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Oligoclonal bands as predictors of multiple sclerosis inclinically isolated syndrome

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Abstract

Clinically Isolated Syndrome (CIS) is the first episode of inflammatory and demyelinating symptoms. According to the classification criteria of multiple sclerosis (MS) from 2013, CIS is defined as the first clinical manifestation of the disease. McDonald's 2010 criteria, considered the gold standard in the diagnosis of MS, are based on the clinical symptoms and the characteristic changes in magnetic resonance imaging (MRI). Unfortunately, up to 60-70% of patients with CIS do not meet the criteria for diagnosing MS at an early stage. At the same time, approximately 85% of patients with CIS will develop clinically defined MS(CDMS) in the future. When looking for other diagnostic tools, attention was paid to the role of oligoclonal bands (OBs) as predictors of MS development. Oligoclonal bands are immunoglobulins produced intrathecally by B-lymphocytes and plasma cells. Their level is examined in cerebrospinal fluid (CSF) collected by lumbar puncture. Studies carried out on a group of patients with CIS showed that people with positive testresultsfor oligoclonal bands are twice as likely to develop MS than people with negative OBs. These conclusions are reflected in the revised McDonald's criteria in 2017, where OBs are used in the diagnosis of

CIS patients with absence of new symptoms of the disease and changes in MRI.Early diagnosis makes possible to implement modifying disease drugs in the initial stage and, consequently, to achieve better therapeutic effects. The emphasis is also put on the development of other predictors in body fluids, which are effective in the diagnosis of people with CIS and negative oligoclonal bands. Many factors, including Epstein-Barr virus, chitinase-3 like 1, chitinase-3 like 2, chitotriosidase, multi-specific response to measles, rubella and varicella known as "MRZ reaction" orT-cell gene mutation are studied as a potential risk factors for MS development. Their use in diagnostics would improve the detection of MS in earlier stages, and thus the treatment of largerpopulation of patients.

Key words: Oligoclonal bands; Clinically isolated syndrome; Multiple sclerosis; Cerebrospinal fluid; Predictor.

Introduction

Clinically Isolated Syndrome (CIS) is the first, monophasic episode of neurological symptoms with the character of inflammatory demyelination [1]. Has anacute or subacute course with a duration of not more than 24 hours [2,3]. After revising the classification of multiple sclerosis (MS) from 1996, CIS was included in the new classification from 2013 as the first clinical manifestation of multiple sclerosis [4]. However, CIS cannot be identified with clinically defined multiple sclerosis (CDMS). According to the McDonald's 2010 criteria for MS diagnosis, early multiple sclerosis patients can be diagnosed on condition of clinical symptoms and changes in magnetic resonance imaging (MRI) in the form of central nervous system (CNS) damage in typical areas and asymptomatic lesions reinforcing the contrast. The conditions of spreading in space and in time are then fulfilled.Meanwhile, only changes in the clinical picture occur in CIS, usually without changes in MRI or with changes that do not meet the dissemination criteria in time [5].The sources report that up to 60-70% of patients with the first clinical episode do not complete the criteria for MS [6]. Nevertheless, as many as 85% of patients will develop future full-blown MS in the form of chronic autoimmune demyelinating disease [6,7].Early diagnosis of patients with a high risk of developing MS is

the key to the fast inclusion of disease-modifying drugs, which are then much more effective. Insufficient usefulness of MRI in early diagnosis of MS motivates to searching for new predictors.Oligoclonal bands (OBs) next to MRI are used in the diagnosis of demyelinating lesions. Their synthesis occurs not only in patients with MS but also in patients with CIS. This allows them to be used as another prognostic factor [8].

In McDonald's 2010 criteria, oligoclonal bands are not sufficient evidence of MS diagnosis in the absence of changes in MRI. Meanwhile, the new McDonald's criteria from 2017 underline usefulness of OBs [9].

Definition of oligoclonal bands (OBs)

Oligoclonal bands are immunoglobulins, mostly IgG, produced by stimulated clones of plasma cells. They are not serum antibodies because they are produced inside the nervous system,intrathecal. Although oligoclonal bands have been found to be a product of intrathecal B lymphocytes and plasma cells, it is still unclear how these cells enter the central nervous system and establish immunologically active points.It is believed that the final maturation of B lymphocytes and their affinity for a closer unknown antigen results in the formation of peritoneal infiltrates and meninges [10]. What is more, the process of B lymphocyte infiltration occurs through continuous exchange across the blood-brain barrier [11].

OBs level is assessed based on cerebrospinal fluid (CSF) obtained by lumbar puncture. The presence of oligoclonal protein is imaged by isoelectric focusing (IEF) gel electrophoresis of cerebrospinal fluidin the form of so-called bands.OBs are considered the main immunodiagnostic feature of multiple sclerosis, detected in more than 95% of patients [12].The study in which Poser criteria for MS diagnosis were applied, the presence of oligoclonal protein was found one of the strongest predictive factors of multiple sclerosis [7].It has also been proven that positive OBs predict clinically defined MS in children with optic neuritis [13].However, this is not a specific indicator for this disease, because an increased level of OBs can occur in many other inflammatory and infectious diseases of the central nervous system[14].

Research on oligoclonal bands as predictors of multiple sclerosis

The importance of oligoclonal bands as a predictive factor of MS changes with the development of knowledge about the pathogenesis of MS.After the revision of the McDonald's 2010 criteria, many studies were carried out. Schwenkenbecher et al. observed 120 patients with CIS, with whom conversion to MS was demonstrated in 42% of cases, the remaining 58% was defined as stable CIS. Among the same group of patients, positive OBs were detected in 61% of patients with CIS at the beginning of the study. During follow-up, 55% of patients with positive OBs were converted to MS compared to 21% of patients with negative OBs who developed MS. Patients with OBs positive at the start of the study were more than twice as likely to be converted to clinically definite MS as patients with negative OBs (Figure 1. and Figure 2.). The median time needed for conversion was similar in both groups, so it did not depend on the results of oligoclonal bands [15].

Another retrospective study conducted by a German-Austrian team of scientists included 406 patients, of which 11% (44 people) met the diagnostic criteria for MS and the remaining 89% (362 people) had CIS diagnosed. In the cerebrospinal fluid test, OBs was positive in 86% of patients with CIS, of whom 74% developed multiple sclerosis. In 14% of patients no OBs were detected, 44% of them were converted to MS. The median conversion time for patients with CIS and positive OBs was 25 months compared to 47 months for patients with negative OBs. As in the previous study, patients with CIS and positive OBs were twice as likely to develop MS as those with negative OBs(Figure 1. and Figure 2.) [16].Moreover, in the second study, the conversion time to MS was almost twice as long in patients with negative OBs as in patients with positive OBs.

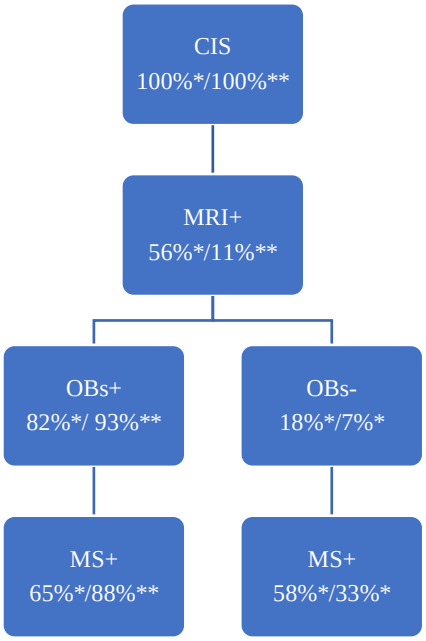

Figure 1.
Conversion of patients with CIS and MRI meeting the criteria for MS depending on the result of OBs in CSF.

* TheSchwenkenbecher et al. research results [15].
** The German-Austrian team of scientist's research results [16].

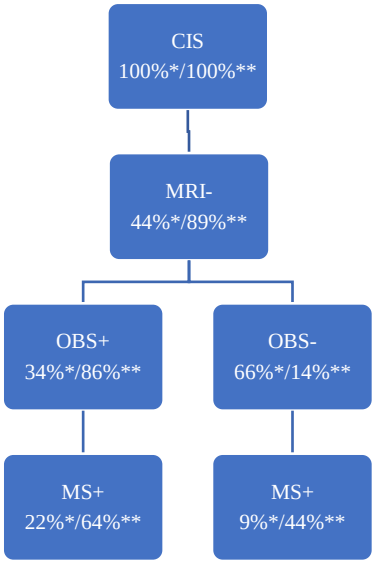

Figure 2.

Conversion of patients with CIS and MRI not meeting the criteria for MS depending on the result of OBs in CSF.
* The Schwenkenbecher et al. research results [15].
** The German-Austrian team of scientist's research results [16].

Many studies, included two cited above,strongly argue for the importance of oligoclonal bands in early diagnosis of MS [7,15-19]. According to results, the incidence of CIS conversion in MS in patients without changes in MRI and with positive OBs test was on average twice as high as in patients with negative OBs. In turn, the positive MRI examination for MS and positive OBs test results show the highest risk of MS development [15,16].

It must not be forgotten that many variables such as gender, age, nationality or even skin colour affect the test results [20-23].However, these resultsillustrate that oligoclonal bands in cerebrospinal fluid are high risk factor for the conversion to CDMS.

Application of oligoclonal bands testing

In the McDonald's 2010 criteria, considered the gold standard for MS diagnosis,oligoclonal bands are mainly used in the diagnostic process of primary progressive form of multiple sclerosis (PPMS). The relapsing-remitting phenotype (RRMS) is diagnosed based on the clinical picture and changes in MRI. Oligoclonal bands play additional function, but only if MRI lesions are characteristic for multiple sclerosis. They do not matter as an independent factor [5,24].

The revision of McDonald's criteria carried out by the group ofexperts in 2017, updated the McDonald's 2010 criteria to increase their sensitivity and specificity in MS diagnosis.

The main assumptions have been sustained. However, more emphasis has been placed on the early and accurate detection of clinically isolated syndrome. Improvement in diagnostics has been achieved thanks to the use of oligoclonal bands. In patients with a typical clinically isolated syndrome in which MRI revealed dissemination in space, without dissemination in time and without subsequent relapses or changes in another MRI scan, MS can be diagnosed based on the presence of OBs in CSF. These changes speak not only for faster diagnosis but also for faster inclusion of patient into treatment in drug programs.This, in turn, results in better therapeutic effectsand avoid spreading of the disease [9, 25,26].

New potential predictors of multiple sclerosis

The McDonald's criteria aim to develop new predictive factors for multiple sclerosis, which would be useful in patients with CIS and negative OBs. There are many potential substances whose presence in body fluids is examined under the diagnosis of MS. One of them is Epstein-Barr's virus (EBV), which was recognized as the triggering factor for MS. Studies have detected antibodies against the Epstein-Barr virus, which were considered a prognostic marker of MS conversion [27].There have even been hopes of stopping the progress of MS by

treating and preventing EBV infection through vaccination, treatment with antiviral drugs or EBV-specific cytotoxic cells [28].On the other hand, polispecific response to neurotrophic viruses such as measles, rubella or varicella, referred to as "MRZ reaction" is detected in patients with CIS who developed MS [29]. Chitinase-3 like 1 is another potential predictor of conversion to MS [30,31]. In addition, it is considered a significant indicator of long-term physical and cognitive disability [31]. It is also reported that chitinase-3 like 2 and chitotriosidase are promising biomarkers in the diagnosis of patients with the first episode of demyelination [32]. In turn, the unique gene mutation in cerebrospinal fluid B cells and specific molecular changes in CD4 + T-lymphocytes were also recognized as a factor in the conversion to CDMS [33,34]. New biomarkers bring hope to accelerate the diagnosis, which is associated with the earlier implementation of treatment and prevention of disease progression.

Conclusions

Over the years, oligoclonal bands, tested in cerebrospinal fluid, have proven to be a strong predictor of conversion from clinically isolated syndrome to clinically defined multiple sclerosis. Studies have shown that people with CIS and positive oligoclonal bands are twice as likely to develop full-blown MS than patients with negative OBs. The research results are reflected in the revised McDonald's criteria from 2017, where the oligoclonal bands are used in the diagnosis in patients with CIS and without progression in MRI. This results in earlier MS detection, faster implementation of treatment and better therapeutic effects. At the same time, new criteria draw attention to the need of identifying new predictors that will be used in patients with CIS and negative oligoclonal bands. Proven effectiveness and rapid introduction of at least one of new potential predictive factors will increase the detection of MS. As a result, more patients will be treated, which in turn will reduce the development of the disease and disability.

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