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Addressing Global Care Challenges for Chronic Neurodegenerative Disorders: Enhancing Understanding, Expanding Treatments, and Embracing Telehealth

James Baker*

Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy

Introduction

Neurological disorders stand as the primary contributors to both physical and cognitive disability on a global scale, impacting approximately 15% of the world's population [1]. Over the past three decades, there has been a substantial surge in the absolute number of affected patients. Furthermore, the burden of chronic neurodegenerative conditions is projected to at least double within the next two decades. This significant evolution can be largely attributed to the expanding aging population. Consequently, ensuring accessible neurological care for all poses a tremendous challenge. Recognizing the impending threats, esteemed institutions like the World Health Organization and the United Kingdom's National Health Service have already sounded the alarm, highlighting that available resources for neurological services are insufficient in most countries of the world compared with the global need for neurological care and stressing the necessity for a redesign of neurological services as they are currently unsustainable [2]. Beyond the direct expenses associated with the (para) medical management of neurodegenerative disorders, it is crucial to recognize that the overall financial impact, encompassing costs related to diminished quality of life and employment, can reach even more significant proportions. This is especially pertinent in the case of prevalent and debilitating conditions that persist over several decades, like multiple sclerosis (MS) and Alzheimer's disease (AD). For instance, in MS, it is approximated that up to 80% of those affected become unemployed within the first 15 years after diagnosis, resulting in an annual cost about $4000 higher compared to healthy individuals of similar age and gender [3]. Additionally, the majority of the yearly total patient care expenses in AD, amounting to approximately $300 billion, are utilized for institutionalization [4,5]. This study is dedicated to the belief that advancing next-generation research is imperative in order to push the boundaries of current neurology knowledge and address the aforementioned concerns. Our mission revolves around a multi-level effort aimed at overcoming these challenges. Points to be focused on:

(a) Enhancing our understanding of the pathophysiology of neurological disorders.

(b) Formulating new strategies for disease prevention, modification, and cure.

(c) Developing innovative biomarkers for early diagnosis, detecting subclinical disease progression, and monitoring treatment response.

(d) Improving care delivery for individuals with chronic neurodegenerative disorders.

By combining these strategies, we anticipate that we can prevent and/or delay neurological decline in a significant number of people. Moreover, this approach is likely to alleviate the strain on available logistical and financial resources and lead to a modernized healthcare system for individuals with such conditions. Along this journey, we recognize the value of bravery, out-of-the-box thinking, and creativity. Therefore, we strongly encourage studies exploring innovative hypotheses grounded in robust conceptual frameworks, even if they challenge existing paradigms, concepts, or customs. Embracing these qualities will undoubtedly prove to be invaluable in advancing our understanding and treatment of neurological disorders. Multiple sclerosis (MS) stands as a prominent cause of chronic non-traumatic disability in young adults, making it an appropriate illustrative model. The cornerstone of addressing any condition lies in comprehending its origins and progression. Recent paradigm shifts in the pathophysiological understanding of MS have been transformative, challenging older beliefs. Notably, B-cells have emerged as crucial mediators of subacute inflammatory tissue damage, leading to the development of potent anti-CD20 disease-modifying treatments [6]. Additionally, the chronic neurodegeneration seen in progressive MS has been attributed to local innate immune responses [7,8]. Furthermore, cognitive impairment has been recognized as a potential early manifestation of the disease [9].

For long time, epidemiological evidence linked Epstein-Barr virus (EBV) infection to MS, but establishing a definitive causative relationship was challenging. However, a groundbreaking study in early 2022 by Bjornevik and co-workers, analyzing data from over 10 million US military recruits monitored for 20 years, revealed that EBV seropositivity preceded MS onset in nearly all patients. Following EBV infection, the risk of MS increased by a factor of 32, while infection with other similarly transmitted viruses did not show such an association. Moreover, serum levels of neurofilament light chain (NfL), a well-established neurodegeneration biomarker, rose exclusively after EBV seroconversion. These findings, devoid of any other known risk factor, compellingly point towards EBV as the primary cause of MS [10]. This discovery provides a mechanistic link between the viral infection and B-cell mediated targeting of the central nervous system (CNS). Such novel insights may pave the way for future antiviral and/or vaccination strategies aimed at disease modification, and potentially even prevention or cure.

In the traditional teaching of multiple sclerosis (MS), three distinct clinical phenotypes were recognized: relapsing-remitting, secondary

***Corresponding author:** James Baker, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, E-mail: james.baker@gmail.com

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progressive, and primary progressive disease. The relapsing phase was thought to be driven primarily by recurrent autoimmune inflammatory attacks on the central nervous system's myelin, while progressive MS was attributed to a slower neurodegenerative process that was less well understood. However, recent literature has challenged this linear view. Research has revealed that gradual disease progression, independent of inflammatory relapses, known as Progressive Inflammation and Neurodegeneration Independent of Relapses (PIRA), plays a significant role in accumulating disability even in patients with a relapsing phenotype, including early stages of the disease. Additionally, features previously associated mainly with progressive MS, such as accelerated brain volume loss and cognitive decline, can be present at the time of relapsing-remitting MS diagnosis or even earlier. The current understanding of MS pathology suggests that both inflammatory and neurodegenerative mechanisms evolve concurrently throughout the disease course, regardless of the historic clinical phenotyping. Notably, it has been recognized that progressive MS may be driven by a specific form of inflammation occurring within the central nervous system, behind a closed blood-brain barrier. This inflammation is characterized by submeningeal collections of lymphoid cells forming follicle-like structures and chronic enlarging demyelinating lesions (also known as smoldering lesions) with an expanding border of iron-loaded activated microglia. These smoldering lesions can be visualized in humans using susceptibility-weighted magnetic resonance imaging as paramagnetic rim lesions, which appear to correlate with clinical disability and brain volume loss. Recent studies have associated these chronically expanding lesions with toxic sodium accumulation and the release of neurofilaments in the central nervous system, both of which are part of the neurodegenerative cascade in MS. As a result, microglial targeting has emerged as a new treatment strategy for both progressive and relapsing MS, with several agents currently undergoing phase III trials.

Conclusion

In conclusion, addressing the global care needs for chronic neurodegenerative disorders presents challenges due to their high cost and limited logistic resources, which are likely to worsen with an aging population. Using multiple sclerosis (MS) as an example, we emphasize the significance of enhancing our fundamental understanding of the disease's pathophysiology to develop more effective drug treatments and preventive strategies. Exploring non-pharmacological interventions like physical rehabilitation and electrical stimulation techniques could serve as valuable additional treatment options. Moreover, adopting multimodal biomarkers will enable us to stratify patients better and implement precision medicine approaches tailored to individual needs. Additionally, we see great potential in telehealth to enhance accessibility to care while also reducing clinical care costs. By leveraging technology, telehealth can offer greater convenience for patients and healthcare providers alike, making it a promising avenue for the future of neurodegenerative disorder management.

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Conflict of Interest

Author declares no conflict of interest.

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