Multiple sclerosis research paper

Technology, Innovation

1. 0 Introduction

Multiple sclerosis (MS) is a neural degenerative condition involving the progressive degeneration of the myelin sheath (the protecting cover to the nerve fibres (axons)) around the nerve cell leading to a break down in transmission of nerve impulses. The impairment of the transmission results in loss of the body's ability to control and coordinate muscle movement. The disease progresses through a complex and diverse symptoms making it challenging to diagnose, treat and manage. The symptoms of MS may range from gentle to severe weakness, impaired body movement, lack of ordered senses, uncontrolled bowel and bladder, damaged cognition, impaired vision and a variety of many other symptoms often leading to disability. The disease is often difficult to identify in the early stages because the signs appear and disappear after some period of time. Advanced diagnostic techniques, such Magnetic resonance Imaging (MRI), are used to distinguish the disease from other diseases with similar symptoms. The treatment and management of MS utilizes different drugs as well as some non-pharmacological strategies such as physiotherapy and psychotherapy (Johnson, 2000).

The biochemical changes accompanying MS are complex and poorly understood especially because of the variety of the subtypes of the disease. MS is involves complex pathophysiological mechanism including neuronal damages, inflammation, demyelination, remylination, neurotoxicity, disruption the blood brain barrier and alteration of the immune system. Through studies of the blood, cerebral spinal fluid and the brain tissue several biochemical changes have been identified and are useful biomarkers

in indicating the disease progression, the response to therapy and optimizing and regulating therapy. This paper explores the biochemical aspects of MS, the historical background of the disease, the current treatment available and the future prospects of treatment.

2. 0 Flow chart of history

- Earliest Recorded MS Case-1433 Dutch Saint Lidwina
- First description of MS Disease by Dr. Jean-Martin Charcot of France-1868
- Introduction of Corticosteroids to reduce severity of relapses-1960s
- Trials with immunosupressants (cyclosporine, cyclophosphamide,
- methortrexate, glatramer acetate (GA) and azathioprine) -1970-1980
- Discovery and advancement of MRI-1981-1990s
- Trials with interferon and other immunomodulators-1990s-present
- (Interferon beta 1b was the first effective agent to alter the relapsing-remitting MS in 1993)

4. 0 Biochemistry involved in MS

The biochemistry of MS is complex and poorly understood due to the complex pathophysiological processes and prognosis of the disease. The MS condition has been attributed a spontaneous and progressive attack of the myelin sheaths that insulate the axon of nerves by the immune system resulting in the scaring of the white matter of the spinal cord and the brain which mainly comprises the myelin. The brain is an immune privileged site protected from the immune system by the blood brain barrier (BBB). When the integrity of BBB is compromised by infection or physical injury T-cells

reach the brain and attack the myelin hence impairing the communication between the CNS and the rest of the body. Though the actual cause of the disease is unknown the aetiology of the disease involves an interaction of genetic, infectious and environmental factors. MS has been shown to correlate with various biochemical changes.

One of the most prominent biochemical changes that have been established by magnetic resonance spectroscopy (MRS) on the MS lesion is the shift in the energy metabolism. MRS study show that people with MS have reduced levels of phosphocreatine relative to adenosine triphosphate (ATP) and increased phosphodiester indicating energy metabolism abnormalities. Scientists have also established a change in the quantities and the structure of the myelin basic proteins (MBP). MBP is a complex protein that is thought to be vital for the compaction myelin sheath and is one of the targets of the autoantigens associated with MS. Several isomers of MBP have been identified and there is considerable data indicating that the protein plays a vital role in the pathophysiology of MS although the mechanisms are not clear. Studies using mass spectroscopy on MBP from white matter of infected patients suggest that the posttranslational modification of this protein appear to be affected by the disease resulting in increased methylation; decreased (and even absent) phosphorylation and elevated deamination. The mechanism involved in the disruption of the posttranslational events remains unknown (Kim, et al., 2003). The study by Kim, et al., established that mythilation (mono- and di-) on arginine 107 was higher in MS samples than in normal subjects. A more recent study indicates that these posttranslational modification of MBP results in reduced compaction of the

myelin sheath which initiates a cascade of events that make the sheath susceptible to degradation[CITATION FGM05 l 2057]. Another study presupposes that the posttranslational modification of MBP results in a net reduction of the positive charges which in turn alters the myelin compaction and exposes the antigenic sites of MBP to immunocompitent cells. The posttranslational modifications of MBP also make the protein more susceptible to digestion by proteases associated with the myelin sheath[CITATION AAM06 l 2057]. In general the posttranslational modifications of MBP, the second most abundant protein in myelin, make myelin more susceptible to degradation. Below is the structure of MBP

Figure 1: Structure of Myelin Basic Protein 87-99 adopted from Kim et, al., (2003)

Other biochemical findings associated with MS include elevated levels of Tumour necrosis factor, interleukin and interferon in the blood and in the CSF reflecting a disturbance in the immune system. Specific antibodies directed towards CNS antigens like MBP, myelin associated glycoprotein (MAG), myelin oligonedenrocety glycoprotein (MOG) and proteolipid protein (PLP) have also been found in the blood and CFS of MS patients. Finally proteins associated with the axonal cytoskeleton such as the neurofilaments, actin, tubilin and tau proteins are also elevated in CSF of the MS patient[CITATION Arz07 l 1033].

5. 0 Current Treatment and future prospects

Currently there is no cure for MS but certain drugs are used to manage the disease. Corticosteroids are usually administered to curb inflammation and

irritation that occurs during relapse. The common formulations include oral administration of prednisone and intravenous methylprednisolone. The side effects of these drugs include high blood pressure (HBP), cataract, high blood sugar and increase risk of infection. Another treatment is plasma exchange (plasmapheresis) aimed curbing severe symptoms of MS relapses especially in victims not responding to intravenous steroid. The procedure mimics dialysis in which plasma (liquid part) is separated from blood cells. Other drugs used in the treatment of MS include Beta interferon drugs which include Avonex, Betaseron, Extavia and Rebif which have been found to reduce the rate of disease progression of MS symptoms[CITATION Fre05 l 1033]. The side effects of interferons include hepatotoxicity thus liver functions should be monitored during the period of drug use. Glatiramer(Copaxone) is another drug used in MS treatment. The drug is believed to inhibit immune system attack on myelin. The drug is injected subcutaneously once a day. Flushing and shortness of breath are some of the negative effects of this drug. Fingolimod (Gilenya) is an orally indicated drug which traps the immune cells in the lymph nodes. It is used for people with short term disability and reduces relapses. Natalizumab (Tysabri) which curbs the autoimmune responses is prescribed for people who do not show response to other drugs. Mitoxantrone (Novantrone) is an immunosuppressant used in treatment of advanced and severe MS. The drug has been associated with cardiac side effects and may lead to blood cancers [CITATION Fre05 l 1033].

Another strategy for treatment and management of MS focuses on the symptoms. Muscle relaxants are used to curb excruciating uncontrolled

muscle stiffness, especially in the legs. Relaxants like Zanaflex (tizanidine) Lioresal (bacofen) have been used in these regard. Drugs such as amantadine (symmetrel) may also be used to reduce fatigue that is associated with MS. Other drugs may be recommended to counter bladder control problems, pain and depression. The advent of stem cell research has provided hope of finding a cure for MS by repairing damaged Myelin sheath[CITATION JSJ00 l 1033].

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