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Editorial

Prolonged Undiagnosed Prodromal Symptoms

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Medically unexplained symptoms (MUS) are physical complaints for which no organic cause can be found after evaluation. They are distinct from somatic symptom disorder which require additional psychiatric criteria [1], and may encompass up to 40–49% of patients in primary care [2] and over 20% among hospitalized patients [3]. Recent data suggest a different perspective in a subgroup of these patients. An important, carefully-conducted study demonstrated an unequivocal increase in physician visits rates, as early as 14–15 years prior to the onset of clinically-recognized multiple sclerosis (MS). Visit rates were significantly increased compared to a matched cohort from the general population, and often involve non-specific, ill-defined complaints such as fatigue, pain, gastrointestinal and urinary disturbances, anxiety, depression, and insomnia, recorded 4–15 years prior to multiple sclerosis onset [4]. The design of the study precludes elucidation of the patients' experience, but this aspect is too important to be neglected. These relatively young patients (mean 37.9 $\pm$ 10.9 years) of all socio-economic quintiles (74% female), repeatedly presented over years with diverse, poorly-understood symptoms. They likely required multiple referrals and tests with substantially increased health services utilization and cost. However, their recurrent complaints evaded explanation (or relief) for a long time, yet by inference these complaints were multiple sclerosis-related, due at least in part, to early, "subclinical" pathology. In all probability, they were labeled by their physicians as "medically unexplained symptoms" (i.e., persistent physical symptoms), 'difficult patients', or patients with psychological/psychiatric problems [1–3]. These patients may feel a sense of relief, even in the face of a serious diagnosis, to finally be given a name—a cause of their longstanding poor health and an end to frustrating clinical encounters. Similar diagnostic delays have been reported in systemic lupus erythematosus (SLE), where early disease manifestations may be highly diverse, affect any system, and accrue over time, associated in some cases with years of undiagnosed symptoms and compromised quality of life [5]. Quite a few other conditions exhibit insidious onset, slow progression, and protean manifestations—often associated with diagnostic delays of several years from the onset of symptoms. Notable examples are endometriosis (approximately 7–8 years), coeliac disease (approximately 3.5 years), and acromegaly (approximately 12 years). Even common conditions may present atypically, such as the prodromal symptoms of Parkinson disease which can precede the overt classic motor symptoms by >10 years, leading to long diagnostic delays [6]. Other rare diseases such as gastrointestinal neuroendocrine tumours, type 1 multiple endocrine neoplasia (MEN1), primary immunodeficiency, sarcoidosis, chronic inflammatory demyelinating polyneuropathy (CIDP), or idiopathic pulmonary fibrosis (IPF) may also cause symptoms over years, before a diagnosis is made. Thus, a recent retrospective survey of patients living with a rare disease found that the average time from first medical contact to a confirmed diagnosis was 4.3 years, and 25% waited more than 5 years to be diagnosed [7]. The "takeaway message" for clinicians is surely not to subject all patients with poorly-explained complaints to magnetic resonance imaging (MRI) to rule out multiple sclerosis or CIDP. The majority of MUS remains MUS, and not a prodrome of a later diagnosis. However, it is definitely a call for more humility among clinicians [8]. This is especially needed since much of our clinical work is "in the judgment and articulation of uncertainty in the face of imperfect information and evidence" [9]. Humility enhances tolerance of uncertainty, and promotes an attitude of patience and respect towards patients, even when their complaints are repetitive, or poorly understood. Thus, the patient may be right, and subjective grievances need to be recorded, contemplated, and followed. Several key principles may facilitate a more timely diagnosis in these patients. First, listening attentively to the patient, bearing in mind the entities mentioned above. This is especially important since there may be few objective findings in the early stages. Second, a positive family history may point the finger in the right direction, and trigger a more focused search [10]. Third, longitudinal tracking of symptom evolution and health care utilization is essential. Noticing a crescendo pattern or the discovery of new findings on physical examination or laboratory tests may signal an underlying prodromal phase of an evolving disease. Either can provide a lead towards a diagnosis. Fourth, artificial intelligence (AI) search tools for physicians may be utilized to check on perplexing symptom clusters that evade explanation. Clinical decision support tools may also aid in systematically identifying clinical key red flags in patients with prolonged nonspecific symptoms [9]. Finally, person-centred biopsychosocial consultations are indispensable in managing medically unexplained symptoms [1], and highly

selected patients may be considered for possible referral to a tertiary centre.

Thus, the main 'take home' message is the need of an increased awareness that "medically unexplained symptoms" (MUS) may sometimes signify a yet-unrecognized rare or slowly-evolving disease. Diagnostic delays are one type of diagnostic errors, which unfortunately remain an obstinate problem [11]. Patients who present with persistent medically unexplained symptoms, are more susceptible. Although the majority of patients with unexplained medical symptoms will not go on to develop a related illness, practitioners need to be aware that in a significant minority, they may represent the tip of the iceberg of a rare disease or an unusual, unexpected presentation of a more common condition. A higher index of suspicion and application of the suggested attitude and approach, may lead to a more timely diagnosis, and treatment at a stage that can prevent further loss of tissue and function.

Key Points

• Patients with medically unexplained symptoms (MUS) are often encountered in general practice, specialist, and hospital settings alike.

• In a significant minority, repeated visits with such symptoms signify a rare disease or an unusual presentation of a more common condition, and years may elapse before a diagnosis is confirmed—a diagnostic delay which is both frustrating and deleterious to the patient.

• Several techniques may facilitate a more timely diagnosis, including physician's humility; equanimity in the face of uncertainty; and use of dedicated information technology.

• Patient-centred biopsychosocial consultations are recommended for managing persistent medically unexplained symptoms.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

All elements of the study and subsequent write-up were carried out by the author [AS]. The author read and approved the final manuscript. The author has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Ami Schattner is serving as one of the Editorial Board Members of this journal. We declare that Ami Schattner had no involvement in the review of this article and has no access to information regarding its review. The author declares no conflict of interest. Full responsibility for the editorial process for this article was delegated to Edwin C Jesudason.

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