

Solitary Sclerosis: Is it a New Disease in the Category of Connectomopathy?

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Abstract

Connectomopathy is a novel term referred to a set of diseases in which not only the whole brain connectome is involved, but also the damaged connectome itself acts as a context for the progression of these diseases. The best example of connectomopathy is Multiple Sclerosis (MS), which is caused by the malfunction of the immune system. Solitary Sclerosis (SS) is a rare disease, which progresses in patients following a solitary demyelinating lesion and then becomes incapacitated despite using various medications. Few studies have indicated that the pathology is not limited only to the lesion and would involve a large area in the brain. The present study aimed to address more aspects of connectomopathy by addressing SS as a relatively new term in the inflammatory diseases related to the CNS.

Keywords: Solitary sclerosis • Connectomopathy • Connectome • Multiple sclerosis • Progression

Introduction

Connectomopathy is a novel term referred to a set of diseases in which not only the whole brain connectome is involved, but also the damaged connectome itself acts as a context for the progression of these diseases. In this set of diseases, although the causative agent can be outside the Central Nervous System (CNS), when the connectome is damaged, it can independently and regardless of the main pathology helps the diseases' progression. The above-mentioned issue would bring the following two consequences: First, the elimination of the primary pathology cannot prevent the course of the disease, so the disease continues in a progressive manner with a different mechanism from the primary pathology; and second, some effective treatments on the entire connectome should be proposed, in order to prevent the progression of the diseases [1]. The best example of connectomopathy is Multiple Sclerosis (MS) [1], which is caused by the malfunction of the immune system [2]. For a long time, it has been demonstrated that MS has a progressive course in a significant number of patients [3]. Accordingly, these findings indicate the neurodegenerative nature of this disease [4]. The significant point in this regard is that despite numerous treatments employed for regulating or suppressing the immune system, patients with MS may still experience a progressive phase. In addition, such treatments would have little effect on patients with progressive MS [5]. Moreover, it seems that the mechanisms involved in the neurodegenerative nature of this disease are different from the inflammatory mechanisms [6]. Furthermore, several imaging studies have previously revealed that the entire connectome is involved in this disease. Perhaps, the generalized brain atrophy is the most obvious manifestation of this general involvement. Of course, previous studies have indicated the involvement of both the structural and the functional communication pathways in this disease [7,8]. Although a significant number of studies have been conducted on the diagnosis, pathogenesis, and treatment of MS, this aspect of this disease, which can also be considered as an Achilles' heel, has not been taken into consideration so far. All the treatments proposed in this field have been devoted to the immune system and to its control or suppression. However, if we consider MS as a connectomopathy, the degenerative phase of this disease, causing its progression and the

consequent disability, practically occurs independent from the functioning of the immune system. The primary destruction of the connectome by the immune system acts as a stimulus in initiating the autonomic process, which is called connectomopathy. Imaging studies have also confirmed this ongoing destruction of CNS by passing time [9]. Although no studies have been performed on the evaluation of the connectome acting as a context for the progression of MS, conducting such studies can provide a better understanding of what is happening during the course of this disease and what leads to the patient's disability as a consequent. In addition, providing more evidence from other diseases considered as connectomopathy, could also shed more light on this new term.

Solitary Sclerosis

Solitary Sclerosis (SS) is a progressive disorder caused by an isolated CNS demyelinating lesion, which may be located in different areas, including the spinal cord, the brainstem, or the cerebral hemispheres. Although the patients with this disease do not meet the criteria for MS, in 13% of cases, one of their first-degree relatives suffers from MS, and in 50% of cases, there is an evidence of inflammation in the cerebrospinal fluid. In addition, conventional drugs used for MS, whether immunomodulatory or immunosuppressive, were shown to have no effect on the progressive course of this disease [10]. However, the long-term follow-up of these patients has indicated no increase in demyelinated lesions related to the CNS [11]. It was well-recognized that the isolated lesions of the cord or brainstem could lead to the development of progressive myelopathy [12-14]. These diseases progress rapidly and consequently result in their disability [15]. The same rapid and progressive course of the disease, resulting from a solitary lesion in the cord as well as the absence of any other evidence in favor of MS in these patients have led it to be considered as a distinct disease [16,17]. The strategic site of the lesion can somewhat justify the above-mentioned issue. Since the cord or brainstem is a very small area with a high density, the lesion occurring in this area could be associated with a significant neurological defect. Although the progressive course of the disease and the solitary lesion in the cord or brainstem primarily highpoint tumor diseases, the courses of the disease as well as

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Received: 22-Mar-2022, Manuscript No. CSRP-22-58029; **Editor assigned:** 24-Mar-2022, PreQC No. CSRP-22-58029 (PQ); **Reviewed:** 08-Apr-2022, QC No CSRP-22-58029; **Revised:** 15-Apr-2022, Manuscript No. CSRP-22-58029(R); **Published:** 25-Apr-2022, DOI: 10.3371/CSRP.MA.042522.

the atrophy of the lesion both indicate the demyelinating nature of the lesion [18]. However, the above-mentioned studies [10] have previously revealed that solitary demyelinating lesions associated with the patients' progressive symptoms can occur in hemispheres as well. Such a finding suggests that the basic pathophysiology of this disease may possibly be beyond the solitary brain lesion. Progressive neurological deficit similar to progressive Multiple Sclerosis (MS) disease courses may occur from an isolated demyelinating lesion in the upper cervical cord, cervico-medullary junction, brainstem, or cerebral white matter. Current criteria preclude a diagnosis of MS in such cases, because of the failure to document dissemination in time. Progressive solitary sclerosis can cause progressive quadriparesis after an attack of diplopia without evidence of dissemination in the time and space even after a prolonged period. However, solitary sclerosis may also evolve to progressive disease (progressive solitary sclerosis), a recently described phenotype, without any relapses. This rare entity should be included in the differential diagnosis of demyelinating lesions, and the clinicians, both surgical and medical should be aware of such a diagnosis for appropriate management.

Increasingly, some cases with different manifestations have been reported. For example, Sahraian, et al. in their study reported a 24-year-old patient who was initially presented with diplopia, which healed completely. The patient had only one lesion in the pontomedullary region; however, she has then developed a progressive course of quadriparesis and became completely incapacitated within 6 years [19].

Evidence of Extensive Brain Involvement in Solitary Sclerosis

Solitary sclerosis is a rare disease regarding which there are few reports of this disease. Moreover, there has not been much complementary research in this regard. Undoubtedly, one of the most significant studies directly related to the current discussion is the evaluation of the extent of nervous system's involvement with the use of new imaging methods. Accordingly, conventional Magnetic Resonance Imaging (MRI) is used for this disease's diagnosis. It is well-acknowledged that conventional MRI cannot indicate the extent of CNS damage. For example, it has been demonstrated that a significant amount of white matter, which is considered to be normal in conventional MRI, would be damaged in patients with MS [20]. Therefore, it can be conjectured to observe such a disorder as well as a high level of involvement in SS due to the progressive nature of the disease along with the high degree of disability. In 2019 Lee, et al. conducted a similar study on two patients with SS. In this study, the first patient was 51 years old with a lesion in the cervical cord and progressive myelopathy from 8 years ago. The second patient was 38 years old with a progressive disorder, a lesion in the cervicomedullary junction, and severe disability from one year ago. They used multicomponent-driven equilibrium single-pulse observation of T1 and T2 (mcDESPOT) to determine Myelin Water Fraction (MWF), which is a marker for myelin measurement. In addition, Proton Magnetic Resonance Spectroscopy (1H-MRS) was used to study the amount of brain metabolites. In both of these patients, the aforementioned evaluations revealed an abnormal myelin and metabolic dysfunction in areas of the brain that have shown no involvement in the normal brain MRI. This study indicated that the pathology in SS is not limited only to the lesion area, but it is much wider than a specific area. As a result, the authors suggested that the secondary wallerian degeneration to the primary lesion could be known as an indicator of the high degree of involvement in these patients [21]. Unfortunately, no further studies have been performed on the determination of both the degree and density of lesions in SS and its change over time. The reason may be that the rarity of the disease and the few number of reported cases have been considered as barriers to perform such extensive studies.

Solitary Sclerosis as a Connectomopathy

As it can be noticed, SS can be considered as a type of

connectomopathy. Apart from the progressive course of this disease, which severely disables the patient in a short period, a previous study has shown that the rates of damage and involvement are much more than the lesion observed in the conventional MRI. Therefore, solitary sclerosis has some specific conditions that should be considered. Dissimilar to MS, which can have multiple plaques in the brain, brainstem, or spinal cord, only a solitary lesion is present in SS, which sometimes is not located in strategic areas like the spinal cord or brainstem. However, despite this solitary lesion, we are currently facing the progressive course of the disease from a clinical point of view, as the wider brain involvement can be detected using more accurate imaging techniques. Therefore, SS may be considered as a better example of connectomopathy to examine the disease with more details. The crucial point in connectomopathy is that the damaged connectome itself becomes a context for the progression of this disease. Although clinically continuous and deteriorating connectome damages have been observed in MS, more studies are required to specify whether the connectome itself causes the disease's progression. Accordingly, these studies can be performed using several ways. The first way is to study how the connectome changes during the course of the disease, which can be examined using imaging techniques. It should be noted that this change is not merely examining the loss of neural pathways in the brain, but it may indicate that the development of new pathways between neurons, which occur during the neuroplasticity process, could contribute to this damage as well. Neuroplasticity is defined as the ability of the brain to change and reorganize itself against the environmental stimuli [22]. Of note, this response is not always positive and constructive; rather, it can cause further damages to the brain and connectome by creating wrong pathways [23]. The second way is evaluation the substances secreted by neurons. The release of oxidants can lead to the development of pathology [24]. As well, oxidants are regarded as one of the candidate substances for this study. Examining other metabolites and their changes over time can also provide a better insight on connectomopathy as well as its treatment options.

Discussion and Conclusion

Solitary sclerosis is a rare disease, which progresses in patients following a solitary demyelinating lesion and then becomes incapacitated despite using various medications. Few studies have indicated that the pathology is not limited only to the lesion and would involve a large area in the brain. Therefore, solitary sclerosis can be considered as a connectomopathy. Given that only one lesion is observed in this disease in the conventional MRI images, it is a very good sample for examining different dimensions of connectomopathy.

Disclosure

The author declares there is no conflict of interest.

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How to cite this article: Moghadasi, Abdorreza Naser. "Solitary Sclerosis: Is it a New Disease in the Category of Connectomopathy?" *Clin Schizophr Relat Psychoses* 16S (2022). Doi: 10.3371/CSRP.MA.042522.