Review Article

Update on Promising Biomarkers for Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic autoimmune disease, in which there is chronic inflammation leading to neurodegeneration and demyelination. To detect MS at an early stage is impossible as it includes environmental factors and genetic factors as it varies from person to person. There are various methodologies that have been developed for the treatment of this disease; however, several complications as well as obstacles have been seen which are yet to be resolved. This review describes the biomarker for MS including microRNA and vaccine as a biomarker. Some of the drugs which are under phase II clinical trials are also discussed here. Testing and continuous validation is required for improvement where MS biomarkers are brought into clinical settings.

Keywords: *Biomarker, diagnosis, multiple sclerosis*

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Introduction

Multiple sclerosis (MS) is the most chronic autoimmune disease affecting the central nervous system (CNS) and generally starts at the cerebellum, spinal cord, and optic nerve.[1,2] In this, myelin sheath gets degenerated and myelin gets removed by the microglial cell. After demyelination, conduction of nerve impulses gets distorted. According to the research, MS causes one's own human body to attack the myelin. The most common symptoms are fatigue, vision problem, muscle weakness, and spasm. Some of the symptoms are very less common such as sexual dysfunction, mood swing, depression, cognitive dysfunction, bladder and bowel dysfunction, and speech and swallowing problem.[3] There are four phases of MS, i.e., relapsing–remitting disease, secondary progressive disease, and primary progressive disease. It causes functional disability which generally shows its symptoms at early childhood and is characterized by relapsing and progressive courses.[4] A large number of people are diagnosed with MS between 20 and 40 years of age. The ratio of women versus men in MS is 2:1. The number of cases reported is more in the northern state than southern states of the equator.[5] It affected approximately 2.3 million people worldwide. Around the globe, Canada is most affected by MS, followed by the UK and USA. According to surveys, the prevalence ranges from 74 to 112. There is a myth that "UK and Scootish people have MS mutated genes in their ancestors."[6] According to a recent survey done in India, the prevalence rate had increased from 1.3/1,000,000 to 8.35/1,000,000. In Kashmir, till now, no case of MS has been recorded because of the environmental (cold climate) factor. Obese individuals with high leptin levels are more vulnerable toward MS. Cigarette smoking is considered one of the major environmental factors in MS. Smoking causes DNA methylation through blood and there is a change in gene expression in the AHRR gene. Now, Vitamin D metabolism is emphasized as the environmental and genetic risk factor as before hypovitaminosis is considered as the major risk factor.[7,8] According to the current finding, Vitamin D influences the regulation of T lymphocytes. Based on the worldwide study, still hypovitaminosis is considered as the major risk factor for the globe.[9,10] High salt intake is also considered as the cause of MS rise in the level of immunoglobulin G (IgG) in cerebrospinal fluid (CSF) is considered as the major genetic factor which causes MS.[11] Epstein–Barr virus causes infection mononucleosis (IM), which is associated with an increased rate of causing MS. Change in major histocompatibility

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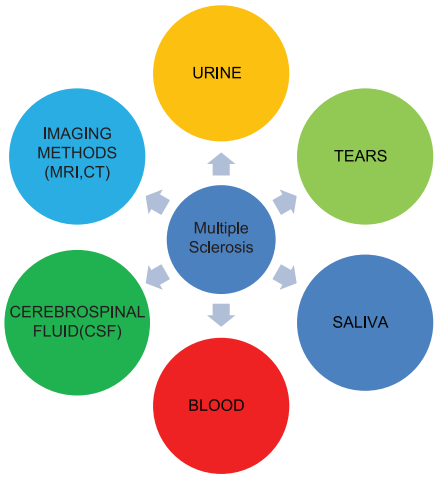

Figure 1: Different biomarkers for multiple sclerosis

complex (MHC) is also considered as the major cause of MS.[12,13]

Treatment for this disease is still not effective. The US Food and Drug Administration (FDA) and the European Medicines Agency approved injectable[1] therapies such as interferon beta (INF beta) and glatiramer acetate,[2] oral therapies (teriflunomide, dimethyl fumarate, fingolimod, and infusion therapies. In relapsing–remitting disease, IFN-β1a, IFN-β1b, and glatiramer acetate show promising effect in reducing magnetic resonance imaging (MRI) lesions.[3] It is believed that MSC transplantation in MS will reduce CNS inflammation and severe clinical disability by controlling inflammation and reducing relapsing phases.[14-18] This review focuses on the various developments and mechanisms for the treatment of MS along with its future perspectives and challenges in the advancement of MS cure.

Mechanism

MS is the most chronic autoimmune disease which causes chronic progressive neurological disability. It affects the CNS.[19] It originates from the spinal cord and optic nerve. It starts in early to middle adult life between 20 and 40 and it affects women more than men. It is idiomatic in nature and some recent evidence proves that genetic (class II MHC) and environmental factors play a major role. In environmental factors, cigarette smoking and[4] vitaminosis are considered a major cause.[20]

Two different types of episodes were seen during disease. According to neurologists, it has two phases combined active progressive and general active phase. Patient with combined active progressive MS, demyelination and neuronal axon damage whereas in normal MS there is only demyelination.[2,21] However, during the management, there is a change in the symptoms of disease, which made it difficult to diagnose 85% of the people are diagnosed with relapsing–remitting MS, 10% people with primary progressive MS, and 5% with progressive relapsing MS. After first exacerbation, the patient does not get any symptom of disease for many years. The symptoms of MS are fatigue, vision problems, vertigo and dizziness, muscle weakness and spasms, and problems with balance and coordination.[22,23] Symptoms which are less commonly seen are speech and swallowing problems, cognitive dysfunction, sexual dysfunction, depression, and mood swings. More than 30% of MS patients have moderate-to-severe jerkiness in the legs and have neuropathic pain. The most accurate test to diagnose MS is MRI, which shows accuracy in 85%–95% in symptomatic people.[24]

The diagnosis is not based on a single test. There are also few more parameters as follows:

1. Presence of two difference types of lesions (scares) in the white matter of CNS
2. Chronic inflammation in CNS is based on CSF.

In relapsing–remitting disease, three agents such as IFN-β1a, IFN-β1b, and glatiramer acetate are able to reduce the number of lesions and exacerbation. Aggressive physiotherapy is considered as the promising long-term treatment.[Figure 1]

Advancement on the diagnosis of multiple sclerosis with magnetic resonance imaging

MRI technique has proven its major impact in the last 10-20 years in the diagnosis of MS. It is able to detect lesions. At present, researchers are focusing on MRI T2 sequences. Fast spin echo-lied turbo spin echo and fluid-attenuated inversion recovery help to visualize lesions. In a recent study in Manitoba, Canada, 2763 MS cases were reported, in which individuals were less than 50 years. Gray matter is the most common finding in all MRI reports. Research performed an experiment and monitored a brain to find association between NFN level and last 10-year BPF (whole-brain atrophy). The results show a negative correlation between 5-year NFN level with 10-year NFN level and we found that there is an increase in fatigue level. These data prove that the patient needs more aggressive rehabilitation. When we study the brain at 3 Tesla, there is NAWN without tissue or GM atrophy and these data prove that functional dissociation can be the main cause of fatigue.[25,26]

Advancement on the diagnosis of multiple sclerosis with cerebrospinal fluid – human data

The pathogenesis of MS is still unknown. The typical feature of MS is the presence of oligoclonal immunoglobulin in CSF.[27] In a recent study out of 107 patients, 40 children with less than 11 years had higher CSF-NBC count than 67 adolescents. Young children have higher neutrophil count than that in CSF in the first sign of MS. The above study was done on 254 patients with PPMS. From 4 different university hospitals in Germany. In these routine CSF parameters, there was no change in cell

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count and albumin concentration in CSF and no change in normal values. 24.6% of the patients with elevated CSF serum albumin quotient (QALB) while 91.1%intrathecal IgG oligoclonal (OCBS) bound was detected in person. Expanded disability statement scale says that CSF lactate level, as well as IgM and IgA synthesis, are correlated with progression in disease every year.[28,29] When oligoclonal immunoglobulin is present on CSF, it is called oligoclonal bands (OCB), which is detected by isoelectric focusing.[30,31] Genetic polymorphisms in loci on the human chromosome 6, 14, 18 had been identified as major determinants of CSF antibody level in MS.

Advancement on the diagnosis of multiple sclerosis by checking pathway on mouse model

The NRF2 pathway is considered as a potential biomarker for dimethyl fumarate in the treatment of MS. Interleukin 33 (IL-33) pathway in CNS under MS is still unknown.[32] A researcher checks the cellular expression of IL-33 and its receptor ST2 by immunohistochemistry in the brain tissues of MS patients under appropriate controls *in vitro* using a myelinating culture system. The results show that IL-33 is expressed by neurons, astrocytes, and microglia as well as oligodendrocytes, while ST2 is expressed in the lesions by oligodendrocytes and within and around axons, and the expression levels and patterns of IL-33 and ST2 in the lesions of acute and chronic MS patients' brain samples are enhanced compared with the healthy brain tissues.[11] When this experiment data were performed using rat myelinating cocultures show that IL-33 plays an important role in MS development by inhibiting CNS myelination. IL-1RI induces human Th17 cell differentiation in an IRF4-dependent manner. It has been identified that IL-1RI-mediated signaling pathway is constitutively activated, which increases Th17 cell differentiation in IRF4-dependent manner in patients with RRMS.[33] It will be a useful therapeutic approach in remyelination in MS patients if we target the PI3K/mTOR pathway.[34,35]

Methods for Biomarker Development – State of the Art and Future Strategies

There is no need for ethics committee approval.

Diagnosis of MS with functional MRI at an early age should fulfill two criteria. First, the lesion should spread across the various regions of CNS and the second formation of the new lesion over baseline time. The advancement in the field of proteomics leads to the development of biological fluid marker CSF.[36] In PPMS phase, the level of oxidation products is fourfold higher than other phase patients, but there is no clinically proven evidence between the worse clinical course and oxidative stress. Neurovax and MIS416 is a vaccine, which is under the phase II clinical trial. Personalized medicine is the latest therapeutic approach, which states which therapy suits well for which single individual patient.[37,38] Bone marrow infusion improves visual acuity and response latency (reflex action). microRNAs are noncoding RNAs and their function is post-transcriptional regulation of gene expression and RNA silencing. The upregulation of miR-376c-3p is seen in PPMS and overexpression of miR-191-5p was seen in both subtypes of progressive MS.[39]

Countering multiple sclerosis

Through the development of adult stem cells, it is believed that adult stem cells can treat MS. There is a hope that MSCs have the immunomodulatory and neuroprosthetic effect that adult stem cells can repair CNS and differentiate into neural cells. The ideal therapy for MS to prevent disability to improve quality of life. The US FDA and the European Medicine Agency have proved dimethyl fumarate as an effective drug as it has a neuroprotective effect and immunomodulatory activity on MS patients. Another drug, fingolimod, was approved in 2010 for the treatment of the patient from relapsing–remitting (RR) form of MS. It has the capability to reduce disability and exacerbations. Teriflunomide (pyrimidine), it synthesis Mitox Amare inhibit T cells, B cells, and macrophages which reduce SPMS, relapsing MS, and CRMS.[40,41] Current therapies for MS include inferno beta and glc pirate acetate, which decrease the number of replaces partially and prevent disability. According to the latest research, dimethyl fumarate gives better response than teriflunomide in RRMS phase. Disease-modifying therapies reduce inflammation in relapsing MS and provide neuroprotection and neuropain in progressive MS.[42,43]

Biotin is vitamin B which shows it results in SPMS and PPMS phase of MS. Hematopoietic stem cell transplantation boosts up the immune system to defend against an advanced form of MS.[44,45]

Future Challenge and Conclusion

Future research should be related to daily life as an environmental and genetic factor has an equal contribution in causing MS. It was clearly highlighted in the review that the reason for it is still unknown. The drug can only reduce the symptoms in RRMS. Some drugs such as fluoxetine, lithium, oxcarbazepine, riluzole, and amiloride are under clinical trials for the treatment of MS. Phase II clinical trial of adrenocorticotropic hormone therapy is still going, which seems to be effective in progressive MS. Ibudilast and Idebenone are in the phase trial II PPMS and lipoic acid for SPMS phase II clinical trial.[6] MRI and CSF are still playing a major role in detecting MS, but to detect MS at first stage is impossible. The development of novel biomarkers now seems impossible because several candidates lack reproducibility, accessibility, and specificity. There is no actual treatment because of lack of study of PMS pathogenesis. PMS is still considered due to axonal damage and myelin loss. The patient's response to drugs

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depends on various genetic factors. For complex mechanism disease like MS, multiple biomarkers are needed to detect the phase of disease at different levels. Pharmacogenetics is also considered to play a major in MS as it links the genetic mechanism and drug with the MS. As the genetic component also plays a major role in a biomarker for MS, different patients have different responses toward the treatment. Protein level, immune dysfunction, oxidative stress, and neural degeneration will prove better therapeutic biomarkers if they become successful in clinical trials. The aim of the review is to focus on all types of biomarker available. To bring biomarkers into validation, continuous testing is required and considered as a time-consuming process.

Patient informed consent

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Author contribution area and rate

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