acute intestinal infection.

The patient was examined at the primary healthcare facility and underwent fibrogastroduodenoscopy, which revealed superficial gastrobulbitis. The levels of alanine aminotransferase and aspartate aminotransferase were 17.6 U (normal range, 0–8 U) and 18.6 U (normal range, 0–8 U), respectively. The general blood test results revealed a minor 8% stab shift, with lymphocytes of 33%.

With the subsequent sensations of heaviness in the neck and occiput, gait instability, and elevated blood pressure (160/90 mm Hg) with a suspected stroke, he was hospitalized in the neurological department of the hospital for war veterans in Kazan.

No pathology in the somatic status was detected. Unsteadiness in the Romberg position, nystagmus, and tremor of the right hand in the Mingazzini test were noted. Magnetic resonance angiography of the brain detected a decrease in blood flow in both posterior communicating arteries and hypoplasia of the right vertebral artery. Data for pathological changes in brain matter were not obtained. The cervical spine radiographs revealed degenerative and dystrophic changes as a decrease in the height of the intervertebral discs, uncovertebral arthrosis, and Kimmerle's anomaly.

Complete blood count, clinical urine analysis, and biochemical blood test did not show significant changes. Coagulogram revealed a slight increase in the international normalized ratio to 1.33 (normal range, 0.8–1.2), prothrombin index of 75% (normal range, 80%–120%), and activated partial thromboplastin time of 40 s (upper limit of the norm). The test results on infections caused by human immunodeficiency viruses, hepatitis B and C, and syphilis were negative. Electrocardiogram had no signs of pathology.

Diagnosis of the syndrome involving the vertebral artery, hypoplasia of the vertebral artery on the right, and osteochondrosis of the C_{III}–C_{VI} cervical spine was made.

The patient's gait disorder was regarded as "a functional neurological disorder due to depression." The patient consulted a psychiatrist and was diagnosed with astheno-depressive syndrome. Amitriptyline (25 mg/day) was prescribed; during the treatment course, the condition worsened, ataxia intensified, and the patient lost the ability to walk and could move only with a wheelchair.

After the second consultation with a psychiatrist, with a diagnosis of conversion disorder ac-

[1]GABA, γ-aminobutyric acid.

companied by depression, he was referred to a day hospital in a psychiatric hospital, where he underwent examination and treatment from October 15, 2014, to November 17, 2014.

Contrast-enhanced magnetic resonance imaging of the brain was performed. A small size (10 × 10 × 11 mm) paraolfactory meningioma was detected on the left (disregarded during the previous magnetic resonance imaging), as well as the tight posterior cranial fossa with narrowing of the size of the fourth ventricle.

The patient was consulted by a neurosurgeon, who concluded asymptomatic left-sided olfactory meningioma. Neurosurgical treatment was not required. The patient was also consulted by an ophthalmologist and an infectious disease specialist, and no eye pathologies and infectious diseases were registered.

The patient was consulted by a psychologist who assessed the patient's personality as strong, strong-willed, with sufficient intelligence, preserved criticism of his condition, passive–defensive attitude, need to defend his viewpoints, practical judgments, rationalism, and a tendency to a systematic approach to solving problems. The psychologist identified mild cognitive-amnestic disorders. Severe asthenia was pronounced, which was manifested as rapid fatigue during a conversation that required rest, decreased attention, inability to concentrate, and need for external stimulation and guidance.

The therapy included duloxetine 60 mg/day (the patient took 47 tablets for a course of treatment), sulpiride 100 mg, bromdihydrochlorophenylbenzodiazepine (phenazepam) 1.0 mL as daily intravenous drip infusions (No. 14), and four injections of metoclopramide were made. During therapy, the patient noted the disappearance of nausea and improvement in mood. The patient began to walk with support; however, after the completion of infusion treatment with sulpiride and phenazepam on day 2 (10 weeks after the disease onset), the patient experienced twitching of the head, limbs, and eyeballs, which impaired the ability to fix gaze on objects. He was discharged with a diagnosis of somatized depression.

Given the persistence of movement disorders that limit self-service and movement, the patient was referred to the neurological department of Emergency Hospital No. 2 in Kazan (3 months after disease onset). Spontaneous fast chaotic thrust movements of the eyeballs in any direction of gaze were observed. He had episodic "trembling" of voice; involuntary movements of the eyelids and head; fast irregular small amplitude and low-frequency movements of the limbs, resembling an arrhythmic tremor, lasting up to several seconds; and twitching of individual cheek regions. They were provoked by any activities, sensory stimuli, light and sound, and fixation of attention. In the upper extremities, they are most clearly noted when performing purposeful movements; as a result, the patient cannot use cutlery. Involuntary movements in the arms and legs intensified when approaching the target. When holding a pose with arms outstretched in front, finger twitchings of different amplitudes and frequencies were observed.

A blow with a hammer on the superciliary arch during the assessment of palpebral and mandibular reflexes caused a shudder with head retraction. This was accompanied by tension in the muscles of the neck and shoulder girdle. A similar reaction occurred following exposure to sharp auditory stimuli. A sudden loud sound caused a sharp shudder of the whole body, which was sometimes accompanied by a fall.

Proprioceptive reflexes were intensified, to some extent predominant on the left. Abdominal reflexes were quickly depleted, especially on the left, and plantar reflexes were absent. The carpal analogs of Rossolimo, Venderovich on both sides, and Yakobson-Lask on the left were determined. On the left, the Babinski reflex was not evident. The gait was unstable, with a change in its characteristics, and the patient could fall without support. The patient falls in the Romberg position, and tandem walking was impossible.

Complete blood count showed lymphocytes of 39.8% (normal, 37%). Biochemical blood tests and urinalysis did not detect pathologies. Electrocardiogram did not show deviations from the normal. Stimulation electromyography did not reveal conduction disorders in motor fibers of *n. tibialis* and *n. peroneus*. Polymerase chain reaction results for cytomegalovirus, Epstein-Barr virus, herpes simplex viruses (types 1, 2, and 6), toxoplasma, causative agents of Lyme borreliosis, and chlamydia were negative. No avidity of the antigens of the listed pathogens was noted for immunoglobulin M. A high avidity of immunoglobulin G for the antigens of the herpes simplex virus (types 1 and 2), cytomegalovirus, and Epstein-Barr virus was detected.

Instrumental studies of internal organs (i.e., lungs, abdominal organs, thyroid, and prostate glands) did not reveal oncological pathology. Hu, Yo-1, CV2, PNMa2, Ri, and AMPH antibodies were negative.

Thus, the patient's medical case history was presented, whose disease developed after taking alcoholic beverages and was regarded as the result of poisoning. It proceeded with an increase in body temperature, nausea, and general weakness.

The examination revealed an increase in the values of aspartate aminotransferase and alanine aminotransferase, as well as superficial gastrobulbitis according to the results of fibrogastroduodenoscopy.

In the following days, he continued to feel unwell, approximately 20 days after the events, and the patient developed signs of damage to the nervous system, namely, unsteadiness when walking and psychoemotional disorders. By day 25 after disease onset, his vision deteriorated, and he could move with external assistance. A cerebral circulation disorder was suggested, which was not confirmed. The recorded gait disturbance was explained by "functional neurotic disorders within depression." The course of therapy in a specialized psychiatric hospital, where he stayed with the diagnosis of somatized depression, was ineffective, and the disease continued to progress.

The features of eye movement disorders in the patient were attributed to opsoclonus ("dancing eyes"), and the complaint of blurred vision was explained by oscillopsia associated with the instability of images on the retina and lack of fixation of a clear image on it.

Forced movements of facial and limb muscles during the monitoring, according to the conditions of occurrence, belonged to the kinetic (occurred during active movement), action (when performing a specific action), and reflex (provoked by a certain influence) forms of myoclonus. Myoclonus was positive (i.e., associated with active muscle contraction) and negative (i.e., associated with a sudden and abrupt interruption of motor contraction due to a short-term deactivation of muscle tone in a certain muscle group) [9, 10]. It was manifested by an unsteady unstable gait with falls and inability to move for a short time.

The anatomical basis of myoclonic hyperkinesis in the patient was the damage to the cortical and subcortical structures of the brain. The presence of cortical myoclonus confirmed the involvement of facial muscles and distal parts of the hands, induction of spontaneous myoclonus by action or stimuli, and presence of negative myoclonus. Subcortical (stem) myoclonus is evidenced by the involvement of the proximal limbs and axial muscles (sensation of a "sinusoidal" movement of the body and limbs in the patient), vocal tremor, diaphragm contraction ("roller coaster" sensation), startle reflex as a shudder with the participation of mantle zone muscles (i.e., head, face, and upper shoulder girdle) in response to sharp auditory and sensory stimuli, hyperekplexia (generalization of the startle reflex) as a fall provoked by a "loud sneeze," etc.

The involvement of the cortical areas of the patient's brain is confirmed by psychological examination data, which revealed cognitive-amnestic disorders, behavioral deviations. The involvement of subcortical areas revealed opsoclonus, startle reflex, and hyperekplexia. The above demonstrates a multifocal brain lesion.

The disease onset with an increase in body temperature, cases with a similar clinical presentation among residents of the settlement where the patient lived, seasonal increase in the incidence of acute intestinal infection according to sanitary and epidemiological surveillance, and high avidity of immunoglobulin G to several herpes virus antigens suggest that the patient has had an infectious disease.

Virus-induced and immune-mediated genesis of damage to brain structures mediated by cytokines was not probable. This was contradicted by the presence of clinical signs in a certain period after the infection and the distinct effect of glucocorticoids. The latter suggests an autoimmune nature of the disease.

Our assumption coincides with literature data, which emphasize the typical development of opsoclonus within 1 month after the infectious prodromal period, which corresponds to the timing of antibody production after antigenic stimulation [2, 3, 5]. A viral or another disease can cause the expression of neuronal antigens with the development of an autoimmune response, which spreads to the brain. In OMS, autoantibodies against neurofilament proteins to neurotransmitter receptors were revealed. Antibodies to the surface antigen of cerebellar/stem neurons that bind to nonsynaptic surface points on neuronal dendrites have been identified and characterized [6].

Based on the analysis and absence of an isolated infectious agent, the diagnoses of post-infectious autoimmune encephalitis with OMS, generalized actions, reflex, kinesiogenic myoclonus; startle reflex, hyperekplexia, significantly limiting the patient's life (requires external assistance); and mild cognitive-amnestic disorders and mild bilateral pyramidal symptoms were established.

A course of prednisolone therapy was prescribed, which demonstrated good effects, and 2 months after discharge, the patient began to work.

Conclusion

The patient's diagnosis comprised the wording "depressive state" for a long time. The assessment of the patient's condition as depressive certainly had a basis, as the patient was in a stressful situation. However, already at the first stages, signs of brain damage did not correspond to this interpretation. It was the underestimation of these signs that led to a diagnostic error.

The appearance of signs nervous system damage before the prescription of antidepressants and

sedatives and the positive effect of their administration gave evidence against the drug-induced OMS. A minor decrease in the manifestations of OMS in a patient was associated with the prescription of bromdihydrochlorophenylbenzodiazepine (Phenazepam) to the patient, which can enhance the inhibitory effect of GABA [11] on the transmission of nerve impulses in the omnipausal nucleus.

An oncological search did not reveal any pathology in the patient. OMS can be the first manifestation of a tumor and occur long before the clinical manifestations of a malignant neoplasm. To rule out this, it is necessary to monitor the patient for at least 3 years with a repetition of oncological search with instrumental and laboratory studies [8].

A prospective follow-up of the patient for >6 years with an oncological search did not reveal any significant deviations in his state of health. The patient holds currently an administrative position and leads an active lifestyle.

OMS is a "difficult diagnosis"; its establishment often requires the participation of many specialists. This becomes especially relevant because the symptoms described can occur in many pathological conditions, and the difficulty of its interpretation delays the diagnostics and worsens the prognosis. We hope that this work will be useful to several specialists.

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