Medical Hypotheses 82 (2014) 300–309

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Intrathecal immune reset in multiple sclerosis: Exploring a new concept

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ARTICLE INFO

Article history:
Received 8 October 2013
Accepted 19 December 2013

ABSTRACT

Multiple sclerosis impairment is mainly driven by the progressive phase, whose pathology remains elusive. No drug has yet been able to halt this phase so therapeutic management remains challenging. It was recently demonstrated that late disability correlates with the spreading of cortical subpial lesions, and tertiary lymphoid organs (TLO) were identified in close apposition with these lesions. TLO are of crucial importance since they are able to mount a complete local immune response, as observed in the intrathecal compartment from the moment MS is diagnosed (i.e. oligoclonal bands). This article examines the consequences of this intrathecal response: giving a worst clinical prognostic value and bearing arguments for possible direct brain toxicity, intrathecal secretion should be targeted by drugs abating both B-lymphocytes and plasma cells. Another consequence is that intrathecal secretion has value as a surrogate marker of the persistence of an ongoing intrathecal immune reaction after treatment. Although it is still unsure which mechanism or byproduct secreted by TLO triggers cortical lesions, we propose to target TLO components as a new therapeutic avenue in progressive MS.

Whereas it was long considered that the inability of therapies to penetrate the blood–brain-barrier was a crucial obstacle, our proposed strategy will take advantage of the properties of the BBB to safely reset the intrathecal immune system in order to halt the slow axonal burning underlying secondary MS. We review the literature in support of the rationale for treating MS with intrathecal drugs dedicated to clearing the local immune response. Since many targets are involved, achieving this goal may require a combination of monoclonal antibodies targeting each cell sub-type. Hope might be rekindled with a one-shot intrathecal multi-drug treatment in progressive MS.

Introduction

Multiple sclerosis (MS) is the most frequent chronic inflammatory and demyelinating disorder of the central nervous system (CNS) in young adults and remains the second cause of disability in young people. Although most patients during the early phase of the disease suffer from a relapsing–remitting form of MS (RR-MS) characterized by acute relapses usually followed by a complete remission, the majority will develop a secondary progressive form (SP-MS). The impairment is mostly independent from the initial RR phase and is mainly driven by the late SP phase. Although treatments directed against the RR phase may have a slight preventive effect on the SP phase, none of them has unfortunately been shown to halt the ongoing secondary phase. Considering that most of the debilitating burden is driven by the progressive phase, building-up a therapeutic strategy dedicated to this phase remains a challenging goal.

Even if the exact pathophysiology of SP-MS remains to be completely clarified, the hallmark of this phase is the restriction of the immune response down to the intrathecal compartment, leading to progressive extensive cortical lesions and clinical impairment [1]. Interestingly, this partition occurs so early in the disorder that IgG intrathecal synthesis and oligoclonal bands are even part of the diagnostic criteria.

We briefly review the main actors in this intrathecal response leading to slow axonal burning. Then we hypothesize the exploration of a new potential therapeutic avenue in progressive MS. In other words, whereas it has long been considered that the inability of therapies to penetrate the blood–brain-barrier (BBB) is a crucial obstacle, we propose to take advantage of this to safely reset the intrathecal immune system in order to halt the slow axonal burning underlying secondary MS. We review the literature in support of the rationale for treating MS with intrathecal drugs dedicated to safely clearing the local immune response.

Abbreviations: Ab, antibody; AI, antibody index; AICD, activation-induced cytidine deaminase; ASC, antibody secreting cells; BBB, blood–brain barrier; CDR, complement determining region; CIS, clinically isolated syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; EDSS, expanded disability score; HSCT, hematopoietic stem cell transplantation; Ig, immunoglobulins; MRZ pattern, intrathecal reaction against measles rubella and zoster viruses; OCB, oligoclonal bands; PML, progressive multifocal leukoencephalopathy; PP, primary progressive MS; rAb, recombinant antibody; RR, relapsing–remitting MS; SP, secondary progressive MS; TLO, tertiary lymphoid organ.

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http://dx.doi.org/10.1016/j.mehy.2013.12.015

Drugs for relapsing–remitting (RR) phase fail to prevent atrophy and conversion to SP-MS: treatment of progressive MS is required

All the available treatments are directed against the inflammatory component of the RR phase but they fail to actively delay or prevent the onset of SP-MS, to cure it, or to prevent any kind of steady impairment. Furthermore, in primary progressive MS (PP-MS), no treatment has ever proved to be efficient [2]. Another clue to the limited efficacy of drugs in the early phase is the brain atrophy rate, which is a key point when considering the dynamic of impairment. This rate remains essentially constant and high throughout the course of MS, from clinically isolated syndrome (CIS) to PP-MS [3,4]. Interestingly, even in the RR-MS phase treated by the most active treatments for preventing relapses, i.e. alemtuzumab or autologous stem cell transplantation, the brain atrophy rate decreases but always fails to normalize and remains high [5–8].

Spreading of subpial cortical lesions drives the late disability

Although demyelination of the cortex and deep gray matter nuclei has long been known, the extent of cortical demyelination remained grossly underestimated until recent immunohistochemical methods demonstrating their presence in the very early stages of the disease [9]. Lesion burden increases with time to become more prominent than white matter lesions in the secondary phase (review in [10,11], and the cortical lesion load may even be a key event in the transition from RR-MS to SP-MS [12,13]. Cortical pial lesions (type III) extend from the pial surface to the superficial cortical layers [14] and represent approximately half of the cortical lesions [15], affecting 60% of the cortical ribbon of the brain, cerebellum and hippocampus [16–18]. They harbor distinct features: constant depth of demyelination waning at cortical layer 5 [15] and a large extension over the multiple gyri [15]. Cortical lesions are different from white matter lesions. They are devoid of inflammatory cells and macrophages [15,19], have sparse deposition of complement and immunoglobulins (Ig) (in [20]) and lack detectable serum-derived proteins, suggesting that an immune response underlying the cortical pathology occurs in the meninges [11,21]. Regional gray matter demyelination and atrophy are not driven by underlying white matter lesion load [22,23]. Progressive MS is associated with cortical demyelination and diffuse normal appearing white matter injury, which invariably occurs on a background of meningeal, perivascular and parenchymal inflammation [16,24].

Cortical inflammatory lesions are highly correlated with cortical atrophy and disability within each MS subgroup [25,26]. In a large five-year follow-up study, change in cortical matter fraction, new cortical lesions and clinical impairment (expanded disability score, EDSS) were highly correlated [25]. Age at onset of wheelchair use and death are correlated with extent of grey matter damage [10]. On the other hand, benign MS is characterized by an initially low cortical lesion charge (of about a third in RR-MS patients) and significantly lower new cortical lesions [25], whereas the number of shadow plaques in the white matter is not different in benign MS [10]. In a long-term cohort, benign MS demonstrated higher normal gray matter volume than non-benign MS that were close to those of controls [26]. On the contrary, patients with a high level of cortical lesions at baseline showed greater progression of both clinical and grey matter atrophy at 5 years [25]. Several studies have found cognitive skills and motor impairment to be correlated with cortical atrophy [26–28]. Moreover, cortical pathology evolves at similar rates in all MS subtypes, with a higher baseline cortical lesion load in SP-MS due to the longer disease duration [25]. In conclusion, whereas the cortex is mostly spared in benign MS, a high load of subpial cortical lesions drives the brain atrophy and the clinical burden in non-benign MS.

Intrathecal synthesis is robust over time and treatments

Intrathecal synthesis occurs as a very early disease event and the proportion of patients with OCB tends to increase over time [29]. In longitudinal CSF studies, OCB pattern is robust and OCB have never been seen to go away with time [30] although changes in band intensity and acquisition of new bands [31] may occur. Regarding the clonal repertoire of CSF Ig, clonal rearrangements are conserved over time and a higher number of clones is found in patients with the longest disease duration, suggesting a continuous clonal expansion over time [32,33]. Antibody index [34–36] and peptidic targets of the OCB IgG are constant over time [31].

Each patient has a unique pattern ('OCB fingerprint') of CSF OCB [37,38] that is resistant to high-dosage steroid infusions [30,39,40]. Even if steroids transiently decrease the IgG index in most but not all patients, the decrease in range of CSF IgG synthesis is low and the CSF total protein concentration remains unaffected [39]. Weekly intramuscular or intrathecal β-IFN [37,41], azathioprine [42], natalizumab [43], rituximab [44–46] or daclizumab [47] have essentially no effect upon intrathecal secretion.

In conclusion, intrathecal secretion and OCB pattern are early-occurring events in the course of MS, which, once acquired, persist essentially unchanged throughout life, whatever the various therapies available, and then remain stable or gradually worsen over time.

Intrathecal synthesis confers a worse prognostic value

Demonstration of CSF OCB at the index event is a highly independent predictor of clinical recurrence [48–51], especially if OCB target lipid antigens [52]. The presence of an MRZ pattern (intrathecal reaction against *M*easles, *R*ubella and *Z*oster viruses) in CIS predicts progression to definite MS [53]. The number of OCB and the IgM index are thought to positively correlate with the course of the disease [54,55]. Mean EDSS is higher in patients with OCB, especially in the event of IgM OCB [56,57], and EDSS correlates with IgG1 index and CSF free light chains [58,59].

In numerous studies, CSF IgM have been associated with a poorer clinical long-term outcome [57,60–63], a lower brain volume [64], and a decrease in brain parenchyma fraction over time [65].

Absence of intrathecal secretion in some patients reflects technical limitations but not absence of intrathecal inflammation

About 3% of MS patients in cohorts lack intrathecal IgG synthesis [35]. This might just be due to the low sensitivity of test since MRZ reaction, high CSF IgA synthesis, high IgA index [66,67], oligoclonal free κ light-chains [68], clonal V_H and complement determining region (CDR) rearrangements [69,70] are observed, suggesting that OCB tests are insufficiently sensitive in OCB-negative patients. Moreover, OCB negativity at baseline tends to become positive for half of patients in whom lumbar puncture is repeated [71]. Cumulated data suggest that MS patients apparently devoid of intrathecal secretion may in fact have a milder secretion below the sensitivity threshold of the common tests. However, this smoldering intrathecal reaction may have clinical consequences since many studies have confirmed that OCB-negative patients are more prone to have lower EDSS, a benign form, and a delayed and lower risk of impairment milestones [54,71–76].