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Effect Of Covid-19 on Emergence of Multiple Sclerosis Cases in India.

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Abstract

India is the most populous country of the world where majority of the people do not have proper access to the healthcare facilities due to financial constraint. In such situation a pandemic like COVID-19 has severely affected the health system and life of people. Although the mortality was low in comparison to other developed nations, a large proportion of people were affected by COVID-19. There are various reports of development of post infectious autoimmune disorders after viral infections, and a surge in autoimmune diseases is inevitable. Multiple sclerosis (MS) is one of the autoimmune conditions which can be due to both genetic and environment condition. Apart from genetic condition, it has been suggested that viral infections can cause induction of multiple sclerosis. A large proportion of Indian population was affected by COVID-19 and risk of sudden increase in multiple sclerosis cases is possible in future. A well prepared health care system would help in proper diagnosis and treatment of possible upsurge of MS cases.

Keywords: *COVID-19, Multiple sclerosis, Autoimmune, Molecular mimicry*

Introduction

India is a huge developing nation with constrained resources and accommodates roughly 18% of the global population. Neurological disorders, comprising both fatal and non-fatal conditions, emerge as prominent factors in the collective load of non-communicable and communicable diseases within the country. Disability-adjusted life years (DALYs) serve as a crucial measure for evaluating the worldwide impact of neurological disorders, a burden that shows a persistent upward trend [1]. In India, the burden of non-communicable neurological disorders is assuming a significant share of total DALYs, particularly noteworthy as it escalates within the aging demographic [1]. The repercussions on human well-being and financial expenditures associated with non-communicable neurological disorders in India are experiencing a notable escalation. The scientific and clinical care expenses are poised to reach unsustainable levels across all strata of Indian society [2].

Situation of Neurological Disorders in India

Neurological disorders have become a significant concern with the ageing population. As people grow older, the risk of developing conditions such as Alzheimer's disease, Parkinson's disease, and stroke increases. These disorders not only have a significant impact on the individuals affected but also pose challenges for healthcare systems and society as a whole [1]. The burden of neurological disorders is also expected to increase in India due to the rapid demographic and epidemiological transition occurring in the country. Evidence regarding the incidence, prevalence, and disease burden associated with neurological disorders in India is scarce. Only a few local studies have reported disease burden for some neurological disorders.

In 2019, the proportion of non-communicable neurological disorders in total DALYs due to all neurological disorders in India was 82.8%, while the proportion of communicable neurological disorders was 11.2% and that of injury-related neurological disorders was 6.0%. Among all neurological disorders in India in 2019, stroke, headache disorders, and epilepsy contributed to the greatest disease burden in terms of DALYs [1]. A very small proportion of 0.2 % had multiple sclerosis. From 1990 to 2019, there were significant increases in the overall

prevalence and disability-adjusted life year (DALY) rate of multiple sclerosis. Additionally, females had a higher prevalence of multiple sclerosis compared to males [1].

Epidemiology of Multiple Sclerosis

In India, the prevalence of Multiple sclerosis (MS) is estimated to be approximately 8 per 100,000 people, which is significantly lower than the prevalence among white individuals of European and North American descent. However, among Indians, the genetic susceptibility to MS seems to be similar to that of white individuals [3].

Multiple sclerosis (MS) is a progressive, debilitating and heterogeneous neurological disease characterized by demyelination caused by an atypical immune response in the body. It is the most common neurological disease affecting the central nervous system (CNS). Many internal factors, such as genetic factors, and external factors, such as environmental factors, are believed to cause the disease. Therefore, it is considered to be the result of complex interactions between these components. It was previously thought to be widespread in many regions of Europe and America. However, over time, it has become a global problem [4].

Due to increased awareness, a significant increase in the number of neurologists, and easy access to magnetic resonance imaging (MRI), current estimates range from 7 to 10/100,000. This figure is likely to be higher because the majority of India's population still lacks access to adequate health facilities, especially in the rural sector [5].

Causes of Multiple Sclerosis

The exact cause of MS is unknown. Extensive research has shown that environmental and genetic factors play an important role. Additionally, all studies show the role of environmental factors in MS. Alter [6] suggested that people living in developing countries with poor hygiene may develop protection against diseases. The increasing MS and increasing latitude in Europe support the role of natural factors. Variations in solar radiation and thus serum vitamin D3 levels may play a role in explaining these latitudinal differences [7].

Although a definitive virus triggering or causing MS has yet to be identified, Bansil et al.[8] conducted a case-control study among Indian patients which observed a higher exposure to dogs in MS patients compared to those with other neurological diseases, hinting at a possible involvement of the canine distemper virus in MS. Additionally, recent research suggests a significant role of the Epstein-Barr virus (EBV) in MS pathogenesis [9]. However, Pandit et al.,[10] in a study involving 140 MS patients, did not find strong evidence for a direct association with remote EBV infection. Vitamin D is thought to exert a protective effect against MS development, with its deficiency increasing the likelihood of relapses in MS patients [11]. Defining the role of vitamin D deficiency in MS in India is challenging due to its widespread prevalence in the country. Nonetheless, the study by Pandit et al supports the hypothesis that low levels of vitamin D are inversely related to MS, with individuals deficient in vitamin D facing a higher risk of MS and increased chances of relapse [12].While the role of infectious and viral agents in MS remains a subject of debate, mounting evidence suggests that certain viruses contribute to disease progression. Notably, the detection of viral nucleic acids or antigens, along with antiviral antibody responses in MS patients, provides compelling support for this notion. Viral infections can impact MS through various mechanisms and in combination. These pathways encompass molecular mimicry, direct toxicity, bystander activation, dual T-cell receptors, and epitope spreading [13]. SARS-CoV-2 (COVID-19), has been suggested to affect the CNS through molecular mimicry and cause acute cellular damage and dysfunction, and remain dormant or latent in infected cells for long periods [13].

Possible Mechanism for post viral Multiple Sclerosis

In general, the nervous system damage following a viral attack is more likely caused by the activation of the immune system rather than the direct effect of the pathogen itself. A combination of mechanisms, such as those mentioned below, is probably involved.

"Molecular mimicry" refers to the activation of autoreactive cells against the body's own antigens due to similar sequences between foreign, particularly viral, peptides and self-peptides. The most plausible mechanisms linking SARS-CoV-2 with multiple sclerosis (MS) include molecular mimicry between autoantigens and viral antigens, as well as delayed activation of autoimmunity post-infection. In patients with SARS-CoV-2 who exhibit neurological symptoms, anti-neuronal and anti-glial autoantibodies in the cerebrospinal fluid (CSF) are more commonly found than in those without such symptoms. Additionally, anti-neuronal autoantibodies have been detected in the serum of SARS-CoV-2 patients, targeting intracellular and neuronal surface proteins, vascular endothelium, and astrocytic proteins, all of which are crucial in the development of MS. Another study revealed that antibodies against

the SARS-CoV-2 Spike (S) protein can strongly cross-react with myelin basic protein (MBP) and other tissue proteins. This evidence of virus-specific antibodies cross-reacting with central nervous system structures suggests a specific autoimmune link between MS and the COVID-19 pandemic [14].

"Epitope spreading" refers to the immune system's activated response against additional antigenic epitopes beyond the primary one. This phenomenon can occur intramolecularly, targeting different epitopes on the same molecule, or intermolecularly, targeting epitopes on different molecules. CNS damage, often resulting from persistent viral infection, can expose numerous new self-antigens, facilitating epitope spreading. Experimentally, it has been demonstrated that proteolipid protein (PLP) can stimulate lymphocytes in mice chronically infected with Theiler's murine encephalomyelitis virus (TMEV), leading to myelin sheath destruction in organotypic cultures [14].

"Bystander activation" involves the activation of autoreactive cells due to the nonspecific inflammatory environment that follows a viral infection ."Superantigens" are capable of activating T cells specific for other self-antigens and have been shown to reactivate experimental autoimmune encephalomyelitis (EAE) processes. "Cryptic antigens," which may be exposed and activated during a subsequent infection, can induce another wave of immune responses, potentially attacking the CNS and triggering autoimmune responses [14].

Reports of Multiple sclerosis after covid 19 infection

The global pandemic caused by the SARS-CoV-2 virus has resulted in various potential neurological complications, including meningitis, encephalitis, Guillain-Barre syndrome, cerebrovascular disease, seizures, and demyelinating diseases.

Moore et al reported a case of newly diagnosed multiple sclerosis (MS) occurring concurrently with an active COVID-19 infection in a 28-year-old male patient. The patient presented with optic neuritis, and prior evidence of COVID-19 infection was indicated by positive serum antibody testing despite a negative PCR result. Here the patient exhibited active viral infection, confirmed by nasopharyngeal PCR findings and typical COVID-19 symptoms. This temporal relationship between the viral infection and the onset of demyelinating episodes suggests a para-infectious mechanism, rather than a post-infectious one[15].

In another study, a 47-year-old female patient diagnosed with multiple sclerosis (MS) was confirmed based on the presence of signs and symptoms separated in space and MRI findings. Given these criteria, it is reasonable to infer that the pathogenic process of MS had already initiated before the SARS-CoV-2 infection, likely influenced by geographical, environmental, and genetic factors. This suggested that COVID-19 may have acted as a precipitating or triggering factor rather than being a direct consequence of the infection itself [16].

Saeed et al, presented a case of a 36-year-old female with a history of migraines, hospitalized to the emergency department (ED) with complaints of right-sided eye pain and throbbing, intractable headache over the past week. The pain exacerbated with eye movement, and the patient noted color changes in her vision. Notably, she had been hospitalized for coronavirus disease 2019 (COVID-19) three weeks prior to this presentation. Initial evaluation in the ED revealed white matter changes in the right frontal lobe on a computer tomography (CT) scan of the head. Subsequent Magnetic Resonance Imaging (MRI) scans of her brain, cervical, and thoracic spine confirmed left optic peri-neuritis and scattered foci in the periventricular white matter, corpus callosum, and cervical spine. Based on these findings, she was diagnosed with multiple sclerosis (MS), and treatment commenced with high-dose corticosteroids. The patient exhibited a favorable response to treatment, with resolution of her symptoms, and was discharged on a tapering course of steroids. [17].

Future perspective

The occurrence of the COVID-19 pandemic, and the impact of coronaviruses (CoVs) and SARS-CoV-2 appear to have on the activation of autoimmunity and their potential to cause demyelination in the CNS, has renewed interest in the viral hypothesis of multiple sclerosis (MS). Experimental studies have shown that CoV infections can induce MS-like demyelinating diseases, and epidemiological data, along with findings from MS patients, support the idea that an environmental factor could trigger autoimmune and pathological reactions in genetically predisposed individuals. These insights, coupled with new data emerging from the current pandemic, have provided substantial support for the viral theory, particularly concerning CoVs. Recent findings suggest that SARS-CoV-2 could indeed trigger demyelination and autoimmune reactions, raising the possibility that the incidence of autoimmune diseases, including MS, may increase in the coming years.

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