Multiple Sclerosis

Subjects: Pathology

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Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system (CNS), caused by genetic and environmental factors. It is characterized by intermittent and recurrent episodes of inflammation that result in the demyelination and subsequent damage of the underlying axons present in the brain, optic nerve and spinal cord [1][2][3].

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1. Introduction

There are four courses of MS: (a) relapsing–remitting, (b) primary progressive, (c) secondary progressive and (d) progressive relapsing [3]. There are a number of illnesses that can mimic the clinical manifestations of MS and this can include several pathologic processes because they all share a common pathway of demyelination and ensuing damage to the underlying axons present in the brain, optic nerve and spinal cord [1][2][3][4]. Over the years, the similarity of symptoms has led to numerous instances of neurologic conditions being misdiagnosed as MS and vice versa [1][3]. The McDonalds criteria established in 2001 aimed to rectify this by setting guidelines for MS diagnosis [5]. However, because MS is often a diagnosis of exclusion, there is still a considerable portion of time where patients may take unnecessary medications for other plausible diseases before a diagnosis is established [1][3][6][7]. With the advent of immunomodulating therapy, it has become more important to diagnose or even exclude MS more effectively earlier on in the course of the illness [1][3][6][7]. By being aware and cognizant of the various diseases which mimic MS, this can empower clinicians and researchers to help deliver accurate counseling and treatment to their patients for their specific diagnosis [8].

2. Biomarkers

2.1. Biomarkers in Pathophysiology of MS

One of the most prominent biomarkers of MS are miRNAs, which target several protective or pathogenic signaling pathways, and they have been found to be upregulated or downregulated in MS patients [9][10]. It is reported that protective miR-199a, pathogenic miR-320, miR-155, miR-142-3p and miR-142 are increased in MS lesions or peripheral blood mononuclear cells (PBMCs) [9][10][11]. On the other hand, miR-219, miR-34a, miR-103, miR-182-

5p, miR-124 and miR-15a/b are decreased in the Cerebrospinal fluid (CSF), Tregs or PBMCs of MS patients [9][10][12][13][14]. There is a strong correlation between miRNAs and various manifestations of MS such as cognitive dysfunction and oxidative status, which can result in depression or fatigue [9][10][11][12][13][14].

Another oxidative biomarker is nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (Nox2); an enzyme that catalyzes the reduction of oxygen to produce reactive oxygen species, which plays a role in the pathogenesis of MS [15].

Recent research has suggested that reactive T cells directed against neuronal protein β-synuclein can invade and destroy the gray matter, which is a hallmark of MS [16]. In addition, a high level of β-synuclein reactive T cells in the peripheral blood of MS patients indicates that this biomarker has a key role in provoking T cells in MS [16].

2.2. Biomarkers in Diagnosis of MS

It has been suggested that the levels of specific complement proteins such as C1q, C3d and C5b-9 in the serum and CSF could potentially serve as novel biomarkers to diagnose the various MS subtypes and determine the disease activity [17]. miRNAs levels such as low miR-219 and high miR-150 in CSF are novel biomarkers that can distinguish MS from other neurologic conditions [18][19].

Recent studies have also shown that brain-derived neurotrophic factor (BDNF) and soluble isoform of the interferon-β (IFN-β) receptor (sIFNAR2) levels may serve as useful biomarkers for the diagnosis of MS [20][21].

2.3. Biomarkers in Treatment and Prognosis of MS

Several studies demonstrate that a vast number of immune modulators or oxidative stress biomarkers can be used as therapeutic targets and for further studies on MS. The most notable examples are miR-497-5p, semaphorin-3A, coenzyme Q10, interferon gamma-stimulated dendritic cell exosomes (IFNγ-DC-Exos), glutathione (GSH) and dimethyl fumarate (DMF) [22][23][24][25][26].

It has been suggested that GSH (the major antioxidant in the brain) can be used for therapeutic applications as well as to predict and monitor the disease progression [26]. Monitoring disease activity in MS can be done by the use of total antioxidant status (TAS), high levels of total hydroperoxides and ceruloplasmin transferrin ratio (Cp:Tf) ratio (strictly related to Fe management) [27][28].

The potential biomarkers which can be used to predict the prognosis of relapsed or progressive forms of MS, as well as the responsiveness to treatment in patients with MS are SIRT1 (a NAD-dependent deacetylase sirtuin-1) mRNA, *Response gene to complement-32 (RGC-32)*, Fasl, IL-21, Tau proteins (proteins that stabilize microtubules), miR-191-5p, miR-128-3p and serum netrin-1 (an axon guidance protein) [17][21][29][30][31][32].

The primary CSF biomarkers which can be used to predict the prognosis of MS are β-amyloid (Aβ) levels, neurofilament light (NF-L), neurofilament heavy (NF-H), chitinase 3-like-1 (CHI3L1) and immunoglobulin M (IgM)

[33][34]. Elevated levels of lysophosphatidic acid (LPA) in the serum and CSF of relapsed MS patients can also be used as biomarkers to monitor the disease activity [35].

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