GUILLAIN -BARRÉ SYNDROME WITH BULBAR DISORDERS, ATAXIA AND HYPERSOMNIA AT THE ONSET OF THE DISEASE

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Bulbar disorders in Guillain-Barre syndrome (GBS) are observed in approximately a third of patients [1], however, at the very beginning of this disease they occur rarely, mainly in such atypical variants as the pharyngo-cervico-brachial form, M. Fisher syndrome and brainstem encephalitis Bickerstaff [2–5]. In 2016, JK Kim et al . proposed to identify an independent atypical variant of GBS, which they designated as "acute bulbar palsy plus" (ABPP) [6]. Its distinctive feature is the acute development of pronounced bulbar syndrome at the onset of the disease in the absence of motor deficits in the extremities. This form of GBS always creates diagnostic difficulties, since it requires differentiation with another pathology, the early manifestations of which may be acute/subacute bulbar disorders (brain stroke, encephalitis, myasthenia gravis, botulism, etc.). Under our supervision was patient N., 55 years old, a gas station operator, who was hospitalized at the Nizhny Novgorod Regional Vascular Center (RSC) with suspected stroke. 2 weeks before hospitalization, the patient suffered an acute respiratory infection complicated by bronchitis. She received outpatient treatment at her place of residence (took antibiotics). On the eve of hospitalization, on the way home from the night shift, she felt that she was swaying when walking. She went to rest at home, and when she woke up after a long day's sleep, she noticed a slight nasality in her voice. The next morning, the nasal tone intensified, speech became slurred, and when drinking, water began to pour out through the nose. There was general weakness and increased drowsiness, and coordination of movements in the left hand worsened. The patient was admitted to the hospital with suspected stroke. There were no foci of acute ischemia in the brain according to computed tomography (CT) and magnetic resonance imaging (MRI), however, based on clinical data, the patient was diagnosed with lacunar brainstem ischemic stroke. When substantiating the diagnosis, we took into account the rather acute development of bulbar symptoms and ataxia, as well as the fact that the sensitivity of MRI in diagnosing brainstem lacunar strokes is not one hundred percent. The patient was hospitalized in the intensive care unit, and a day later transferred to the department for patients with acute cerebrovascular accidents. During examination, the patient complained of slurred speech, nasal voice, difficulty drinking ("water pours out through the nose"), instability when standing, general weakness, and increased drowsiness. Her condition was assessed as serious due to the presence of bulbar disorders associated with a potential threat to life. Objectively: body temperature, heart rate and breathing rate, blood pressure are within normal values. The patient is oriented in place, time and personality, answers questions adequately, although she has difficulty concentrating her

attention, quickly becomes exhausted, and periodically falls asleep. There are no meningeal signs. Movements of the eyeballs are complete, nystagmus is not detected. The pupils are of medium size, their reactions to light and convergence are preserved. There are no changes in the V–VIII pairs of cranial nerves. There are nasolalia , decreased mobility of the soft palate during phonation, more pronounced on the left, bilateral decrease in pharyngeal and palatine reflexes, dysarthria (speech is slurred, unfluent, with pauses, with distortion of articulation of both consonants and vowels, approaching "chanted" speech). Swallowing solid food is not impaired, tongue movements are preserved, and the tongue is positioned in the midline when protruding. The finger-nose test on the left is performed with a miss and intention, the finger-nose test on the right and the heel-knee test on both sides are performed correctly. The range of active movements in all joints is full. The resistance when examining all the main muscle groups of the arms and legs is sufficient, there is no paresis in the limbs. Tendon reflexes from the hands are of normal amplitude, symmetrical; knee and Achilles reflexes are low. There are no pathological hand or foot signs.

On the same day in the evening, the patient felt discomfort in the neck - according to the patient, "the neck seemed to be swollen", and tingling in the left, and a few hours later - in the right hand ("as if the hands were resting"), although upon examination there was a decrease in the superficial and no deep sensitivity was detected. Paresthesia persisted over the next three days. Laboratory and instrumental examinations were carried out in accordance with the regulations for the provision of medical care to patients with acute cerebrovascular accidents. Along with this, other possible causes of bulbar syndrome were excluded, since the diagnosis of ischemic stroke was in doubt due to an increase in nasal voice and dysarthria noted throughout the day; absence of dysphagia and paresis of the tongue muscles in the presence of unilateral paresis of the soft palate; absence of risk factors for stroke. The possibility of botulism was rejected due to the lack of an appropriate nutritional and epidemiological history, the absence of visual impairment, dysphagia and gastrointestinal syndrome in the clinical picture. Results of general clinical and biochemical blood tests (cellular composition, ESR, hemoglobin, glucose, total protein and protein fractions, C-reactive protein, transaminases, creatinine, lipoprotein fractions, electrolytes, thyroid hormones), indicators of the blood coagulation system, blood gas composition and blood electrolytes were within normal limits. Blood pressure monitoring and ECG did not reveal any pathology. No changes in the lungs were detected according to X-ray data. According to the results of duplex scanning, there were no hemodynamically significant disturbances in blood flow in the extracranial arteries of the brachiocephalic system. CT angiography did not reveal any cerebral vascular pathology. On the 2nd day after the onset of the first symptoms of the disease, a lumbar puncture was performed. The cellular composition and results of biochemical studies of cerebrospinal fluid (CSF) were not changed. During the first three days, the patient continued to have a pronounced nasal voice, dysarthria, ataxia, paresthesia, general weakness and pronounced drowsiness - not only at night, but also most of the daytime, she slept, and when she got up and tried to walk, she held on to an assistant to maintain balance. Heart and respiratory rates, swallowing, and muscle strength in the limbs

remained intact. From the end of the third day of illness, rapid improvement began in the form of a decrease in the severity of ataxia, nasal voice and general weakness/drowsiness. After 5 days, the mobility of the soft palate during phonation was restored, instability in the Romberg test and mis-hits when performing the finger-nasal test on the left disappeared. However, on the 6th day of illness, a neurological examination noted the disappearance of the knee and Achilles reflexes. During this period, the examination of the patient continued to identify/exclude antiphospholipid syndrome and vasculitis as possible causes of "young stroke," as well as myasthenia gravis, neuroinfections , and porphyria as alternative diagnoses to stroke. Blood tests for thrombophilia and homocysteinemia did not reveal any pathological changes. Antibodies to the human immunodeficiency virus, hepatitis C and B viruses, cardiolipin , antibodies to beta2-glycoprotein 1, as well as antibodies to cytoplasmic antigens of neutrophils and antinuclear antibodies were not detected in the blood plasma. The rapid test for porphyria was negative. A proserine test performed to exclude myasthenia gravis was also negative. The results of an electroneuromyographic (ENMG) study of the nerves of the upper extremities, performed on the 7th day of illness, were within normal limits. A standard decrement test with tetanization , carried out on the same day, did not reveal a decrement in the amplitude of the M-response of the orbicularis muscle of the right eye, the right deltoid muscle and the muscles of the right hypothenar during electrical stimulation of the facial, axillary and ulnar nerves, respectively, with a frequency of 3 impulses per second, and There were also significant changes in the amplitude of M-responses during periods of post-activation relief and post-activation exhaustion, which indicated the absence of disturbances in neuromuscular transmission. On the 9th day of the disease, against the background of complete restoration of balance and coordination of movements and almost complete regression of the paresis of the soft palate, the patient developed severe pain in the temporal regions and the lower half of the face. Following this, after a few hours, weakness of the facial muscles of the left half of the face developed, and on the next (10th) day, weakness of the right half as well. As the patient later recalled, her "face was petrified, her lips hung, her eyelids did not close, and tears flowed from her eyes." Neurological examination revealed bilateral paralysis of the facial muscles. Strength in the extremities, including the peroneus muscles and the extensor muscles of the foot and toes, remained intact. Tendon reflexes from the hands were evoked, although their amplitude was reduced, and the knee and Achilles reflexes were absent. There were no pathological signs. There were no impairments of coordination or sensitivity. Lasègue's symptom was negative. On this day, the diagnosis of stroke was removed and an atypical variant of GBS syndrome was diagnosed. His clinical characteristics were consistent with those of OBPP described in 2016 by JK Kim et al: bulbar abnormalities, ataxia, and paresthesias in the arms at disease onset; inhibition of tendon reflexes in the absence of paresis of the muscles of the limbs; delayed onset of facial diplegia; an increase in symptoms for less than four weeks followed by regression [6].

The results of ENMG on the 13th day of the disease were as follows: the median (motor and sensory portions), tibial, and sural nerves were normal, M-responses from the facial

and ulnar nerves were slightly reduced, and significantly from the peroneal nerves, which may be the case with axonal neuropathy. nerves. The results of repeated lumbar puncture on the 13th day of illness: cytosis of 19 cells (18 neutrophils, 1 lymphocyte) in 1 μl ; protein 0.26 g/l; glucose 3.60 g/l; chlorides 118.0 mmol/l. The detection of mild pleocytosis and the absence of protein-cell dissociation in the CSF was not a reason to revise the diagnosis of GBS. The final diagnosis was formulated as follows: Guillain - Barré syndrome: acute motor-sensory axonal neuropathy with bulbar disorders, ataxia and hypersomnia at the onset of the disease, facial diplegia, mild sensory impairment. An immunological analysis (line blot) carried out on the 17th day of illness did not reveal antibodies of the JgG /M classes to gangliosides GM1, GM2, GM3, GM4, GD1a, GD1b, GD2, GD3, GT1a, GT1b, GQ1b in the blood serum. After the diagnosis of GBS was established, the patient was started on treatment using plasmapheresis; A total of 3 sessions were conducted every other day. Facial diplegia regressed 3 weeks after the onset of the disease. When the patient was re-examined after 7 months , her neurological status revealed only mild hypomimia , a slight nasal tone of voice and the absence of tendon reflexes in both the arms and legs. The results of repeated ENMG 7 months after the onset of the disease did not differ from the results obtained on the 13th day of the disease.

Discussion Guillain -Barré syndrome , along with the classical form, includes rare clinical variants that can be clearly defined, reduced, atypical or crossed [7, 8]. It is the atypical variants of GBS that pose the greatest difficulties for diagnosis, predisposing to errors in recognizing this pathology and delayed initiation of specific therapy [9]. This situation also occurred in the described case, when the onset of the disease, atypical for GBS, with bulbar disorders initially led to an incorrect diagnosis of stroke and a delayed start of adequate treatment. Atypical variants of GBS are Miller Fisher syndrome, pharyngo-cervico-brachial form, paraparetic motor form with selective involvement of the legs; facial diplegia or paresis of the abducens nerves in combination with paresthesia; sensory ataxic variant; variant with pandysautonomia [1, 4, 5, 7, 9, 10]. To this list in 2016, JK Kim et al . proposed to also add OBPP [6]. The basis for recognizing ABPP as a variant of GBS may be their pathophysiological similarity and the presence of such common clinical signs as inhibition of tendon reflexes, damage along with the bulbar group and other cranial nerves, ataxia, decreased nerve conduction velocity according to ENMG, albumin cell dissociation in the CSF, the presence antibodies to gangliosides in the blood serum, a monophasic course of the disease with progression of symptoms over no more than 4 weeks [6]. At the same time, according to JK Kim et al ., the manifestations of OBPP do not meet the diagnostic criteria of other atypical forms of GBS [10], which served as the basis for describing it as an independent rare variant of GBS. According to JK Kim et al ., the absence of oculomotor disorders distinguishes OBPP from M. Fisher syndrome, characterized by weakness of the extraocular muscles, ataxia and areflexia [11]. As for the acute development of bulbar disorders, they cannot serve as a differential diagnostic sign, since they can be observed (albeit rarely) in M. Fisher syndrome [5, 11]. The difference between OBPP and the pharyngo-cervico-brachial variant of GBS is the absence of paresis of the neck flexor muscles and muscles of the proximal arms [12]. According to JK Kim et al ., ABPP differs from mild manifestations of the classical form

of GBS, as well as from its “crossover” with M. Fisher syndrome , by the absence of weakness of the muscles of the extremities [6]. After analyzing the medical records of 184 patients treated in Korea in 2012–2013. regarding Guillain -Barré syndrome, JK Kim et al . classified 11 cases as OBPP. The first symptoms in these patients most often (in 6 out of 11 or 55% of cases) were dysarthria and/or nasolalia , as well as instability when walking (in 2 out of 11 or 18% of cases); Dizziness, tingling sensation in the limbs, and diplopia were less common. As the disease progresses, areflexia, ophthalmoplegia, bilateral abducens nerve palsy, sensory disturbances, and unilateral or bilateral facial muscle weakness may join the initial symptoms. There were no respiratory problems in any case [6]. In the patient we observed, the first symptoms of the disease were nasolalia and dysarthria, which corresponds to data on their highest occurrence at the onset of OBPP [6]. Ataxia, paresthesia, gradual inhibition of tendon reflexes of the legs and arms in the absence of paresis in the extremities, delayed bilateral involvement of the VII cranial nerves, a short period of progression of symptoms, electrophysiological signs of axonal polyneuropathy with involvement of the nerves of the extremities also testified in favor of ABPP as an atypical variant of GBS in patient N. (mainly legs). The absence of progressive muscle weakness in the extremities is considered an important difference between ABPP and the classical form of GBS and the basis for classifying ABPP as an atypical variant of GBS [6]. In this regard, it can be noted that diagnostic criteria indicating weakness in the limbs as the most significant sign of GBS were created primarily for its classical form [5]. For example, patients with M. Fisher syndrome , in which there is no paresis in the limbs, were excluded from a study to test the validity of the Brighton criteria for GBS [13]. Some authors assume that in M. Fisher syndrome there is mild, with a decrease in strength to 4 points, weakness in the limbs [11], however, if weakness in the limbs progresses and becomes pronounced, then they diagnose the “crossover” of this syndrome with the classical form of GBS [10,12] . Criteria for diagnosing atypical variants of GBS were proposed in 2014 by BR Wakerley et al . [10]. This classification does not include ABPP, which was described as an independent rare variant of GBS two years later [6]. At the same time, in our opinion, in accordance with the classification approach used by BR Wakerley et al ., OBPP can be regarded as an incomplete M. Fisher syndrome, and not as an independent variant of GBS. Indeed, without denying the pathogenetic commonality of GBS and M. Fisher syndrome, BR Wakerley et al . classified them into two different classification groups. In both the GBS group and the M. Fisher syndrome group, they identified the classic variant and several reduced variants (“subtypes”), taking into account the presence of three signs: weakness of certain muscle groups, ataxia and hypersomnia . GBS is characterized by muscle paresis in the absence of ataxia and hypersomnia (in the classical form - the muscles of all four limbs, and in incomplete variants - the facial muscles, bulbar muscles, muscles of only the arms or only the legs) [10]. Weakness of the limb muscles is not typical for M. Fisher syndrome. Its classic form is characterized by ophthalmoplegia and ataxia in the absence of hypersomnia , while hypersomnia indicates variants of M. Fisher syndrome involving the central nervous system: either Bickerstaff brainstem encephalitis , or, in the absence of ophthalmoplegia, such a reduced form as “acute atactic hypersomnia ” [10]. Following this logic, OBPP, in our opinion, could be regarded as a second reduced form

of Bickerstaff brainstem encephalitis , which in turn is recognized as a type of M. Fisher syndrome involving the central nervous system [8, 9, 12]. Indeed, the combination of ataxia and hypersomnia in the patient N. we described indicates the involvement of the central nervous system, which brings her disease closer to an incomplete (due to the absence of ophthalmoplegia) form of Bickerstaff brainstem encephalitis . It was noteworthy that in our patient, despite severe nasolalia and dysarthria, swallowing remained intact. The possibility of dissociation between the presence of dysarthria and the absence of dysphagia and respiratory disorders in atypical forms of GBS is known. Thus, in 2017, S. Izadi et al . described a patient with GBS who was hospitalized due to dysarthria, bilateral paralysis of facial muscles, paresthesia in the distal extremities and absence of tendon reflexes in the legs, which began ten days earlier, but did not have dysphagia or respiratory disorders [14]. The patient did not complain about weakness in the limbs, and upon examination, only a slight decrease in the strength of the muscles of the proximal legs was revealed [14]. Manifestations of the disease as described by S.Izadi et al . case corresponded to the signs of OBPP, although the authors did not use this term [14]. Delayed development of paralysis of the facial muscles, which occurred in the patient on the 9th day of illness against the background of almost complete regression of nasolalia , ataxia and hypersomnia , also occurs in other atypical forms of GBS, for example, in M. Fisher syndrome [11]. As for the absence of an increase in protein in the CSF in the patient we observed in the second week of the disease in the presence of mild neutrophilic pleocytosis, this fact does not contradict the diagnosis of GBS. There is evidence that the protein content in the cerebrospinal fluid during GBS remains within the normal range in half of the patients during the first week of the disease, and during the second week in approximately 10% of patients [12]. C. Fokke et al . found protein-cell dissociation in only 290 of 455 (64%) GBS cases they analyzed [13]. It should also be taken into account that an increase in protein levels in the CSF in atypical forms of GBS is observed even less frequently than in the classical form. For example, with Bickerstaff brainstem encephalitis , protein-cell dissociation in the cerebrospinal fluid is detected in only half of the patients [12]. In ABPP, there was no albumin -cell dissociation in the CSF in 8 of 11 (72%) cases [6]. Cases of pleocytosis in the absence of a significant increase in protein in the CSF have been described in patients with GBS [14,15]. The possibility of predominantly neutrophilic pleocytosis in the CSF is also accepted, provided that the pleocytosis is mild [16]. It is emphasized that a typical sign for GBS is the number of cells in the CSF, not exceeding 50 in one microliter, but the cells themselves can be both lymphocytes and polymorphonuclear leukocytes (mature neutrophils) [5]. ENMG on the 13th day of the disease revealed damage to motor axons, as indicated by the normal speed of excitation propagation along the sensory (median and sural nerves) and motor (facial, ulnar, median, tibial, peroneal nerves) nerves, with a decrease in the amplitude of M-responses. The fact that ENMG did not confirm the sensory component of axonal neuropathy can be explained by the transient nature of the damage to sensory fibers and the insufficient sensitivity of ENMG to verify mild damage to sensory fibers. However, taking into account the positive sensory phenomena in the clinical picture of the disease (paresthesia in the arms and neck on the 2nd day, as well as pain in the lower part of the face preceding facial diplegia on the 9th day of the disease), damage to the

peripheral nerves in patient N. was regarded as acute motor-sensory axonal neuropathy. It is known that in GBS, the target for an immune attack can be not only myelin, but also axons, which served as the basis for identifying its axonal variants (acute motor axonal neuropathy and acute sensorimotor axonal neuropathy) [7]. According to JK Kim et al ., in ABPP, predominant damage to axons is observed less frequently than to myelin, but it is possible [6]. In particular, our observation is consistent with the description of a clinical case by S. Ray and PC Jain , who in a 13-year-old girl with ABPP revealed a decrease in the amplitude of the M-response along the right median and right peroneal nerves (which indicated axonopathy), while clinically only disappearance of tendon reflexes from the limbs while maintaining the strength of the muscles of the arms and legs [4]. The patient we observed had a clinical and neurophysiological dissociation, which consisted in a discrepancy between the presence in the clinical picture of paralysis of the facial muscles - and only slight changes in the axons of the facial nerves according to stimulation ENMG, as well as between the preservation of the strength of the extensor muscles of the feet and toes - and pronounced a decrease in M-responses upon stimulation of the peroneal nerves, indicating damage to their motor axons. We did not find an explanation for the reasons for such dissociation in the literature. Axonal neuropathy in GBS is thought to result from an immune -mediated attack on the nerve axolemma [5]. Antibodies produced in the human body against lipooligosaccharides of certain bacteria, primarily Campylobacter jejuni are capable of damaging human gangliosides in a cross-immune reaction , which are part of the myelin of Schwann cells, synaptic membranes, neuromuscular endings and axolemma [5, 17, 18]. For acute motor axonal polyneuropathies Anti-ganglioside antibodies are represented by subclasses of immunoglobulin G and predominantly bind to gangliosides GM1 and GD1a [17]. In ABPP in patients with autoimmune neuropathies, autoantibodies to gangliosides GT1a and GQ1b are most often detected [6]. These antibodies are also associated with other variants of GBS that manifest as bulbar disorders, including the pharyngo-cervico-brachial variant of GBS [2, 19]. Less commonly, autoantibodies to ganglioside GQ1b are detected in OBPP ; they are also the main antigen in another atypical variant of GBS – M. Fisher syndrome [6, 19]. The patient we observed did not have JgG /M class antibodies to any of the following gangliosides : GM1, GM2, GM3, GM4, GD1a, GD1b, GD2, GD3, GT1a, GT1b, GQ1b. In this regard, it should be noted that circulating autoantibodies to gangliosides are detected only in 60–70% of patients with GBS, and their absence does not exclude this disease [19]. One of the explanations for the absence of these antibodies in the blood serum of patients with acute autoimmune polyneuropathies is the possibility of their rapid endocytosis, that is, capture from the blood by neuronal membranes and retrograde transport into the cell body with subsequent elimination [19]. Since a blood test for gangliosides was taken only on the 17th day of the disease against the background of regression of symptoms, the absence of autoantibodies may be due to their elimination from the blood by this time. The erroneous diagnosis of “stroke” at the onset of the disease was largely due to the lack of awareness among doctors about this rare variant of GBS and the objective complexity of its differential diagnosis. Compared with lacunar brainstem stroke, OBPP is characterized by a more extended development of bulbar disorders over time (in this regard, the adjective “acute” in the name OBPP is used with

the same degree of convention as when designating another variant of GBS - acute inflammatory demyelinating polyneuropathy). A feature of static ataxia in patients with atypical variants of GBS is the absence of lateralization , which is so characteristic of acute vascular lesions of the cerebellum [3]. So, for example, the patient we observed noted that when walking she “swayed to the right and left,” but did not deviate in one direction. A number of symptoms of OBPP, for example, bilateral paresthesia in the extremities and diplegia of the facial muscles, are not at all characteristic of lacunar strokes. Neuroimaging data are important for the verification of stroke , although even MRI using diffusion-weighted images for acute lacunar ischemic foci in the brain stem gives false negative results in more than a third of patients [20]. The clinical difference between OBPP and botulism in the acute period of the disease is the absence of a corresponding epidemiological history, the presence of ataxia and sensory disorders in the clinical picture in the absence of oculomotor disorders, abdominal symptoms and a descending type of spread of paresis [6]. Acute intermittent porphyria, when severe, can be accompanied by the development of bulbar syndrome, respiratory disorders and paresis of facial muscles. Unlike OBPP, cranial neuropathy in acute intermittent porphyria develops against the background of severe weakness in the limbs and pain in them; Patients experience abdominal symptoms (abdominal pain, vomiting, constipation), changes in urine color, increased blood pressure, tachycardia, urinary retention, and mental disorders. The diagnosis of acute intermittent porphyria is verified by identifying increased urinary excretion of delta-aminolevulinic acid and porphobilinogen . Functional recovery in the described patient N. was rapid and complete. Our observation is consistent with the data of JK Kim et al ., who noted regression of all clinical symptoms over 3 months in 10 of 11 (91%) patients with ABPP. Taking into account the fact that the neuropathy in our patient was axonal, this fact is also consistent with the idea that acute axonal neuropathy differs from the classic version of GBS in the more frequent occurrence of not only very severe, but also mild disease [1, 5], and functional restoration occurs quickly [7]. The possibility of good recovery in acute axonal autoimmune polyneuropathy is explained by the fact that autoantibodies to the axolemma can only temporarily disrupt the integrity of the nodes of Ranvier and thereby cause transient conduction blocks, which then quickly regress [19].

Thus, GBS can, in rare atypical cases, manifest with bulbar disorders, ataxia and hypersomnia , which must be taken into account in the differential diagnosis of brainstem stroke in the practice of vascular centers. Knowledge of the clinical features of atypical variants of GBS is determined by the importance of early initiation of its specific therapy, which is necessary to stop the autoimmune process.

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