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A rare case of Bickerstaff's brainstem encephalitis

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ABSTRACT

Bickerstaff's brainstem encephalitis (BBE) is a rare, immune-dependent disease of brainstem characterized by progressive ophthalmoplegia, ataxia and central nervous system involvement, which may take the form of impaired consciousness and/or pyramidal signs. BBE requires differentiation with many neurological conditions and it is extremely difficult to make the proper diagnosis. We describe the case of a 63-year-old female patient admitted to the Department of Neurology due to speech changes, balance disorder, diplopia and weakness of the right limbs. On admission, neurological examination revealed depressed gag and palatal reflexes, central facial nerve palsy on the right side of the face and paresis of the right limbs. On the second day, progression of neurological deficit was observed – quantitative disturbances of consciousness, absence of gag and palatal reflexes and bilaterally positive Babinski sign. Head MRI did not confirm the presence of recent ischemic changes in the brain. From the fourth day, the patient's general and neurological condition was very severe. She was unconscious with ophthalmoplegia and narrow, non-reactive pupils. Multimodal therapy was administered during hospitalization, observing a gradual improvement in the patient's condition from the thirteenth day of hospitalization. Due to the ambiguous clinical picture, the following diseases were considered in the differential diagnosis: ischemic stroke of the brainstem region, venous sinus thrombosis, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, paraneoplastic brainstem encephalitis and Bickerstaff's brainstem encephalitis. On the thirty-fifth day, the patient was discharged home. The patient maintained verbal contact with clear speech, proper eye movement and persistent four-limb paresis. After 5 months, the patient was re-admitted to the Department of Neurology to assess the neurological condition and undergo medical check-ups.

Keywords: Bickerstaff's brainstem encephalitis, Miller-Fisher syndrome, Guillain-Barré syndrome, anti-GQ1b antibodies

1. INTRODUCTION

Bickerstaff's brainstem encephalitis (BBE) is a rare condition characterised by progressive ophthalmoplegia, ataxia and central nervous system (CNS) involvement, which may take the form of impaired consciousness and/or pyramidal signs [1-3]. The disease was described in 1950s by Edwin Bickerstaff [4].

He reported a syndrome of ataxia, ophthalmoplegia and drowsiness, preceded by infection [4, 5]. The pathophysiology of BBE is not fully studied, but it is associated with the autoimmune mechanism caused by previous infection [3].

BBE has some similarities to Miller-Fisher syndrome (MFS) and Guillain-Barré syndrome (GBS), including areflexia and increased protein concentration in cerebrospinal fluid (CSF). Based on this, suspicion of a common etiology was raised, and in the light of the common connection with previous infection, an immunity-based mechanism was proposed. Bickerstaff distinguished BBE from MFS by the presence of disturbed consciousness, which is a feature only in BBE [3].

The key moment in understanding of MFS and BBE was the discovery of the IgG anti-GQ1b antibodies [6]. The GQ1b antigen is strongly expressed in the oculomotor, trochlear and abducens nerves, muscle spindles of the limbs and in the brainstem (Figure 1). Infection with microorganisms containing the GQ1b epitope may induce the production of anti-GQ1b antibodies in patients with predisposition. Binding of anti-GQ1b antibodies to GQ1b antigens induces MFS. The anti-GQ1b antibodies can also enter the brainstem and bind to GQ1b, inducing BBE [7].

The reported incidence of GBS in Western countries ranges from 0.89 to 1.89 cases per 100 000 person-years [8]. In comparison with GBS, both BBE and FS are relatively rare [7].

In this paper, we wanted to analyse the case of a patient diagnosed with BBE.

2. CASE REPORT

A 63-year-old female patient was admitted to the Department of Neurology due to speech and balance disorders, diplopia and weakness of the right limbs (symptoms increasing for two days). Medical history without other significant diseases.

On admission to the ward, the patient was conscious and in logical contact.

The examination revealed:

- dysarthria,
- diplopia,
- weakened gag and palatal reflexes,
- central facial nerve palsy on the right side of the face,
- paresis of the right limbs (Grade 4 Lovett Scale),
- Babinski sign – positive on the right side,
- presence of lower limb ataxia.

In the computed tomography (CT) scan, performed on admission to the department, the brain image was normal. In basic biochemical tests, no significant abnormalities were also found. On the second day, progression of neurological deficit was observed:

- quantitative disturbances of consciousness (sleepy patient),
- worsening of dysarthria,
- absence of gag and palatal reflexes,
- four-limb paresis with predominance on the right side (in right limbs Grade 2/3, in left limbs Grade 3 Lovett Scale),
- bilaterally positive Babinski's sign.

The same day, head magnetic resonance imaging (MRI) [in two sequences: diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR)] was performed for the first time – the presence of new ischemic changes in the brain was not confirmed (Figure 1).

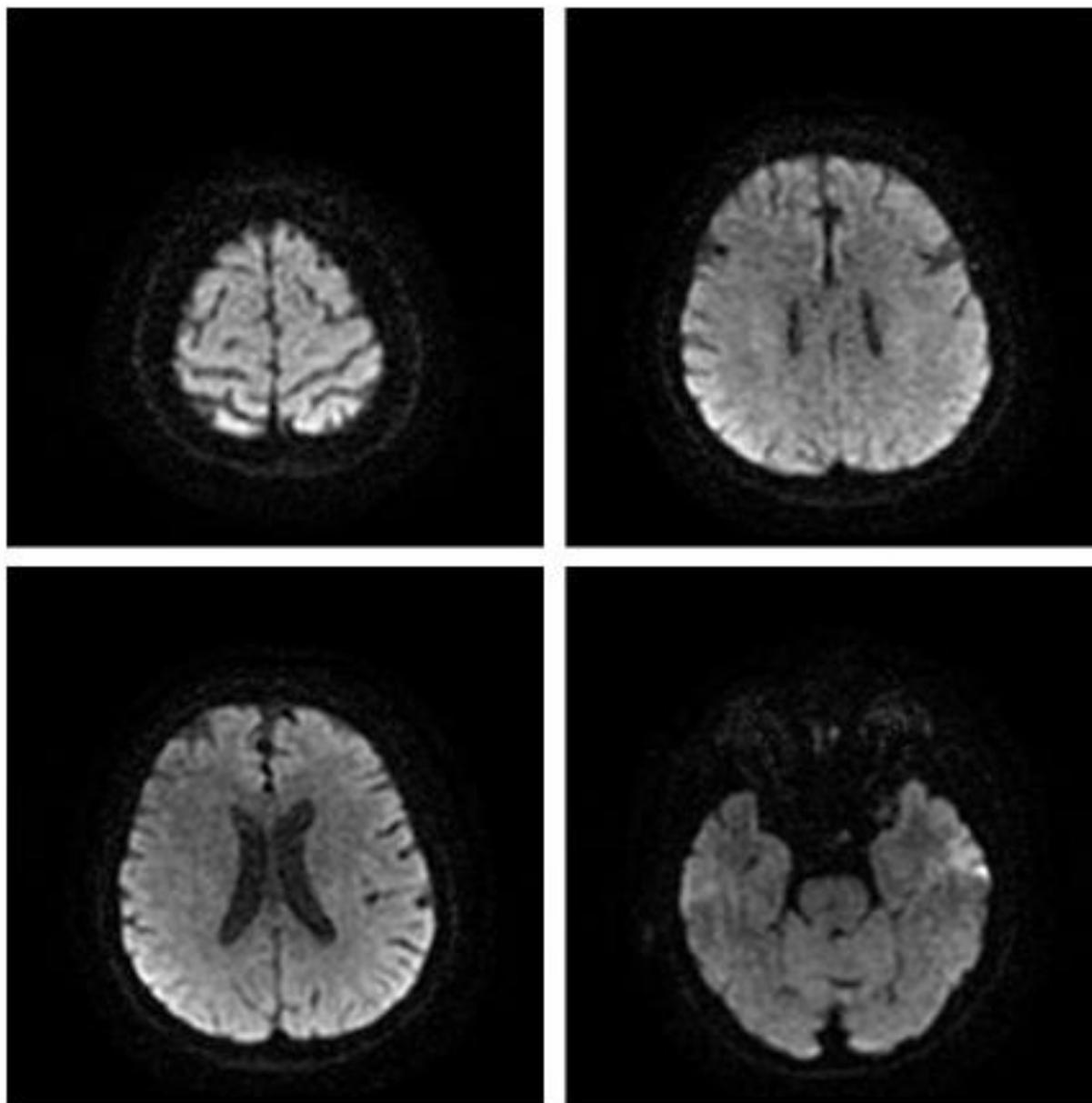


Figure 1. Head MRI (DWI) – second day of hospitalization. The presence of new ischemic changes in the brain was not confirmed (authors' own material)

In the ultrasound examination of the carotid arteries, the blood flow in the assessed arteries was normal, without the presence of atherosclerosis. In transcranial doppler (TCD), flows in the arteries of the anterior cerebral circulation were laminar and symmetrical (Figure 2). However, a significant slowdown in the left vertebral artery and basal artery was found (peak systolic velocity – PSV: 18.9 cm/s).

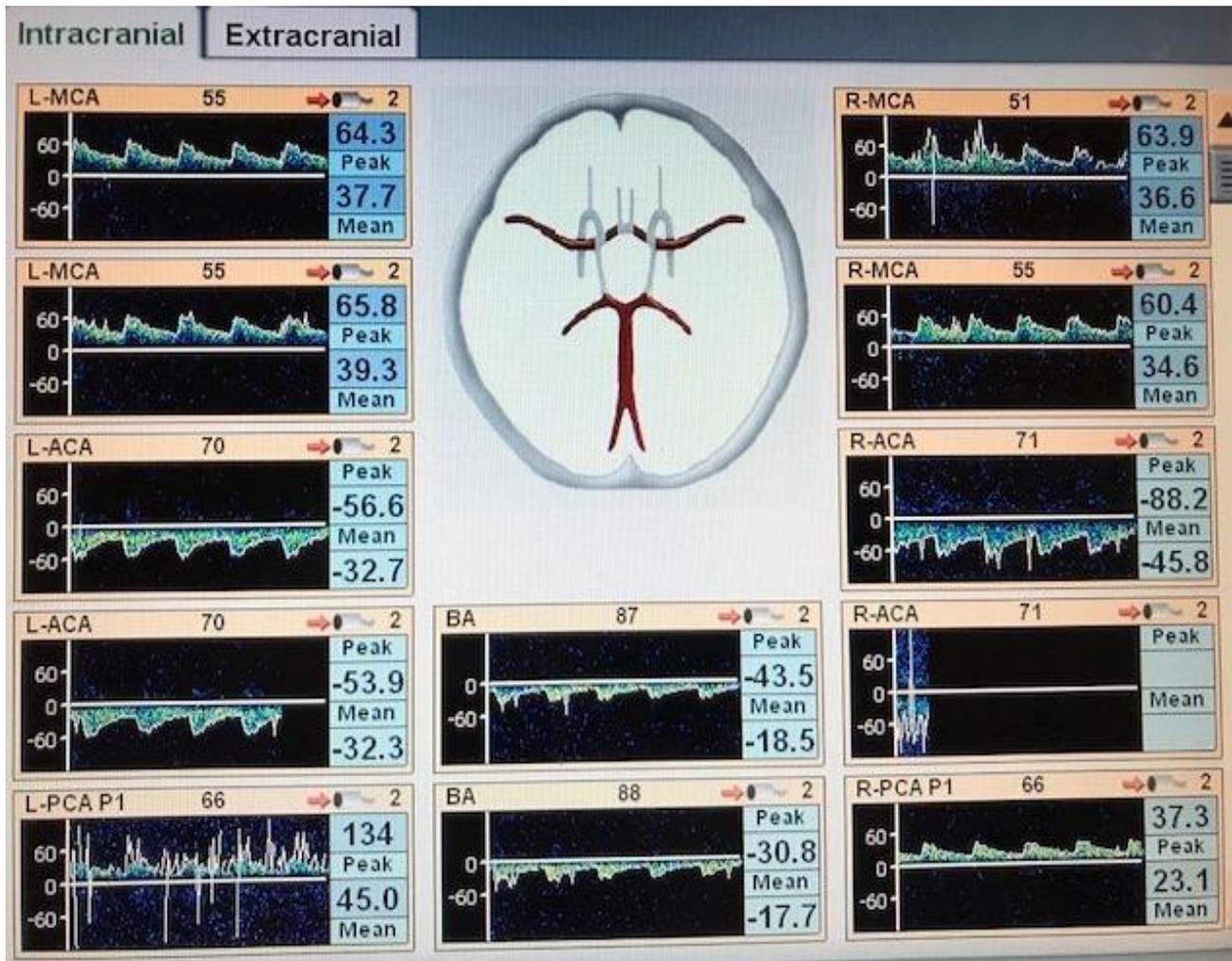


Figure 2. Transcranial doppler (TCD) – second day of hospitalization. Flows in the arteries of the anterior cerebral circulation were laminar and symmetrical, but significant slowdown in the left vertebral artery and basal artery was revealed (authors' own material)

Due to the unclear clinical picture, lumbar puncture was performed on the same day.
Results:

- transparent, water-clear fluid;
- pleocytosis 12/3;
- total protein 343.5 [mg/l], norm: 150-40 [mg/l];
- glucose 68.3 [mg/dl], norm: 40-70 [mg/dl].

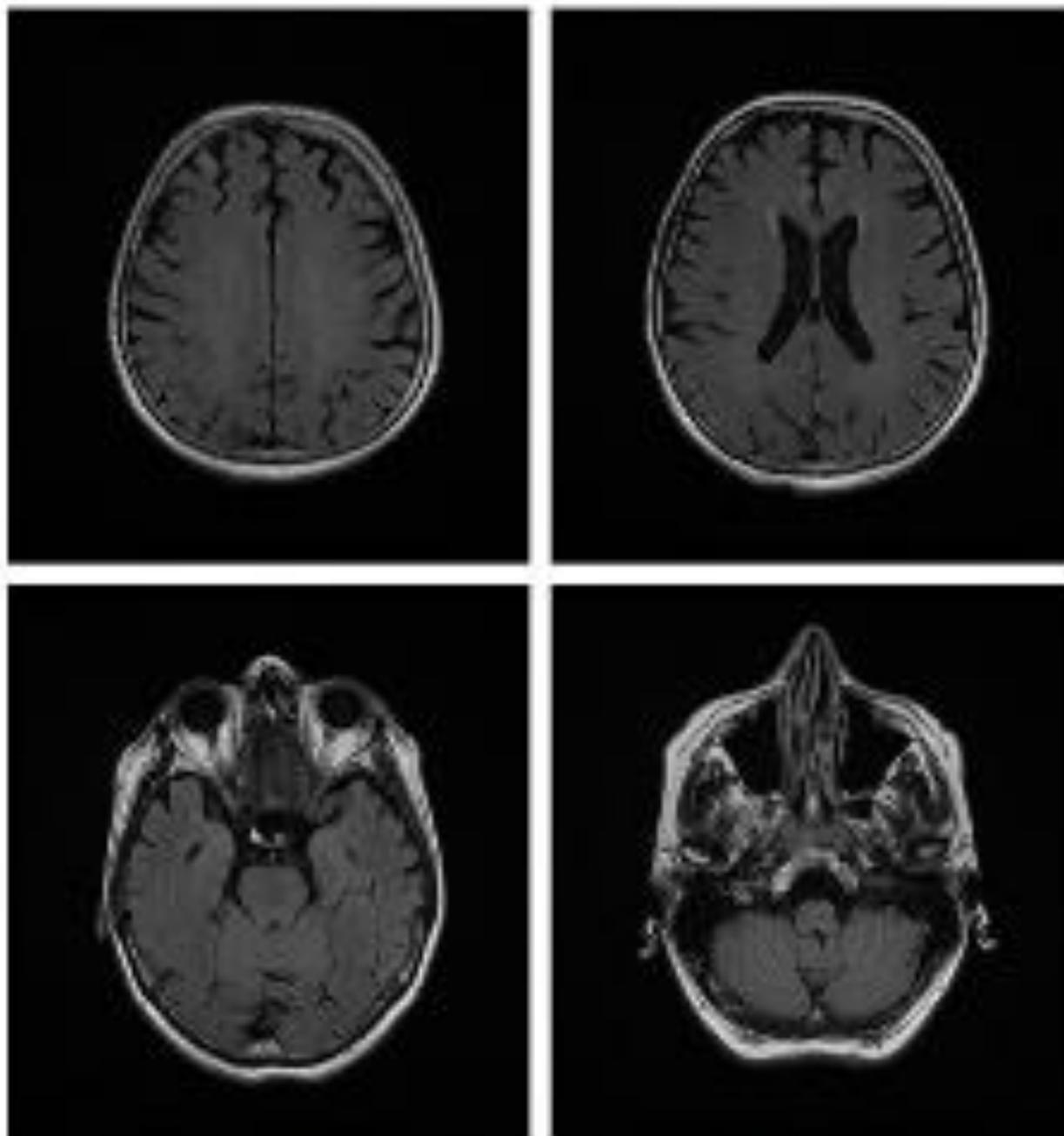


Figure 3. Head MRI – fourth day of hospitalization. No pathology was found except for single vascular demyelinating lesion in the left frontal region and small initial cortical atrophy (authors' own material)

On the third day, there was a further worsening of the neurological condition, intensification of consciousness disorders (patient awakened to a strong pain stimulus), increasing oculomotor disorders, absence of the throat and palatine reflexes, intensification of four-limb paresis and bilateral positive Babinski's sign.

Due to disturbed basal artery flow in TCD, cerebrovascular angio-CT scan was performed, which showed correct contrasting of the arteries of the posterior cerebral circulation.

From the fourth day, the patient's general and neurological condition was very severe:

- unconscious,
- no meningeal symptoms,
- narrow, non-reactive pupils,
- ophthalmoplegia,
- defensive reaction to pain in the left limbs,
- bilaterally positive Babinski's sign.
- circulatory and respiratory efficient, fed with a stomach tube.

On the fourth day, another MRI of the head was performed (Figure 3), in which no significant pathology was revealed (single vascular demyelinating lesion in the left frontal region and small initial cortical atrophy). The diagnostics was extended to MRI of the cervical spine, which showed the presence of degenerative and discopathic changes without signs of cervical spinal injury (Figure 4).

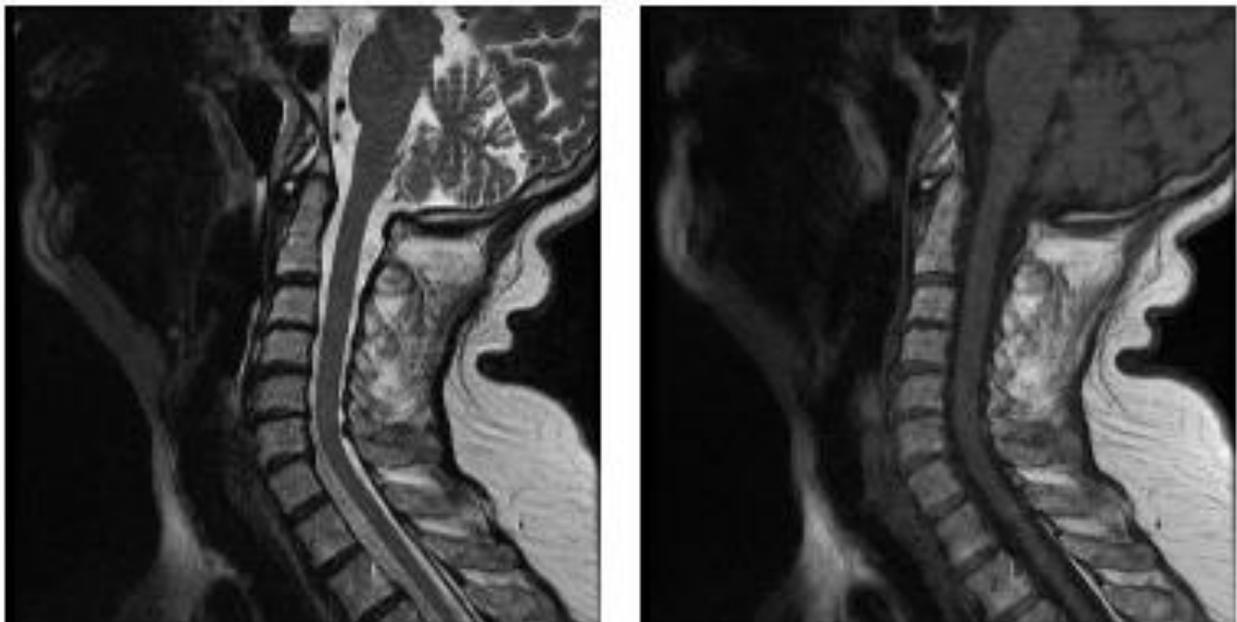


Figure 4. Cervical spine MRI – fourth day of hospitalization. The examination showed the presence of degenerative and discopathic changes without signs of cervical spinal injury (authors' own material)

Also, on the fourth day cerebrospinal fluid (CSF) was again examined. Results:

- transparent, water-clear fluid;
- pleocytosis 14/3;
- total protein 383.4 [mg/l], norm: 150-40 [mg/l];
- glucose 75.2 [mg/dl], norm: 40-70 [mg/dl].

- proteinogram of the cerebrospinal fluid without abnormalities;
- oligoclonal bands were absent.

The diagnostics have been extended to include the tests listed in Table 1.

Table 1. List of additional tests with results

Test	Result
ANA 3 profile	negative
ANCA MPO + PR3 profile	negative
onconeurological panel	negative
anti-NMDA antibodies	negative
anti-cardiolipin antibodies	negative
14-3-3 protein in CSF	negative
<i>Borrelia</i> IgM and IgG in serum and CSF	negative
<i>Herpes simplex virus</i> IgM and IgG in serum and CSF	negative
antiGQ1b antibodies	negative
electroencephalography (EEG)	a record with changes located in the temporo-occipital region with a small tendency to attack, against the background of a well-expressed basic activity
electroneurography (ENG)	features of discrete demyelinating polyneuropathy, coexistence of root syndrome
brainstem auditory evoked potentials (BAEP)	latencies and interferences of the I, III and V waves of auditory evoked potentials within the normal range

In TCD performed serially in consecutive days, gradual normalization of vertebrobasilar flow was observed. From the thirteenth day of hospitalization, a gradual improvement in the patient's condition was observed. Retiring consciousness disorders, improvement in eye mobility and swallowing disorders, improvement in limb paresis. On the thirteenth day of hospitalization, another head MRI was performed, in which no significant pathologies were

found (Figure 5). In the following days, the patient's condition further improved systematically. On day 35, the patient was discharged home. On the day of discharge, the patient was in logical contact with efficient speech, proper eye movement and persistent four-limb paresis with a predominance on the right. The patient walked with the help of one person.

Multidirectional treatment was conducted during hospitalization. Antiplatelet drugs, glucocorticoid therapy, antibiotic therapy (ceftriaxone), antiviral drugs (acyclovir), antifungal, anti-edema and anti-depressant drugs were used. After 5 months, the patient was re-admitted to the Department of Neurology to assess the neurological condition and perform check-ups.

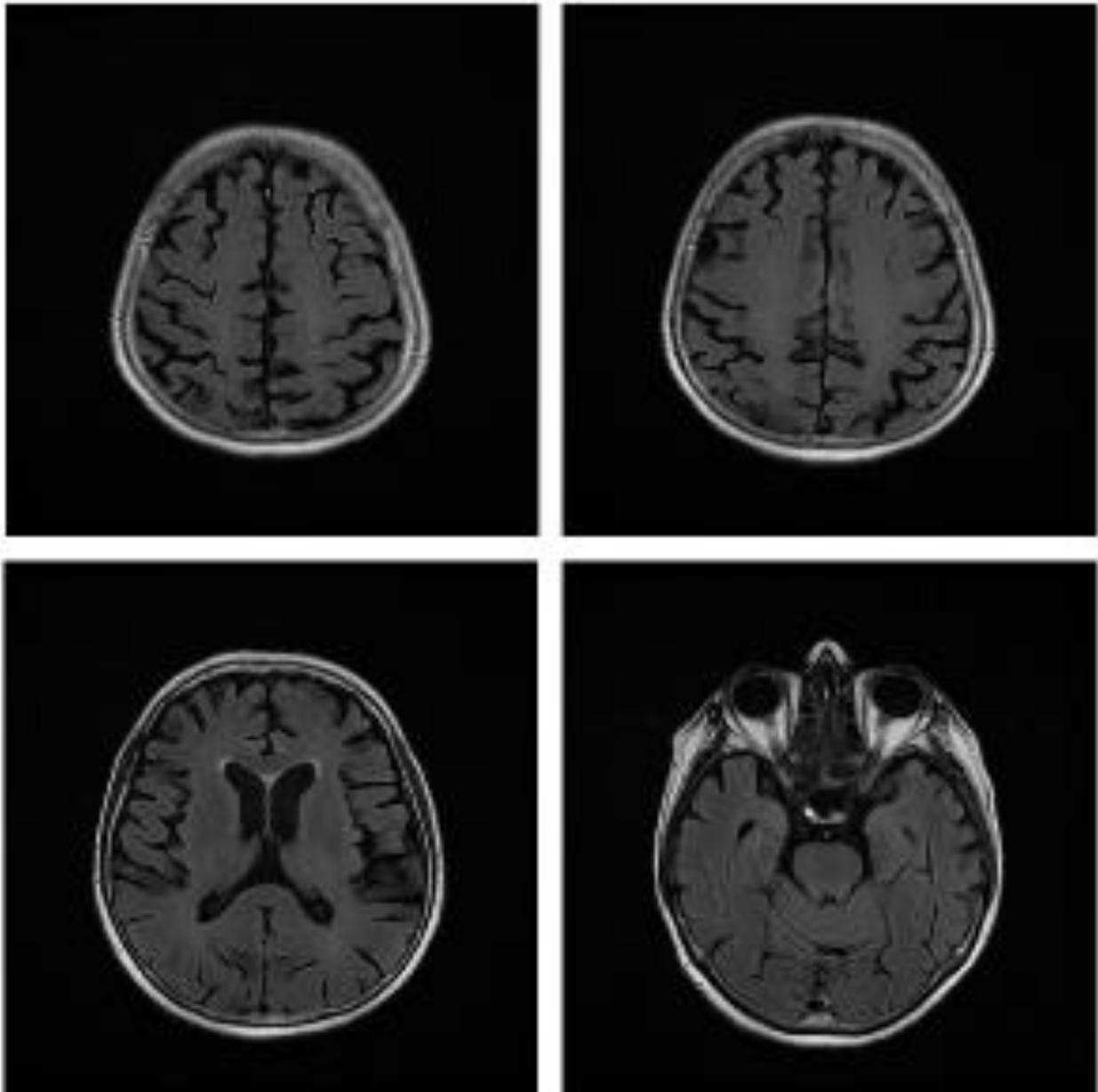


Figure 5. Head MRI – thirteenth day of hospitalization. No significant pathologies were found (authors' own material).

The patient was conscious, in logical verbal contact, with clear speech, proper eye movement, no meningeal symptoms, discrete pyramidal paresis of the left limbs with a tendency to the Babinski's sign on the left.

The patient could walk alone. The head MRI with contrast was performed, which did not show significant pathologies. Brain image comparable to the last examination (the presence of a single, small vascular demyelination lesion within the left hemisphere of the brain) – Figure 6

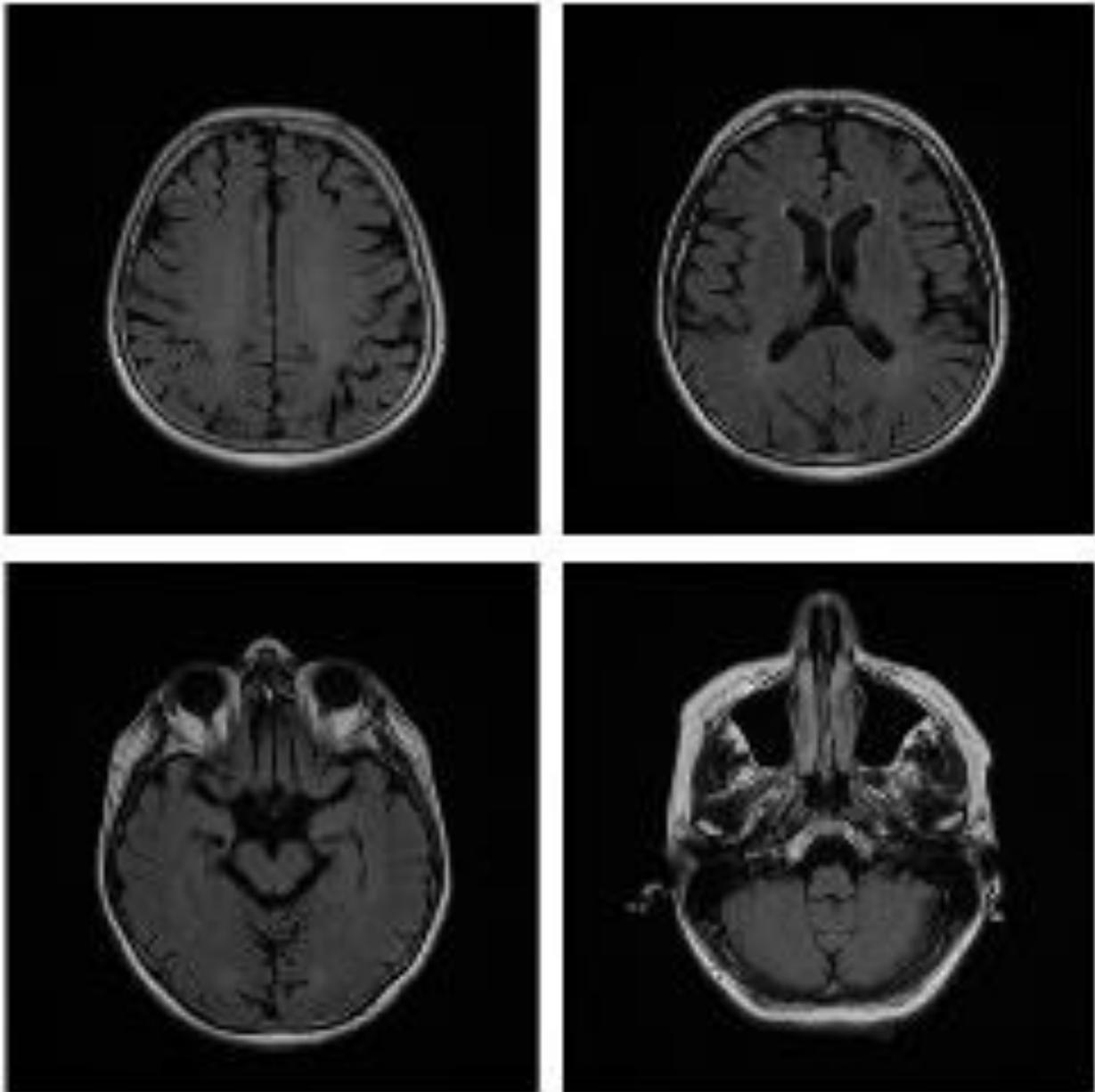


Figure 6. Head MRI, control after 5 months. Brain image comparable to the last examination – the presence of a single, small vascular demyelination lesion within the left hemisphere of the brain (authors' own material)

3. DISCUSSION

Due to the non-specific clinical picture, extensive differential diagnosis was necessary in this case. A negative autoimmune screen, negative *Borrelia* antibodies, negative *Herpes simplex* antibodies and MRI without significant pathologies ruled out the presence of an autoimmune process, Lyme disease, Herpes simplex infection. Due to the ambiguous clinical picture, the following diseases were considered in the differential diagnosis:

3. 1. Ischemic stroke of the brainstem region

The patient's neurological status could correspond to ischemia of the brainstem. However, subsequent imaging studies have not confirmed the presence of any ischemic outbreak in this area.

3. 2. Venous sinus thrombosis

As in the previous case, based on imaging studies (angio-CT scan performed on the third day) venous sinus thrombosis was ruled out, because there were no thrombotic changes in the cerebral venous sinus system. Additionally, no history of headaches was reported.

3. 3. Posterior reversible encephalopathy syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) is caused most often by a sudden increase in blood pressure to values exceeding the autoregulatory capabilities of the cerebral vessels, what leads to cerebral angioedema [10-11]. In the described patient, no similar changes were found in subsequent MRI examinations of the head. In addition, there was no history of hypertension.

3. 4. Reversible cerebral vasoconstriction syndrome

Reversible cerebral vasoconstriction syndrome is a condition with severe headaches and possible accompanying focal symptoms. Doppler examinations show, due to vasoconstriction, a significant acceleration of blood flow in the examined vessels [10-11]. In several studies of intracranial blood flow, no significant acceleration of blood flow was found (initially even a slowing of basal artery flow was noted).

3. 5. Paraneoplastic brainstem encephalitis

Paraneoplastic encephalomyelitis was excluded, because the patient's onconeural panel result was negative. The CT scan of the chest and abdominal ultrasound examination were performed, not revealing the presence of neoplastic lesions.

3. 6. Other diseases

Diseases such as Wernicke encephalopathy, myasthenia gravis and botulism must also be included in the differential diagnosis.

Careful clinical assessment and investigations (head MRI and electrophysiological examinations) could rule out mentioned diseases.

3. 7. Bickerstaff's brainstem encephalitis

CSF albuminocytological dissociation can occur, but its absence does not preclude the diagnosis. In one study, CSF albuminocytological dissociation was present in 25% of BBE patients in the first week, whereas CSF pleocytosis was present in 32% of patients with BBE [12].

Symptoms observed in the described patient occur in the course of BBE: progressive ophthalmoplegia, disturbed consciousness, ataxia and pyramidal symptoms. Anti-GQ1b antibodies often occur in people with BBE. However, the patient we describe was anti-GQ1b negative. This situation occurs in 10% of patients with BBE [9-11]. A diagnosis of BBE was made based on the clinical symptoms, such as ophthalmoplegia, ataxia and impaired consciousness. In MRI of the head, hyperintensive changes in the T2 sequence located in the brain stem are observed (in about 1/3 cases). In EMG, demyelinating changes in motor fibers can be found [9].

4. CONCLUSIONS

Bickerstaff's brainstem encephalitis is a rare disease that must be considered in patients with ataxia, ophthalmoplegia and central nervous system involvement.

The clinical course, the presence of discrete demyelinating lesions in neurography, a significant recession of neurological symptoms within a few months of observation may suggest brainstem inflammation (despite the lack of serological confirmation – which is possible in 10% of patients). Establishing a diagnosis in the present case seems to be extremely difficult.

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