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Factors Affecting Time Elapsed from First Symptom till Complete Diagnosis of Multiple Sclerosis, Initiation of Disease Modifying Treatment and Drug Adherence in Upper Egypt

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Abstract: ***Multiple sclerosis (MS) is a chronic progressive autoimmune inflammatory disorder of the central nervous system, with marked social and economic consequences. It is the leading cause of non-traumatic disability among productive young and middle-aged adults, affecting up to 2.22 million people worldwide. Although there is no cure for MS, marked evolution has been made in the disease modifying treatments (DMT) that can alter the disease course. The earlier that MS can be diagnosed; the sooner treatment can be initiated with timely prevention of disability progression. However, significant delays can still occur between noticing the first symptoms and receiving a diagnosis. Such delays could be due to heterogeneity of clinical and imaging manifestations, lack of awareness of the primary care physicians, the limited accessibility to specialized centers or the non-availability of diagnostic tools. Moreover, delayed initiation of DMT after diagnosis may be related to factors including the inadequate knowledge with DMT and their high coast. Like many chronic conditions, non-Adherence to drug therapies is estimated up to 50%, with increased morbidity, mortality, and health care costs. Therefore, particularly for populations with limited resources, early identification and management of factors leading to delayed diagnosis of MS, initiation, and adherence to DMT is the best strategy that will be reflected on patients, their families and society.***

Keywords: Multiple Sclerosis, delayed diagnosis, disease modifying treatment, treatment initiation, adherence

1. Introduction

MS is a progressive neurodegenerative disease, usually presents at a highly productive years of life in the 20s or 30s when people are planning families and building careers. The prevalence of MS in Egypt is rising and was estimated about 25/100.000 in different centers (1) . Patients can typically live with MS for 30 or 40 years (2, 3) and in such developing country like Egypt particularly the South of it, MS would significantly affect the quality of life of patients and their families with marked economic consequences on the society (4).

At individual level: living with MS have tremendous and even life-changing effects on educational, vocational, and family choices, with consequent decline in employment rate, educational level, and sociodemographic factor restriction (5) . MS is the leading cause of non-traumatic disability among young and middle-aged people (6) . If patients with RRMS were left untreated, 50–60% of them develop SPMS within 15–20 years and an average of 14 years to reach EDSS of 6 (7) . The disability caused by MS is not only physical disability but mental as well, with increased prevalence and severity in the progressive phases (8) . In fact, cognitive impairment appears to predate the appearance of structural abnormalities on MRI, and occurs in all MS phenotypes, including clinically isolated syndrome (CIS) (9) and even was demonstrated in radiologically isolated syndrome (RIS) (10, 11) . Beside the ongoing neurodegenerative process causing physical and cognitive disabilities, associated conditions such as psychiatric manifestations, fatigue, and sleep-related disorders, will add to the physical and cognitive disabilities and the overall disease burden (12).

At family level: as the disease progresses, the need for care gradually increases, which is provided mostly by their relative caregivers who typically spends more than 4 hours per day on caring activities over many years (13) . Spending significant time caring for their patient with MS is not only physically exhausting but also psychologically, social, and financially; therefore, the costs of disability progression extend to their families as well (14).

At the level of the society: the total costs of MS to society include direct medical and non-medical costs, and indirect costs (14) . MS drugs are among the most expensive commercially available medicines particularly those approved for the progressive phase, imposing high costs on patients and healthcare system. Also, Relapses lead to additional costs and burdens on healthcare system including inpatient, outpatient and professional care, consultations, tests, and medications (5) . As regard the indirect costs, MS-related disability represents approximately 40–44 % of total MS-related costs and result mainly from lost productivity (15) .

With delayed diagnosis, initiation, or non-adherence to the prescribed DMTs, the cost of drug utilization will increase as well as the burden on individuals, caregivers (16) . With the increasing landscape of available DMTs, an urge for

early intervention and treatment optimization is created to maximize brain health, productivity, and quality of life (15).

2. Delayed Diagnosis

Onset of MS is usually defined as the appearance of the first symptoms, as recalled by the patients or relatives, however, it is now evident that the disease process begins much earlier than the time of appearance of these first symptoms (17) . In the untreated MS patients, the brain atrophies at a much higher rate compared to healthy adults per year (about 0.5–1.35% compared to 0.1–0.5% respectively) (18, 19) . This accelerated brain atrophy starts early, often before a diagnosis of MS and proceeds throughout the course of the disease if left untreated (20) . The underlying neurological damage early at the onset of the disease is compensated with the neurological reserve and repair mechanisms (17) . However, when neurological reserve and repair mechanisms are exhausted, and can no longer compensate for damage, a stage of progressive disability begins, called secondary progressive MS (SPMS) (21) . The earlier that MS can be diagnosed, the sooner treatment can be initiated, and the remaining brain reserve is rescued.

The advances made in the diagnostic tools and evolution of the diagnostic criteria for MS made it possible to diagnose MS earlier than ever before (22) . However, significant delays can still occur between noticing the first symptoms and receiving a diagnosis which can be divided into two categories: 1) patient delay: the interval between the initial symptoms and the first medical consultation, and 2) system delay: the interval between the first medical consultation and the definite diagnosis (23) . Both categories could reduce the available therapeutic options and the opportunity for early intervention and may result in further disability. Consequently, monitoring the timeline of diagnosis and understanding the reasons for the delay is an important feature when managing MS patients (24).

The delay in diagnosis might be disease-related, due to heterogeneity of clinical presentations and that some symptoms may improve spontaneously make patients reluctant to seek medical attention (25) . On the other hand, some local factors may be involved such as low education levels, cultural factors, living in a rural area, financial and geographical low access to health care facilities (including access to MRI), primary progressive MS, age of onset, and type of first clinical symptoms can explain the observed delay in diagnosis across communities (12) . Conversely, some primary care physicians may have a low index of suspicion for MS, even sometimes can be difficult to be recognized by neurologists especially when clinical or radiological features are atypical (26) . One study reported that one-quarter of patients visited their primary care physicians more than 4 times before being referred to a neurologist (27, 28) . Although early diagnosis of MS is essential for better long-term outcomes, accurate diagnosis of MS can at times be challenging. Heterogeneity of the clinical presentations, misinterpretation of radiological findings, the broad differential diagnosis for mimickers and absence of specific biomarkers are all factors might result in initial misdiagnosis and subsequent delayed diagnosis of MS (29).

Since the choice and opportunity for early intervention will be lost if patients experience significant delays in diagnosis or referral to MS specialists, understanding which factors are associated with diagnostic or referral delay and the possible impact of delay on disability is therefore of particular importance (30) . Such delays could be reduced by improving awareness of MS among the public and primary care physicians who make referrals and by improving access to specialist MS healthcare professionals and diagnostic equipment (31).

3. Delayed initiation of DMTs

It is now undisputable that early initiation of DMT prevents the build-up of immunoinflammatory cascades causing accumulating irreversible parenchymal damage, therefore generates greater benefit to patients both in the short-and long-term (32). Based on large epidemiological studies, the optimal treatment window closes relatively early in the disease course when the patient reaches an EDSS score of 3.0. After which disability is no longer driven by focal inflammatory processes (33).

Despite the improvement of diagnostic criteria as well as the increased availability of treatment options, a significant proportion of patients diagnosed with RRMS may remain untreated or experience delays in starting DMT treatment (34, 35) . In a USA study of 11, 061 patients with MS, 59.7% did not receive any DMTs treatment over a mean follow-up period of 3 years following diagnosis (36). Therefore, to optimize disease management, efforts should be made for better understanding and management of the possible barriers to DMTs initiation (37).

A. Physician-related factors

A study conducted by Grytten et al. found that a large proportion of the people who never started DMT were never offered the drugs, suggesting that non-starting DMT also results from the prescribing doctor's personal opinion and organizational practice (38) . In case of long-term benign disease course, neurologists were found to be reluctant towards DMT and advice patients to wait and see whether the disease will remain stable (38) . A similar attitude was also faced when confronted with patients with later age of onset or with associated comorbidities (39, 40) .

B. Patient-Related:

- Age: The risk of non-starting DMT was associated in several studies with increasing age at diagnosis. This might reflect the fact that older people tend to see neurologists less often and consequently were less likely to use DMT (34).
- Comorbidities: increasing number of comorbidities were found to lower likelihood of DMT use. Perhaps due to hesitancy by people with MS (PwMS) and providers towards multidrug use and the perception of decreased treatment benefits in the setting of other chronic health conditions (12) .
- Disease course: patients may delay treatment or opt for treatments that address sporadic MS attacks. This can be due to the perception that their disease is mild, and they can wait to start therapy (41) .

- Family planning: some young PwMS may not initiate treatment due to family planning and pregnancy plans (39) .
- Side effects and fear of injections: The timely and often painful injections of DMT and the following adverse events might be troublesome in everyday life and work management (42) .
- Psychological: not starting DMT might be a part of an avoiding trauma coping strategy which patients use to elude what might be associated with MS (38) .

C. Factors related to healthcare services:

The most frequently reported barrier to DMT use is insurance authorization requirements and high out-of-pocket costs (39) . Moreover, the difficult access to specialized healthcare services is another obstacle to early start of DMT (38) . Another factor that has been reported was the period at which MS diagnosis has been made, as the introduction of new diagnostic guidelines, and the availability of novel treatment options has led to a shorter duration to DMT initiation (43).

Therefore, by addressing and overcoming those barriers, the duration to first DMT initiation will definitely be shortened, allowing the maximum benefits of DMTs utilization to be achieved.

4. Adherence to DMT

Adherence to treatment has been defined by the World Health Organization as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider" (44, 45) . According to WHO, adherence to long-term therapy for chronic illnesses is only around 50% (44) . Consequently, nonadherence will result in poor treatment outcomes, greater long-term disease sequelae, and increased health care costs (44).

Patients with MS require long-term treatment, without possible treatment holidays, to prevent MS relapses or disease progression (46–48) . Despite the proved benefits of DMTs, the rates of adherence to DMT among MS patients are quite low and the specific consequences of poor adherence in pwMS include increased relapse rates, hospitalizations, accumulated disability, and disease progression withsubsequent higher costs of DMTs for progressive course (46–48) . So, increasing the adherence to DMTs may have a greater impact on both individuals and society.

Barriers to proper adherence to DMTs in pwMS should be spotted to improve the effectiveness of drug utilization:

1) The socio-economic situation and Health care system: the unaffordable prices of MS DMTs force some persons with MS who would benefit from DMTs to go un-or undertreated (49) .
2) Disease nature: the chronicity, and symptoms of MS challenge patients' ability to remain motivated to keep taking their medication and the fact that DMTs do not provide direct relief of ongoing MS-related symptoms further complicates their commitment to treatment (50) .
3) Treatment: Although DMDs for MS patients are of benefit, some problems are associated with their use, including inconvenient modes, needle phobia (associated with injectable DMTs), schedules of administration, long periods of therapy, and significant side effects. Treatment satisfaction has been linked to adherence level as satisfied patients are more likely to adhere better to their medications (51) .
4) The patient profile: Since before diagnosis most MS patients are often young, fit, and healthy; however, upon diagnosis they are asked to acknowledge that they have a potentially chronic condition, of unknown etiology and unpredictable prognosis. Thus, determining what patients expect from a given treatment and setting realistic goals of relapse or disability reduction as opposed to a cure is important (52). Cognitive deficits can reduce patients' ability to adhere to their treatment regimens, moreover, reduce fine motor skills can impair their ability to prepare and administer injections (53) . The high prevalence of depressive symptoms in pwMS as well as the high rates of inadequate treatment is a risk factor for non-adherence, reduced quality of life, and risk of suicide (24) . Despite affecting 74%, Fatigue is a neglected aspect of MS, and is associated with worse adherence MS (54) .

With over 15 DMTs of different efficacy and safety profiles are approved, deciding which DMT to use in a specific patient requires a careful analysis of a patient's high-risk factors for early progression, consideration of the efficacy and safety profile for potential therapy, as well as understanding of a patient's lifestyle and expectations (55) . Moreover, shared treatment decision with adequate understanding of both their disease and the benefits/risks of treatments is crucial to maintain adherence required to optimize the clinical outcomes (55) .

5. Conclusion

Given the finite resources of the health system in the South of Egypt, and the substantial cost burden imposed by MS, undercover obstacles facing early diagnosis, initiation, sequencing, and proper adherence to DMTs are of key importance in achieving optimal outcomes for individuals with MS and by far more important than any improvement in specific medical treatments.

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