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Atypical Multiple Sclerosis – Baló's Concentric Sclerosis: Two Case Reports and a Review

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We present two case reports of patients with diagnoses of Baló's concentric sclerosis. The characteristics of the pathogenesis of this disease are considered in relation to the differential diagnosis against other types of multiple sclerosis and potential therapeutic tactics are discussed.

Keywords: Baló's concentric sclerosis.

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS), with focal lesions of typical size and locations. However, there are also atypical forms of MS, among which Baló's concentric sclerosis (BCS) is now recognized.

The first report on BCS was provided by Marburg in 1906. However, this atypical form of MS was officially described as a rare demyelinating disease with lethal outcome in 1928 by the Hungarian neurologist Baló in a young student with right-sided hemiparesis and optic neuritis developing during life [1]. Previously, diagnoses of BCS had only been made post mortem, though cases of BCS started to be diagnosed during life when MRI scans were introduced into clinical practice; over the last 15 years, the literature has contained increasing numbers of descriptions of clinical cases with benign courses and relatively favorable prognoses.

The curability of this category of patients, when timely correct diagnoses are made, is supported by our two cases presented here. The two patients were followed at the Interregional Department of Multiple Sclerosis at Moscow City Clinical Hospital No. 24 and the Department of Radiological Diagnosis, Neurology Science Center.

Case 1. Patient A, male, born in 1987. In December 2015, the patient noticed numbness in the left limbs and left half of the face, with gradually increasing sensory impairments over the period of a week. After a week, the patient's relatives noted onset of listlessness and disorientation in space. The patient was admitted to the local hospital. An MRI brain scan with contrast revealed multiple focal brain lesions (of the Baló's concentric sclerosis (BCS) type) which at that point were interpreted as "space occupying" CNS lesions. Treatment with dexamethasone (16 mg/day) was started, which decreased the severity of the patient's symptoms. Treatment was terminated at 10 days and sensory impairments, disorientation in space, and listlessness restarted after five days. The patient was transferred to the Blokhin Russian Oncology Science Center for exclusion of a "space-occupying" process. Positron emission tomographic investigations suggested a demyelinating CNS disease.

At the beginning of 2016, the patient was seen at the Interregional Department of Multiple Sclerosis, where attention was drawn to mild dysarthria, left-sided pyramidal insufficiency, left-sided hemihypesthesia, and impaired pelvic organ function (urinary retention) in the neurological status. An MRI scan on January 16, 2016 revealed multifocal brain lesions in the form of numerous "annular" foci in

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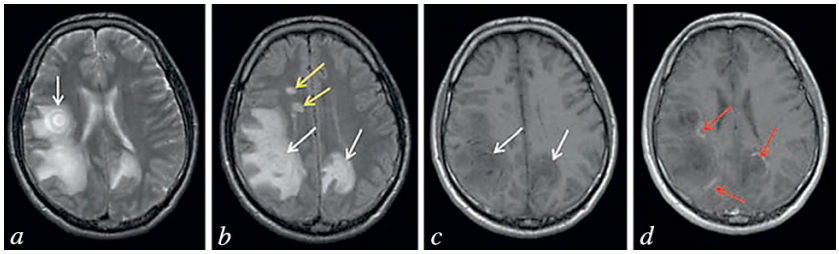

Fig. 1. Brain MRI scan with contrast, January 16, 2106, T2 (*a*), T2 FLAIR (*b*), T1 (*c*), and T1 modes after administration of contrast medium (*d*), axial projection. The white matter of the frontal and parietal lobes of the right hemisphere of the brain and the parietal lobe of the left hemispehre contains three round plaques of heterogeneous structure (alternating annular zones reminiscent of annual growth rings in tree trunks) surrounded by perifocal edema (white arrows). Administration of contrast medium was followed by partial accumulation of medium at the peripheries of these plaques (red arrows). In addition, the white matter of both hemispheres of the brain contain a few typical plaques of demyelination (yellow arrows).

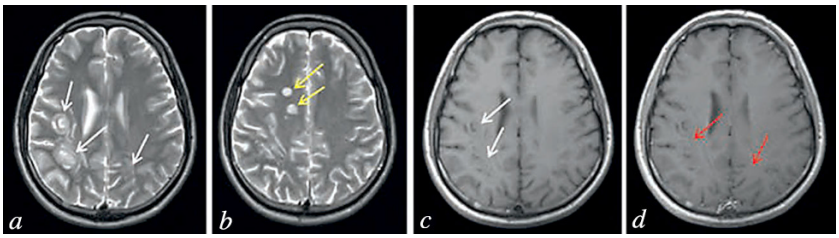

Fig. 2. Brain MRI scan with contrast, March 21, 2016, T2 (*a*, *b*), T1 (*c*), and T1 modes after administration of contrast medium (*d*) modes, axial projection. The white matter of the frontal and parietal lobes of the right hemisphere of the brain and the parietal lobe of the left hemisphere of the brain contain three round plaques of heterogeneous structure (alternating annular zones reminiscent of annual growth rings in tree trunks) without perifocal changes (white arrows). Administration of contrast medium was not followed by its pathological accumulation (red arrows). In addition, the white matter of both hemispheres of the brain contain occasional typical plaques of demyelination (yellow arrows). Comparison of MRI brain scans demonstrated improvement, with decreases in the sizes of "annular" plaques, along with the absence of perifocal edema and pathological accumulation of contrast medium.

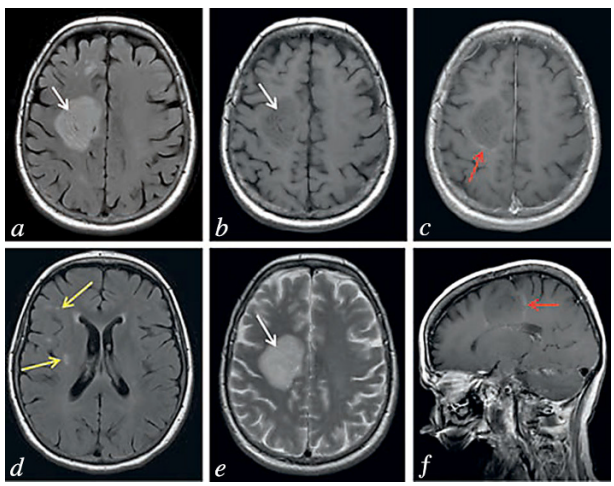

Fig. 3. MRI brain scan with contrast, October 14, 2015, T2 FLAIR (*a*, *d*) T2 (*e*), T1 (*b*) modes, axial projection, and T1 mode after administration of contrast medium, axial projection (*c*) and sagittal projection (*f*). The white matter of the frontal lobe of the right hemisphere of the brain contains a round zone with smooth, clear edges and heterogeneous structure – alternating annular zones reminiscent of annual growth rings in tree trunks (white arrows). Administration of contrast medium was followed by partial accumulation of medium at the periphery of the zone (red arrows). In addition, the white matter of both hemispheres of the brain contains numerous plaques whose origin needs to be differentiated between vascular and demyelinating processes (yellow arrows).

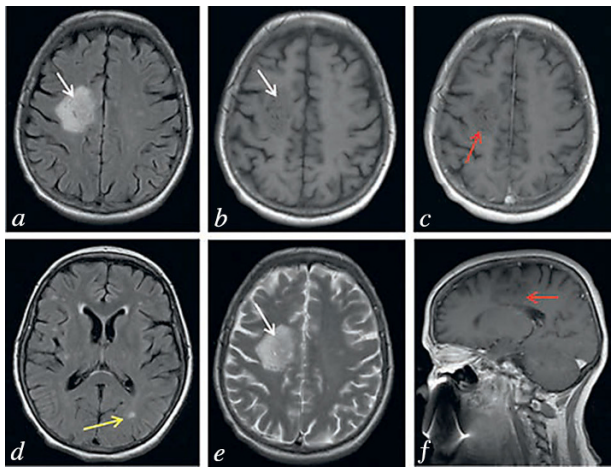

Fig. 4. MRI brain scan with contrast November 24, 2015, T2 FLAIR (*a*, *d*), T2 (*e*), and T1 (*b*) modes, axial projection, and T1 mode after administration of contrast medium, axial (*c*) and sagittal (*f*) projections. The white matter of the frontal lobe of the right hemisphere of the brain contains a round zone with smooth, clear edges and heterogeneous structure – alternating annular zones reminiscent of annual growth rings in tree trunks (white arrows). Administration of contrast medium was not followed by pathological accumulation of medium (red arrows). In addition, the white matter of both hemispheres of the brain contains numerous plaques whose origin needs to be differentiated between vascular and demyelinating processes (yellow arrows). Comparison of MRI brain scans demonstrated improvement, with decreases in the size of the "annular" plaque in the right hemisphere of the brain and the absence of pathological accumulation of contrast medium.

both hemispheres of the brain, accumulating contrast at their peripheries on the background of typical plaques of demyelination (Fig. 1).

History-taking, neurological examination, and the MRI brain scan led to a diagnosis of atypical MS – a variant of BCS. The patient received hormone pulse therapy consisting of seven doses of methylprednisolone 1000 mg, which produced improvement consisting of regression of neurological symptomatology. The patient underwent a repeat MRI scan on March 21, 2016, which showed improvements in the form of decreases in the sizes of the "annular" plaques in both hemispheres of the brain and the absence of perifocal edema and pathological accumulation of contrast medium (Fig. 2). Brain MRI scans at 3 and 6 months (June 21, 2016 and November 26, 2016) showed no deterioration as compared with the MRI investigation of March 21, 2016.

Case 2. Patient B, female, born in 1949. The patient started no notice episodes of headache accompanied by tinnitus from March 2014, with instability on walking and weakness in the left arm from August 2015. An MRI brain scan demonstrated formation of round plaques with partial accumulation of contrast substance at the periphery. A neurology consultation led to a diagnosis of space-occupying brain lesion. The patient was transferred to the Interregional Department of Multiple Sclerosis. At admission, neurological status included dysarthria, left-sided hemiparesis (mild in the leg and moderate in the arm), and a paretic gait. An MRI brain scan on October 14, 2015 showed a round zone of an inhomogeneous "annular" structure in the right hemisphere of the brain, partially accumulating contrast medium at the periphery on the background of several other plaques (Fig. 3).

The patient's history, along with neurological examination and MRI brain scan data, led to a diagnosis of atypical multiple sclerosis (BCS). Hormone pulse therapy using five doses of methylprednisolone 1000 mg plus immunosuppression with mitoxantrone 10 mg led to partial regression of neurological symptomatology: on discharge from hospital, the patient had mild left-sided upper monoparesis. The patient underwent clinical follow-up with repeat MRI brain scan on November 24, 2015, which demonstrated improvement, with reduction in the size of the "annular" plaque in the right hemisphere of the brain and no pathological accumulation of contrast medium (Fig. 4).

At three months (February 25, 2016) the patient underwent repeat MRI brain scan, which showed no deterioration from the appearances of the MRI scan of November 24, 2015.

Discussion. BCS generally arises in young people, with a mean age of about 35 years (3–62 years). Twice as many patients are female as male [2–5]. Until relatively recently, it was believed that BCS could only occur in people of the oriental races [3, 4, 6, 7]. However, a quite large number of cases of this disease in occidental people have now been described [4, 6, 7].

Clinically, BCS can be apparent as acute or subacute neurological symptomatology depending on the volume and location of the lesion. General cerebral symptomatology often includes headache and cognitive or behavioral disorders. Focal neurological symptomatology generally consists of hemipareses, ataxia, dysarthria, and aphasia [2–4, 6–9]. The totality of the general cerebral and focal neurological symptomatology may be misinterpreted by clinicians as the onset of acute disseminated encephalomyelitis, stroke, space-occupying lesion, neoplasm, or abscess [2, 4, 6, 8].

Radiologically, BCS is characterized by "annular" zones of demyelination with areas of relatively preserved myelin, which allows it to be quite easily differentiated from other demyelinating processes on MRI brain scans obtained at the appropriate time [10, 11]. The diagnosis of BCS is based on comparison of the classical brain MRI picture with the results of clinical examination. Liquor investigations often show mononuclear inflammatory reactions, increased protein levels, and, sometimes, oligoclonal IgG. Considering the rapid deterioration occurring without treatment, biopsy for confirmation of the diagnosis is justified [2, 4, 6–9]. Demyelinated areas show loss of oligodendrocytes typical of demyelination [2, 12].

The cause of the concentric nature of the lesion in BCS remains to be understood. The main hypothesis at present is that the inflammatory reaction propagates radially from a "central point," at which there is failure of the blood-brain barrier [13]. The leading element in the pathogenesis of BCS is damage to oligodendrocytes due to oxidant stress, which is induced by a number of mediators, which are in turn produced by activated macrophages and microglial cells. At the same time, there is a hypoxia-induced increase in the expression of inducible factor and heat shock protein 70, high concentrations of which are found in oligodendrocytes and astrocytes in the externally unaltered white matter in the immediate vicinity of the "ring" of demyelination [13]. This leads to an increase in the resistance of oligodendrocytes to oxidant stress. These mechanisms also lead to the formation of zones of externally unaltered white matter as a result of so-called peripheral protection from the demyelinization process. However, the inflammatory process propagates further and reaches areas with anti-inflammatory mediator concentrations below the protective level, which triggers demyelination processes in a new ring. Ans as the lesioned area becomes larger, the alternating rings of demyelination and externally unaltered white matter form the "annular" plaque typical of BCS. The existence of alternating ischemic processes in the concentric plaque may be supported by coefficients of diffusion measured in diffusion-weighted MRI scans [12].

The typical concentric plaques often arise in isolation or on the background of a preexisting radiologically isolated syndrome or entirely typical MS. The results of a number of studies have shown that 53% of cases of BCS develop on the background of typical plaques of demyelination typical of MS [2] – so-called Baló-like plaques. An isolated concentric ring is seen in 42% of cases, MS-typical plaques of demyelination appearing only later – this variant

is true BCS. However, this distinction is relative, as there are as yet no exact criteria for the differential diagnosis of Baló-like plaques and true BCS. Family, a number of authors have described concentric BCS plaques not only on the background of MS, but also in other diseases, such as progressive multifocal leukoencephalopathy, human herpesvirus 6 encephalitis, neurooptic myelitis, and CADASIL [14–17]. This in turn suggests that concentric plaques arise in in patients with an initial predisposition to inflammatory reactions with the centrifugal distribution.

As regards the treatment of BCS, there is little information and no standard protocol for managing patients with this disease has been developed. The international consensus of specialists (based on published data) is that the acute period should be treated with hormone pulse therapy as first-line treatment and with plasmapheresis as second-line therapy [10, 18]. The use of cytostatic therapy with mitoxantrone, cyclophosphamide, and azathioprine should be considered on an individual basis. Data have been published on the use of alemtuzumab in a patient not responding to hormone pulse therapy, plasmapheresis, and cyclophosphamide [19]. Some specialists now take the view [6] that when the criteria of dissemination of demyelination plaques in space and time and for the diagnosis of MS are met, MS disease-modifying drugs should be used to prevent recurrences. However, this point of view is not supported by results from randomized multicenter studies. A number of publications [19, 20] have noted the use of β-interferon formulations as pathogenetic therapy. Data have also been published [20] on the successful use of natalizumab in a patient with a Baló-like plaque of demyelination on the background of clear remitting MS. The question of the tactics for managing patients with asymptomatic disease, i.e., those with no more than radiological signs of disease, remains open.

In conclusion, we again emphasize that BCS is an atypical CNS demyelinating disease variant with typical radiological and clinical characteristics. The active introduction of MRI scanning into clinical practice has shown that the course of this disease is heterogeneous – it varies from fulminating to asymptomatic. Much in the pathogenesis of BCS and the treatment of patients remains unclear. Development of these questions is associated to a large extent with the small number of documented cases, such that large studies cannot be undertaken. A possible approach in this situation is to create international registers (both retrospective and prospective) of patients with BCS. These registers would allow more detailed views of all aspects of the disease to be developed, which in turn would enable the development of a single algorithm for the management of these patients.

The authors have no conflict of interests.

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