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## Relapsing-Remitting Severe Bickerstaff's Brainstem Encephalitis – Case Report and Literature Review

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### Summary

**Background:**

Bickerstaff's brainstem encephalitis (BBE) is a very rare disease of the central nervous system. Aetiology of the disease is auto-immunological. However, it is not entirely understood. Clinically BBE manifests in progressive ophthalmoplegia, ataxia and consciousness disturbances. Clinical symptoms are usually preceded by an unidentified infection of the upper respiratory tract. Usually, the disease has one phase, but individual relapses have also been described. Despite quite severe clinical symptoms, the prognosis is usually good.

**Case Report:**

The article presents a case of a patient with relapsing-remitting severe BBE. The case is presented due to the relapsing-remitting clinical course of the disease that resulted in patient's death, rarely described in the literature. We also present the results of subsequent MR scans in the course of the disease, so far described only in individual reports. It is also the first report in the world's literature presenting the results of series of MR spectroscopy (MRS) examinations in the course of BBE.

**Conclusions:**

MR examination is an important component in BBE diagnostics, allowing to differentiate atypical cases and place them under special supervision due to the possibility of the severe clinical course. MR also facilitates differentiation between Miller-Fisher Syndrome (MFS) and BBE in cases of diagnostic doubts. Adding MRS and MRI to the protocol allows us to define the nature of morphological changes more accurately in patients with suspected or diagnosed BBE.

**MeSH Keywords:**

**Brain Stem • Encephalitis • Magnetic Resonance Imaging • Magnetic Resonance Spectroscopy • Miller Fisher Syndrome**

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### Background

Bickerstaff's brainstem encephalitis (BBE) is a very rare disease of the central nervous system. Aetiology of the disease is auto-immunological, however, it is not entirely understood. Clinically BBE manifests in progressive ophthalmoplegia, ataxia and consciousness disturbances [1,2]. Clinical symptoms are usually preceded by unidentified infection of the upper respiratory tract. Usually, the disease has one phase, but individual relapses were also described.

Despite quite severe clinical symptoms, the prognosis is usually good [1].

BBE was distinguished as a clinical entity in 1951 by Bickerstaff and Cloak, who described 3 cases of patients with drowsiness, ophthalmoplegia and ataxia. They called it "mesencephalitis" and "rhombencephalitis" [3]. Five years later, Fisher described 3 cases of patients with ophthalmoplegia, ataxia and hyporeflexia. Due to the presence of hyporeflexia and changes in the cerebrospinal

fluid he postulated that the disease is a variant of the Guillain-Barre Syndrome (GBS). On the basis of his observations, Fisher syndrome was distinguished (FS) [4]. In 1957 Bickerstaff added 5 new cases to the primary description, using a term *brainstem encephalitis* [5]. In 1978, the author himself introduced the entity, BBE, in the *Handbook of Clinical Neurology* [6].

## Case Report

A patient, 59-year-old lorry driver, was admitted to the Clinic of Neurology due to muscle weakening in legs, lasting about 3 weeks. Medical history: 2 years earlier, hospitalization in the Department of Neurology of the Voivodeship Hospital due to the symptoms of brainstem damage. In the area of brainstem – mostly in the dorsal pons – MRI showed an irregular area of hyperintensity on T2-weighted images, spreading towards the medulla on the left, slightly enhancing in the central area after injection of the contrast medium and slightly modelling the fourth ventricle (Figures 1A, 2A). Proton spectroscopy (1H MRS), using a single-voxel method (PRESS, TE=35 ms, TR=1500 ms, nex=192) showed the correct proportions of the main metabolites in the changed area, NAA/Cr, (N-acetylaspartate/creatine) Cho/Cr (choline/creatine) and mI/Cr (myoinositol/creatine), with the presence of lactate (Lac) and lipid (Lip) bands (Figure 3A).

After the administered anti-oedematous treatment there was a slight clinical improvement – headaches, double vision and walking disorders were reduced. MRI examination conducted after 2 weeks (not presented in the article) showed that there was still hyperintensity on T2-weighted images, affecting the similar area as in the initial examination, with the area of contrast enhancement and slightly smaller oedema. Due to the unclear cause and suspicion of the neoplastic process, the patient had a neurosurgical and oncological consultation. However, he was not qualified for surgical treatment or radiotherapy, and further treatment in ambulatory conditions was recommended under the control of Neurological and Oncological Clinic. After discharging the patient from the Clinic his neurological state systematically improved, and MR repeated after 5 months (Figures 1B, 2B) showed significant regression of changes in the brainstem. The neurological state of the patient was stable for another 1.5 year and deteriorated again 3 weeks before readmission to the Clinic.

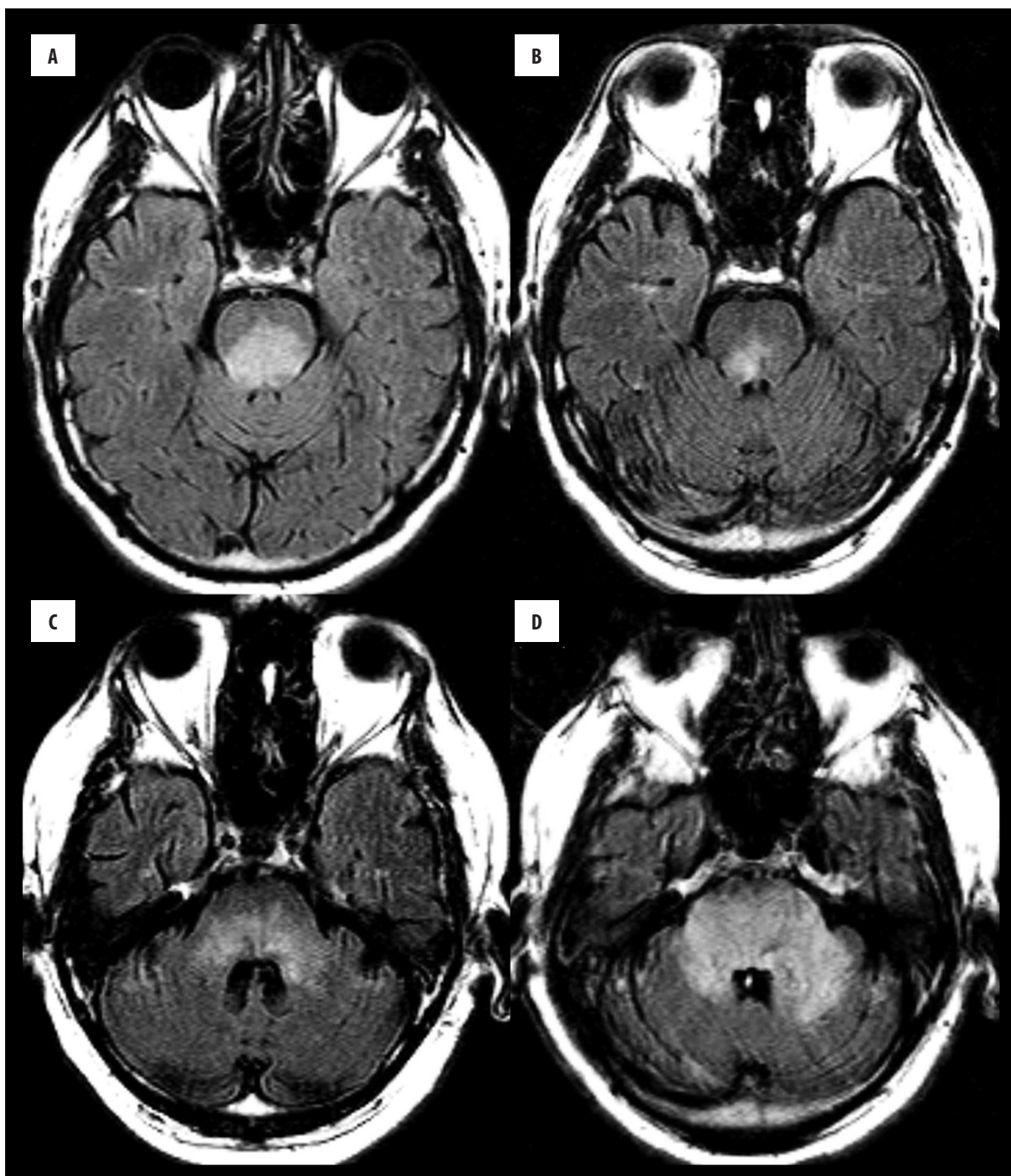
After readmission to the Neurological Clinic, examinations showed eye movement disorder, pyramidal syndrome in a form of tetraparesis, left-sided hypoesthesia and symptoms of bulbar palsy and cerebellar disorder. Brain MRI showed (Figures 1C, 2C) an expansion of the previously stated lesions, which now covered the pons and the cerebral and cerebellar peduncles. In the focal area there were stated irregular areas of enhancement after injection of the contrast medium and a slight mass effect, with a slight pressure on the fourth ventricle. MRS showed a slight reduction of NAA/Cr proportions, a bit higher (in comparison to the previous MRS) values of Cho/Cr and mI/Cr, with a higher content of Lac/Cr and Lip/Cr (Figure 3B).

Additional examinations showed a slightly increased level of protein (76 mg%) in the cerebrospinal fluid, with a correct amount of cells (3 lymphocytes/1  $\mu$ L), whereas, an analysis of the amount and quality of proteins indicated the intrahecal synthesis of antibodies (Reibergram: IgG-3 and type 3 of isoelectric focusing). Blood tests showed the presence of IgG antibodies against HSV1, CMV and EBV. HIV1 and HIV2 IgG antibodies or p24 antigen of HIV were not detected. IgG and IgM antibodies responding to recombinant antigens GM1, GD1b and GQ1b were not detected in the serum either. Due to increasing numbness in distal limbs during hospitalization, EMG was conducted showing damage to the peripheral sensory nerve fibres of demyelinating nature. On the basis of neurological symptoms and additional examinations a diagnosis of auto-immunological brainstem encephalitis was established.

Treatment consisted of 5 intravenous infusions of methylprednisolone (1 g/day). Next, 5 plasmapheresis procedures were conducted, causing significant neurological improvement. A control MRI scan after 2 weeks (not presented in the article) showed reduction of hyperintensities on T2-weighted images. However, strong contrast enhancement in the nuclei of brainstem reticular formation and on the left side of the vestibular nuclei of the cerebellum was still visible. The patient in good general condition with mild tetraparesis, bulbar palsy and cerebellar disorder features was transferred to the Department of Neurological Rehabilitation for further treatment.

After one month the patient was readmitted to the Neurological Clinic due to intensification of tetraparesis, eye movement disorder combined with bulbar palsy and cerebellar disorder (severe dysarthria). Subsequent MRI examination (Figures 1D, 2D) showed considerable increase in the extension of hyperintensity involving the pons, cerebral and cerebellar peduncles, and spreading towards the hemispheres of the cerebellum. Within the inflamed area, in comparison to the previous MRI examination, there was a more intensive, irregular (streaked and lumped) area with strong enhancement after injection of the contrast medium and a higher level of mass effect. The next MRS showed considerable reduction of NAA/Cr and clear increase in Cho/Cr and mI/Cr with considerable accentuation of lactate and lipid bands (Figure 3C).

During the 7<sup>th</sup> day since the admission, contact with the patient suddenly deteriorated. Due to the increasing respiratory insufficiency the patient was intubated and connected to a respirator. For the remaining period of hospitalization the patient's general state was serious, he was unconscious and connected to the respirator. He also had an infection with hospital-associated strains (*Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Proteus mirabilis*). Despite treatment (5 infusions of antibodies, decongestants, antibiotic therapy consistent with antibiogram) the patient's neurological state did not improve. After the 63<sup>rd</sup> day of the general time of hospitalization the patient died, with symptoms of cardio-respiratory insufficiency. At the request of the family an autopsy was not conducted.

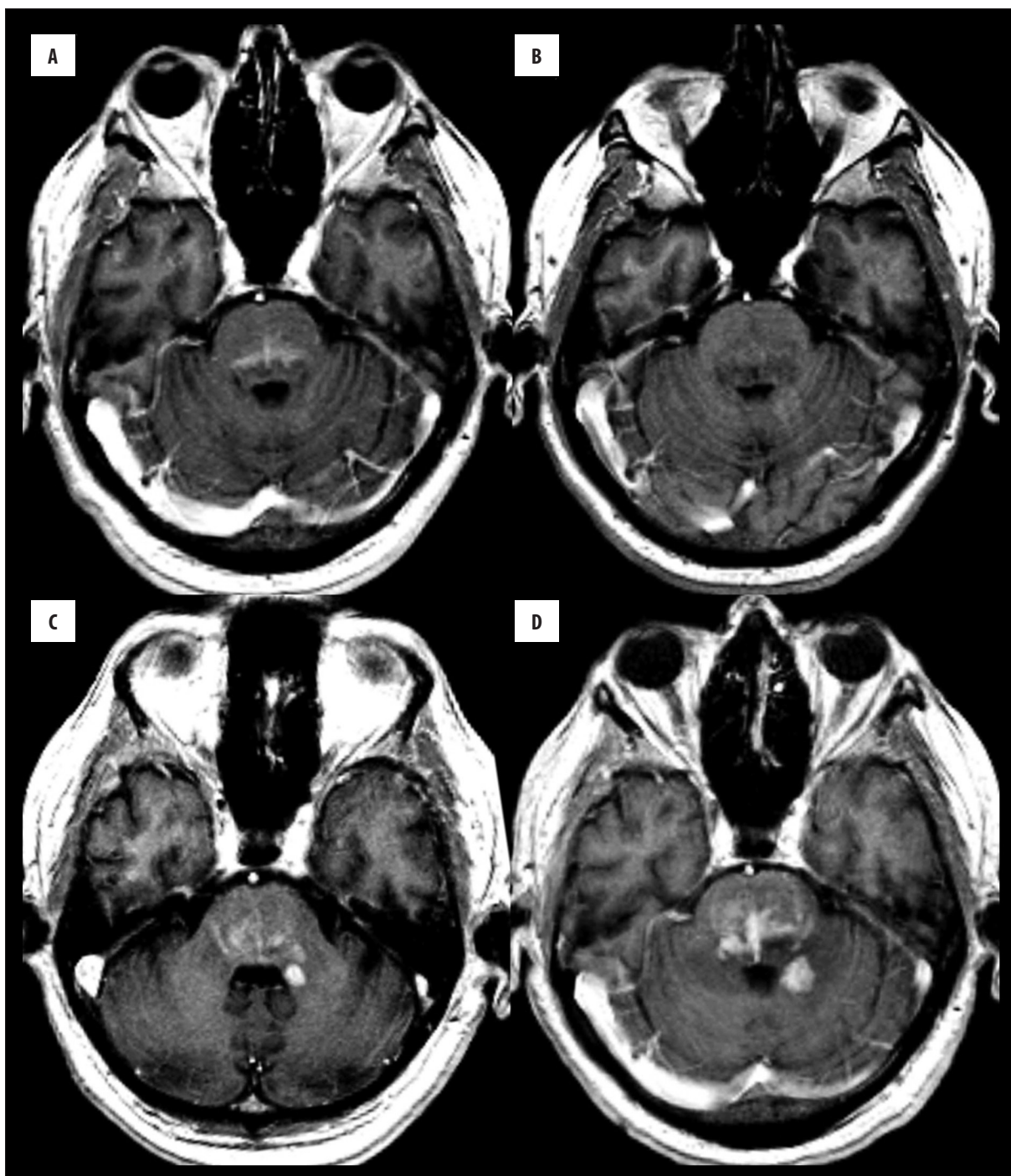


**Figure 1.** Following MRI in a 59-year-old patient with Bickerstaff encephalitis (FLAIR axial images). Admission MRI showed an irregular hyperintensity area in the dorsal pons spreading towards the medulla (A). MRI repeated after 5 months showed a significant regression of changes (B). After 1.5 year MRI showed recurrence of the previously stated lesions, with involvement of the pons, cerebral and cerebellar peduncles (C). Subsequent MRI showed a considerable increase in the extension of hyperintensity involving the brain stem and spreading towards the hemispheres of the cerebellum (D).

## Discussion

Bickerstaff's brainstem encephalitis (BBE) mainly manifests itself with ophthalmoplegia, ataxia and consciousness disturbances. Miller-Fisher Syndrome (MFS) has similar symptoms and is treated as a variant of Guillain-Barre

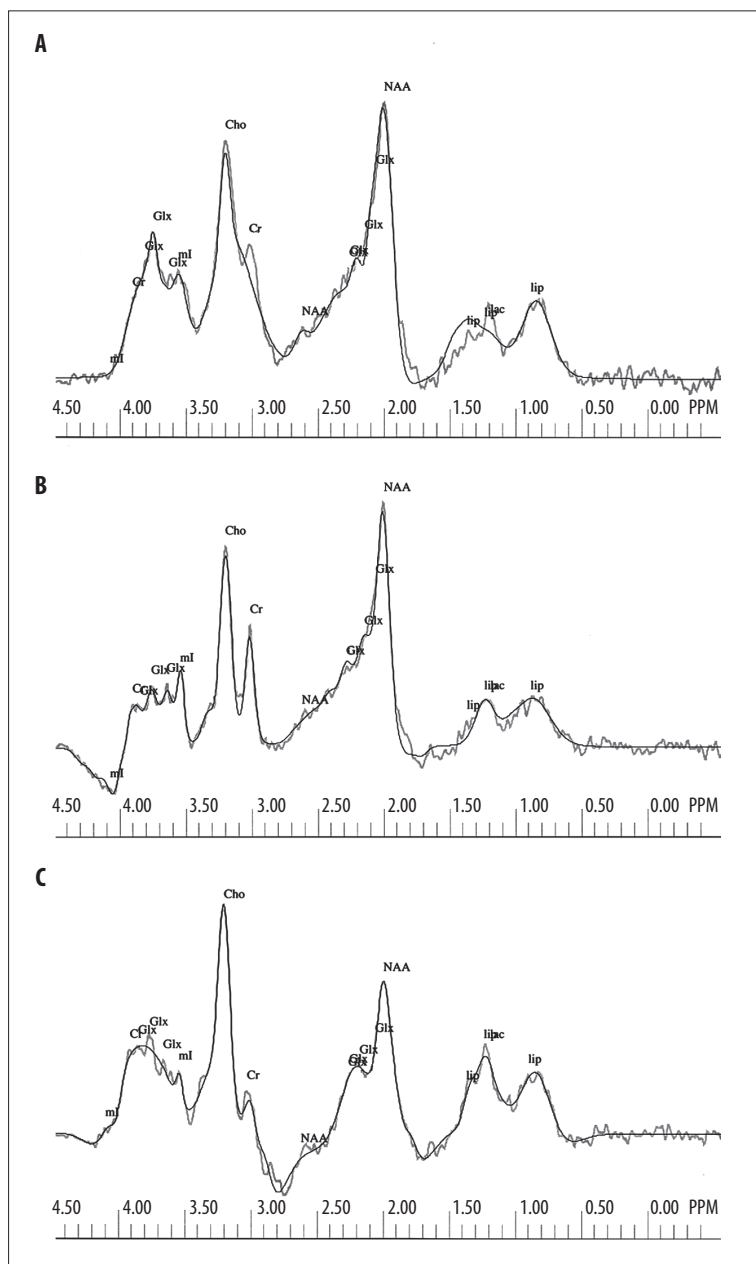
Syndrome (GBS). The difference between BBE and MFS is consciousness disturbances, which occur only in BBE [7]. The literature also describes some cases of simultaneous occurrence of MFS and GBS, BBE and GBS, and individual cases of occurrence of all three diseases – MFS, GBS and BBE [8]. Due to the similarities in the clinical image,



**Figure 2.** Following MRI in a patient with Bickerstaff encephalitis; T1-weighted images after contrast enhancement. In initial MRI, a small central area slightly enhancing after injection of the contrast medium (A). Regression of changes in the brainstem and no significant enhancement lesion in MRI after 5 months (B). MRI after 1.5 year revealed irregular areas of enhancement after injection of the contrast medium (C). An intensive, irregular area with strong enhancement after injection of the contrast in a subsequent MRI (D).

Odaka et al. suggest that these syndromes are included in the constant spectrum of clinical auto-immunological symptoms, which may occur simultaneously and in different configurations, seizing both the central and peripheral nervous system [9,10]. It is also confirmed by the observations of Ito et al. including the biggest group of people (over 500) in the literature, suffering from BBE and/or MFS [11].

Immunological examinations confirm the common origin of these syndromes. In the serum of patients with BBE, MFS, and GBD, antibodies against gangliosides may often be found. The occurrence of anti-GQ1b antibodies is characteristic of BBE and MFS, whereas anti-GM1 antibodies – of GBS. The presence of these antibodies is detected in about 70% of patients with BBE. While in case of MFS the presence of the antibodies is stated in 83–100% of patients,



**Figure 3.** Initial single voxel proton MR spectroscopy showed the correct proportions of the main metabolites (NAA/Cr, Cho/Cr and ml/Cr) in the changed area, with the presence of lactate and lipid bands (A). Control MRS in the second episode after 1.5 year showed a slight reduction of NAA/Cr and an increase in Cho/Cr and ml/Cr with still present lactate and lipids (B). Subsequent MRS showed a considerable progressive reduction of NAA/Cr and a clear increase in Cho/Cr and ml/Cr with a significant increase of lactate and lipid peaks (C).

it is only 8% in GBS [9–11]. Due to the common mechanism, Odaka et al. suggest one term for all the three syndromes – “anti-GQ1b IgG antibody syndrome” [9].

The literature described the occurrence of BBE after infections with Herpes simplex virus, Cytomegalovirus, Epstein-Barr virus, Varicella-Zoster virus and bacterial infections with *Campylobacter jejuni*, *Salmonella typhi* and *Mycoplasma pneumoniae* [9–11].

In the described case clinical symptoms of BBE (MFS) occurred: eye movement disorder, pyramidal syndrome in a form of tetraparesis, cord syndrome with sensory deficit in a form of left-sided hypoesthesia, features of bulbar palsy and cerebellar disorder, and consciousness disturbances, which suggested damage in the central, not the peripheral, nervous system. However, no antibodies against

gangliosides were detected. The patient did not report the occurrence of any preceding infection either. However, the presence of antibodies IgG against HSV1, EBV and CMV was detected in the patient’s serum.

Due to the lack of “the gold standard” in BBE diagnostics, besides MFS one shall also consider e.g. Wernicke’s encephalopathy, CNS histiocytosis, multiple sclerosis, acute disseminated encephalomyelitis (ADEM), Behcet’s disease, primary and secondary vasculitis changes (e.g. in the course of systemic lupus erythematosus), brain tumors – gliomas or lymphomas of the CNS, paraneoplastic syndromes and CLIPPERS (*chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids*), a syndrome that has been lately described in the literature [11,12]. As MFS refers to the peripheral nervous system and BBE is associated with cerebral involvement, MR examination may

be decisive in case of diagnostic difficulties, as in patients with BBE changes in the brainstem are detected [13].

In the treatment of BBE the same treatment is used as in case of GBS: intravenous administration of immunoglobulins and plasmapheresis procedures [10]. Moreover, the available literature describes the use of corticosteroids, antiviral drugs and combinations of the above mentioned therapeutic methods [1,7,9,10]. In the case of our patient we used plasmapheresis procedures with initially good effect, later we also administered immunoglobulins.

Despite the severe clinical course, the prognosis in BBE is usually good. Usually its course has one phase. However, relapses were also described, as in the presented case [1,2]. In the presented case, the second episode of the disease occurred after quite a long period, 1.5 year after falling ill. A similar case of BBE with relapse after 3 years since the first episode of the disease was also described by Mondejar et al. [13]. According to the literature, the disease rarely ends with patient's death – as in case of our patient [10].

There are not many reports in the literature on changes in the course of BBE from the point of view of neuroimaging. In the analysis conducted by Odaka et al. [10], including 62 described cases of BBE, changes in MR examinations were stated only in 30% of the patients. The changes are usually non-specific – there are hyperintensities on T2-weighted images and hypointensities on T1-weighted images [1]. The enhancement after administering a contrast medium is usually not detected. However, Roos et al. [14] described a case, in which strong focal enhancement in the brainstem was detected. Changes in the course of BBE usually refer to the brainstem, sometimes with involvement of the cerebral and cerebellar peduncles; they can also affect the cerebellar hemispheres or vermis [1,13]. In individual reports, changes in the basal nuclei and thalamus were described [1,15,16]. The changes are usually reduced or disappear completely after several months. However, sometimes they may remain longer [13].

In the described case the changes in MR examination were consistent with the data in the literature. Initially, hyperintensities on T2-weighted MR images were only located in the pontine tegmentum, clearly reducing in the subsequent examinations. Initial irregular streaked areas of enhancement and mass effect were also reduced in the subsequent examinations. In the period of relapse the extension of hyperintensities and intensity of contrast enhancement were much greater. Besides the pons involvement, we stated spreading of changes in caudal direction, towards other parts of the hindbrain – the cerebral peduncles and cerebellar hemispheres and peduncles. Similar dynamics was described in 2 casuistic reports, in which subsequent MR examinations showed a tendency for peripheral spreading of changes towards the medulla [17,18]. However, contrast enhancement in the described case was not typical, only in one of the reports strong focal enhancement in the brainstem in the course of BBE was stated [19], although Mondejar et al. suggest that there may occur enhancement, as in case of other auto-immunological diseases [13].

In all MR examinations the results of neuroimaging (extension of hyperintensities and intensity of contrast enhancement) was consistent with the current clinical state. Hagenkötter et al. also described a case in which the intensification of changes in the subsequent MR examinations correlated with severe clinical symptoms [17].

Our report is the first one in the world's literature, presenting the results of the subsequent MR examinations in the course of BBE. Metabolic changes stated in MRS including clinical data and MR images were suggesting an inflammatory process [19,20]. Further examinations showed gradual increase of the content of choline, lactates and lipids, which could have indicated intensification of the inflammatory process and increase in the level of myo-inositol, probably reflecting the accompanying processes of neuroglia activation [21,22]. The level of NAA was initially correct (during the first episode), it was slightly lower in the second episode, and considerably lower in the last examination.

The results of the subsequent MR and MRS examinations corresponded with neuropathological changes derived from literature. However, there is not a lot of data on that subject. Autopsies mostly showed oedema with proliferation of astrocytes and perivascular lymphocytic infiltrates [10]. In one case the areas of neuronal necrosis were also detected [23], which may be connected with the reduction of NAA in the final period of observation. Reduction of NAA may also result from increasing oedema, as Weidauer et al. stated high values of diffusion coefficient within the changed area in the patient with BBE. On that basis, they suggest that the changes are rather a result of vasogenic, and not cytotoxic oedema [18].

In 2012 Koga et al. divided BBE into "typical and atypical" cases. In typical cases, BBE has similar neurological and serological symptoms (presence of antibodies anti-GQ1b) as in MFS and it has good prognosis. However, in atypical cases, antibodies anti-GQ1b do not occur, the results of cerebrospinal fluid tests are incorrect, there are changes on MR images, which results in a negative prognosis [24].

## Conclusions

Summing up, MR examination is an important element in BBE diagnostics, allowing to differentiate atypical cases and place them under special supervision due to the possibility of a severe clinical course. MR also facilitates differentiation between MFS and BBE in cases of diagnostic doubt. Adding MRS and MRI to the protocol allows us to define the nature of morphological changes more accurately.

## Conflict of interest

The authors declare that they have no conflict of interest.

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