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Review of Early Clinical Manifestations of Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic demyelinating disorder that affects the central nervous system. Until recently, little attention was paid to the early preclinical and clinical manifestations of multiple sclerosis. It is only in the past decade that researchers have started to focus on the prodromal phase of the disease. Knowledge of the prodrome is important for suspecting and, eventually, diagnosing the disease. This article synthesizes the current literature regarding the early clinical manifestations observed in patients with MS. The early identification of individuals diagnosed with MS is of considerable significance, as it facilitates the prompt implementation of therapeutic strategies designed to mitigate the risk of relapses and long-term disability.

Keywords: *multiple sclerosis, early clinical symptoms, diagnostic criteria of multiple sclerosis*

INTRODUCTION

Multiple sclerosis (MS) is a multifaceted and chronic demyelinating disorder that primarily affects the central nervous system, and it is particularly prevalent among young adults. This disease is recognized as one of the foremost causes of disability within this demographic, with cognitive impairments often surfacing early in its progression. [16] According to the latest estimates from the Multiple Sclerosis Atlas, it is believed that approximately 2.8 million individuals are currently living with MS worldwide. Over the last decade, there has been a noticeable increase in the incidence and prevalence of this condition, which can be largely attributed to a variety of significant factors. These include enhanced life expectancy, ongoing global population growth, advancements in data collection methodologies, and improved accuracy in diagnostic practices. The prevalence of MS is not uniform across the globe; rather, it exhibits considerable variability depending on geographical regions, as well as demographic factors that include age and sex.[14] The diagnostic process for MS can be particularly challenging, especial-

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ly in regions where the disease is less common or in developing nations where clinical awareness may be lower. In these situations, there may also be a lack of resources that are necessary for thorough diagnostic evaluations. [12]

Purpose of the work: To analyze the latest literature on the early clinical and preclinical symptoms of multiple sclerosis, as well as examine the diagnostic criteria for the disease.

MATERIALS AND METHODS

Sources from PubMed over the past 10 years (2015–2024) that were publicly available, as well as the annual issues of Multiple Sclerosis Journal for the last 3 years (2022, 2023, 2024), consisting of materials from the annual ECTRIMS Congress (The European Committee for Treatment and Research in Multiple Sclerosis), were analyzed about early symptoms and early diagnosis of multiple sclerosis, which are also available in open access. The material for this literature review was selected based on search results from the PubMed website and the collections of the aforementioned journal issues, using keywords: early symptoms of multiple sclerosis and early diagnosis of multiple sclerosis. Based on this search, 20 sources were found, upon which this review was written, summarizing and analyzing the data from these sources. Diagnostic criteria for the diagnosis of "multiple sclerosis" were also reviewed, as clinical symptoms are one of the main criteria for diagnosing this condition.

The primary pathophysiological characteristic of the demyelination process is the reduced speed of impulse conduction along demyelinated fibres, leading to a variety of clinical signs and symptoms.[3] In clinical medical terminology, the term "prodrome" is used to refer to the early signs and symptoms that can precede the formal clinical onset of a disease. While it is understood that neurodegenerative changes may commence years before any clinical symptoms become evident, the initial presentation of MS does not consistently demonstrate clear or recognizable prodromal signs. In contrast, other neurological conditions, such as Parkinson's disease, have well-documented prodromal phases that are recognized in clinical practice. [7] Despite the acknowledgement of prodromal stages in a range of neurological and inflammatory disorders, the concept of a prodromal phase in multiple sclerosis has not received significant attention until very recently. Typically, MS begins to manifest clinically between the ages of 20 and 50; however, it is crucial to note that the prodromal symptoms associated with the disease may begin much earlier, and the specific characteristics of these prodromal symptoms can vary widely among different individuals who are affected by the condition. The most common form of multiple sclerosis is the relapsing-remitting type, which is characterized by episodes of acute neurological symptoms known as relapses. These relapses are interspersed with periods of relative stability or quiescence, referred to as remissions. [15]

The leading early clinical and preclinical symptoms of MS are: persistent headache for several weeks that cannot be corrected with non-steroidal anti-inflammatory drugs or sumatriptans; "unreasonable" appearance of a feeling of numbness in any part of the body, for example, in the lower part of the face on the right, which can persist for several weeks; balance [2][17] and walking impairments [2], depression, anxiety [7]; cognitive impairment: apathy [11], memory loss, attention problems, cognitive fatigue [8], sleep disturbances, problems falling asleep, frequent awakenings, sexual dysfunction [5], a constant feeling of heartburn, which is not relieved by any drug to correct the acidity of gastric juice; unexplained general weakness; cranial nerve dysfunction, sensory symptoms [17], impaired bowel function (persistent constipation); urinary dysfunction (urinary retention or incontinence); unilateral decreased vision, diplopia [13][17], blurred vision; the auditory and vestibular manifestations [13][17], sudden sensorineural hearing loss [4] etc.

Another research indicates that cognitive impairment is a significant concern for individuals diagnosed with MS, with estimates suggesting that between 20% and 45% of patients may experience cognitive dysfunction. [16] Within the first year after diagnosis, approximately half of individuals with MS experience minimal to mild cognitive difficulties, with these issues typically becoming more pronounced over the first decade. While rare, some individuals with MS may present with cognitive impairment as their primary symptom.[6] Notably, these cognitive impairments can often emerge more than a year before the appearance of other clinical symptoms, highlighting the importance of early recognition. Furthermore, studies have indicated that individuals with MS tend to utilize healthcare services more frequently during the decade leading up to their first demyelinating event, suggesting that there may indeed be a measurable prodromal phase that warrants further exploration.[7] The cognitive dysfunctions associated with MS are often heterogeneous, reflecting similarities to deficits seen in subcortical dementias. The domains that are most fre-

quently affected include attention, processing speed, memory, executive functions, and visuospatial skills. In the early phases of MS, it is common for individuals to experience impairments in processing speed and executive functioning first, followed later by deficits in memory and attention.[16]

Recent studies have identified headaches as an important symptom of the prodromal phase, potentially indicating the onset of the disease long before the first demyelinating event. Moreover, headaches may persist even after diagnosis and treatment or may develop de novo as a side effect of the therapy.[1]

Other research indicates that the key predictors of more aggressive disease progression are older age at symptom onset (above 35 years), a high EDSS (Expanded Disability Status Scale) score (≥ 3), and the presence of pyramidal signs within the first year of the disease.[20]

The diagnostic framework for multiple sclerosis relies on the establishment of clear evidence demonstrating dissemination in both time and space, while concurrently ruling out other disorders that may present with clinical features similar to those of MS. The evolution of diagnostic criteria for MS has been marked by significant advancements, beginning with the introduction of the McDonald criteria in 2001, which sought to provide a clear framework for the diagnosis of the disease and to facilitate timely intervention. Over the years, these criteria have undergone various revisions and refinements, leading to the current McDonald 2017 guidelines that are widely used today.[9][18] Alongside these criteria, there has been a growing emphasis on the role of advanced imaging techniques and laboratory tests in confirming the diagnosis of MS. The continuous efforts of researchers and clinicians around the world have led to ongoing enhancements in the precision and applicability of these diagnostic criteria, building upon the foundational contributions made by Charles Poser, who established the classifications of "definite" and "probable" MS, as well as the MAGNIMS (Magnetic Resonance Imaging in MS) recommendations regarding MRI criteria for diagnosing the disease.[15] For a diagnosis of multiple sclerosis to be considered, the clinical history, examination, and MRI findings should align closely with the typical characteristics of the disease, while excluding features that might point to an alternative cause.[10]

An accurate and timely diagnosis of multiple sclerosis is of utmost importance for optimizing the quality of life for patients who are diagnosed with the condition. A correct diagnosis not only allows for the prompt initiation of appropriate therapeutic interventions but also helps to mitigate the risks of misdiagnosis and the administration of unnecessary treatments.[9][19] Therefore, the ability to identify individuals with MS at the early stages of their disease is critically important, as this enables healthcare providers to implement timely interventions designed to prevent relapses and to minimize the risk of long-term disability. Understanding the complexities of MS and recognizing its early signs and symptoms can significantly improve patient outcomes and enhance the overall management of the disease, ultimately leading to better health and quality of life for those affected.[15]

RESULTS AND DISCUSSION

Different authors have described various early preclinical and clinical manifestations of the disease based on their scientific research conducted on patient groups or literary analyses. Some authors do not dispute the validity of other researchers' findings, as multiple sclerosis is often referred to as a "chameleon disease," displaying a wide range of clinical symptoms. However, most authors agree on the role of cognitive impairments, which are more commonly observed among patients. All authors are united in the view that early recognition of the prodromal phase and the first clinical manifestations of multiple sclerosis is crucial for selecting optimal therapy for each patient, preventing relapse frequency, and reducing long-term disability. Additionally, the majority of authors emphasize the importance of combining clinical data with instrumental diagnostic findings by international standards and classifications.

There is increasing evidence for a prodromal phase in multiple sclerosis, suggesting that early symptoms may appear before an official diagnosis. Many of these symptoms are also found in the general population, which complicates their identification.

Studies indicate that mental health challenges, such as higher rates of depression, may emerge during this early phase, potentially linked to underlying inflammatory factors.[15] However, the exact mechanisms remain largely theoretical, underscoring the need for additional research.

CONCLUSION

Neurologists need to be aware of the existence of the prodromal phase of multiple sclerosis and the most commonly observed early clinical symptoms, such as complaints of cognitive impairments. This awareness is crucial for early suspicion and further monitoring of patients, especially young individ-

uals aged 20 to 50, to track their condition in combination with laboratory test results. Early diagnosis is essential to initiate prompt treatment and prevent disability in patients suffering from this disease.

To better understand the MS prodrome, a comprehensive research strategy is essential. This should involve advanced imaging methods and the study of biomarkers to more accurately identify at-risk individuals. Creating established criteria for recognizing prodromal MS is crucial for facilitating early detection and intervention, ultimately enhancing treatment options for those who may develop the disease. Continued research in this area has the potential to significantly improve both scientific knowledge and clinical practices related to MS management.

CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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TARQOQ SKLEROZNING ERTA KLINIK KO‘RINISHLARINI TAHLILI

Yunusova M.R., Rahimbayeva G.S.
Toshkent tibbiyot akademiyasi

ABSTRAKT

Tarqoq skleroz (TS) - surunkali demiyelinizatsiyalovchi kasallik bo‘lib, markaziy nerv sistemasini zararlaydi. Tarqoq sklerozning klinik oldi va klinik ko‘rinishlariga yaqin vaqtlargacha alohida e’tibor berilmagan. Faqat so‘nggi o‘n yillikda olimlar ushbu kasallikning prodromal fazasini ajrata boshladilar. Prodromni bilish shubha qilish, keyinchalik esa diagnoz qo‘yish uchun ham muhim ahamiyatga ega. Ushbu maqolada tarqoq skleroz bilan og‘rigan bemorlarda kuzatiladigan erta klinik ko‘rinishlar bo‘yicha zamonaviy adabiyotlar umumlashtirilgan. RS tashxisi qo‘yilgan shaxslarni erta aniqlash katta ahamiyatga ega, chunki retsidivlar va uzoq muddatli nogironlik xavfini kamaytirishga qaratilgan terapevtik strategiyalarni tezda amalga oshirishga yordam beradi.

Kalit so'zlar: tarqoq skleroz, erta klinik simptomlar, tarqoq sklerozning diagnostik mezonlari

ОБЗОР РАННИХ КЛИНИЧЕСКИХ ПРОЯВЛЕНИЙ РАССЕЯННОГО СКЛЕРОЗА

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АБСТРАКТ

Рассеянный склероз (РС) — хроническое демиелинизирующее заболевание, поражающее центральную нервную систему. На ранние преклинические и клинические проявления рассеянного склероза до недавнего времени не было уделено особого внимания. И только в последнее десятилетие ученые стали выделять продромальную фазу данного заболевания. Знание продрома имеет важное значение для подозрения, а в дальнейшем и постановки диагноза. В данной статье обобщена современная литература относительно ранних клинических проявлений, наблюдаемых у пациентов с рассеянным склерозом. Раннее выявление лиц с диагнозом РС имеет большое значение, поскольку способствует быстрой реализации терапевтических стратегий, направленных на снижение риска рецидивов и длительной инвалидности.

Ключевые слова: рассеянный склероз, ранние клинические симптомы, диагностические критерии рассеянного склероза