FUNCTIONAL NEUROLOGICAL DISORDERS AND MISDIAGNOSIS OF MULTIPLE SCLEROSIS

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Functional Neurological Disorders

Neurologists frequently encounter patients with symptoms for which no clear pathophysiology or structural disease can be identified.\(^1\)\(^,\)\(^2\) Terminology for such syndromes has included “psychogenic”, “non-organic”, and “conversation” disorders, but the preferred term “functional neurological disorders” has been adopted most recently\(^1\)\(^,\)\(^3\) as this heterogeneous group of syndromes appear to be best explained by a disturbance of nervous system function.\(^2\) Instead of a diagnosis of exclusion in the presence of psychosocial factors, the diagnosis of a functional neurological disorder appears most reliable in the setting of demonstrable positive findings\(^2\)\(^,\)\(^4\) on neurological exam or laboratory evaluation. A variety approaches have been used to understand the mechanisms underlying functional neurological disorders\(^5\) and recent functional MRI studies suggest alterations in areas in the brain involved in the planning, execution, interpretation and attribution of movement, as well as emotional regulation are implicated.\(^3\)

Misdiagnosis of Multiple Sclerosis

The Institute of Medicine recently described the need to study misdiagnosis as a “moral, professional, and public health imperative.”\(^5\) A 2016 study suggested that medical error is the third leading cause of death in the United States.\(^6\)\(^,\)\(^7\)

Multiple sclerosis (MS) remains a clinical diagnosis, as no specific biomarker for MS has been identified. While diagnostic criteria for MS are well-established,\(^7\) correct diagnosis relies on the appropriate interpretation of clinical and radiologic data in the setting of multiple disorders that can mimic MS.\(^6\)\(^,\)\(^8\)\(^-\)\(^10\) As a result, MS misdiagnosis, or the incorrect diagnosis of MS, remains a problem.\(^11\)\(^-\)\(^13\)

Recent studies have demonstrated that patients misdiagnosed with MS are exposed to prolonged and unnecessary risks, morbidity, and in some cases mortality, as a consequence of misdiagnosis.\(^12\) These studies have suggested that misinterpretation and misapplication of MS diagnostic criteria is likely an important contributor to MS misdiagnosis, and in many cases there may be an earlier opportunity to prevent or recognize a potential misdiagnosis.\(^11\)\(^,\)\(^12\)

Misdiagnosis of Multiple Sclerosis and Functional Neurologic Disorders

In a recent study of 110 patients incorrectly misdiagnosed with MS,\(^12\) in 65% of cases application of MS diagnostic criteria to a neurological syndrome that is not typical for MS contributed to misdiagnosis; MS diagnostic criteria fail in this situation but are often applied to atypical syndromes in clinical practice. In 60%, declaring MS MRI diagnostic criteria satisfied in a patient with nonspecific symptoms contributed to misdiagnosis. Ultimately, these two errors perpetuate one another. Nonspecific symptoms acquire additional and unwarranted attention when nonspecific MRI lesions are present, and nonspecific MRI lesions are accorded undue attention in the presence of symptoms of common conditions. Given such findings, it is not surprising that patients with functional neurological disorders with nonspecific MRI abnormalities have been identified as patients commonly misdiagnosed with MS.\(^12\)\(^,\)\(^13\)

Although the reasons for MS misdiagnosis and types of disorders mistaken for MS have changed along with the evolution of MS diagnostic criteria over the years, the misdiagnosis of functional neurological disorders for MS is likely a longstanding problem. In a study published in 1984,\(^14\) 13% of 400 consecutive patients referred to an Dalhousie University’s multiple sclerosis unit in Nova Scotia from 1979 to 1983 did not have MS. Although thirty alternate diagnoses were identified in these patients, the most common was psychiatric disease (27%). In similar a study in 2005 at the University of Colorado Multiple Sclerosis Center\(^15\) only 33 % of 281 patients referred for evaluation for MS from 2001 to 2003 met diagnostic criteria for MS or possible MS. Again, although thirty-seven alternate diagnoses were identified in the patients who were not ultimately diagnosed with MS, the most
common diagnosis was psychiatric disease (23%). In a follow-up study, many of these patients met diagnostic criteria for somatoform and/or conversion disorder. As part of an epidemiological study performed in Western Australia in 1981 and published in 1987, records of 387 patients who were either diagnosed with MS or informed they might have MS were reviewed. In this study 17% were determined to have been incorrectly diagnosed with MS, and of those approximately 9% had symptoms or signs suggestive of a functional neurological disorder.

Thus prior studies have demonstrated that patients with functional neurological disorders are frequently referred for evaluation for MS, and in some cases, such patients are misdiagnosed with MS. Recent data confirms this remains a problem. In 2012 a survey of 122 MS specialists, 95% reported having evaluated at least one patient in the last year who carried a diagnosis of MS for a year or longer who they strongly felt did not have MS. Many recalled numerous such patients. Respondents were asked to recall the most likely alternative diagnoses in these patients, and 45% chose psychiatric disease. In a 2016 multicenter study that collected data on 110 patients determined to have been misdiagnosed with MS, conversion or psychogenic disorder was identified in 11%—the fourth most frequent diagnosis.

The diagnoses most frequently mistaken for MS among the 110 patients in the 2016 study, including functional neurological disorders, lack a specific biomarker. The correct diagnosis relies instead on clinical acumen alone for the interpretation of history, exam findings, and radiographic results. Of note 24% of the patients in this study were misdiagnosed with MS by neurologists with subspecialty training in MS or MS-focused practices, suggesting that this problem is not confined to non-specialists. After seeing many atypical presentations of MS, it is possible that MS specialists may dismiss “red flags” appearing later in the course of the disease as being within the spectrum of MS, rather than a clue to an alternative condition.

Although the often-cited expansive differential diagnosis of MS includes consideration of “red flags” for a variety of rare disorders, this study confirms that instead, common disorders such as functional neurological syndromes may account for misdiagnosis in the majority of cases of misdiagnosis. Emphasis on further education and recognition of “positive findings” or such “red flags” specifically for functional neurological disorders is therefore especially important in the evaluation for suspect MS.

“Positive findings” on neurological examination in the evaluation for MS associated with functional neurological disorders

Visual impairment
- “Fogging Test”
- tubular visual field
- optokinetic nystagmus
- “Fingertip touching test”
- “Signature test”
- “Sunglasses sign”

Motor impairment
- arm drop test with “pseudo waxy flexibility”
- arm drift without pronation
- “Finger abduction sign”
- “Elbow flex-ex sign”
- tremor entrainment test
- distractible tremor
- “Hoover sign”
- “Hip abductor sign”
- ankle plantar flexion weakness intact toe-walking
- variable loss of function (“giveaway”, “breakaway”, or “collapsing” weakness)
Sensory impairment

- distraction during Romberg
- romberg falling toward examiner regardless of examiner position
- whole limb anesthesia with sharp demarcation at shoulder or groin
- splitting midline/hemi-sensory loss to all modalities

Gait impairment

- dragging monoplegic gait w/inverted or everted foot
- fluctuating gait abnormality

Clinical history atypical for MS-related demyelination that may be associated with a functional neurological disorder or other alternate diagnoses

- symptoms or exam findings that do not logically localize to central nervous system
- historical “relapse” without objective correlate on neurological exam or imaging
- stereotyped symptoms
- transient symptoms lasting seconds to minutes

Diagnosis of MS and a Functional Neurological Disorder

It is important to note that people with a confirmed diagnosis of MS can have functional neurological symptoms. Positive exam findings noted above facilitate recognition of such symptoms. In patients undergoing evaluation for MS where findings associated with functional neurological disorders are identified, additional evaluation such as spinal cord imaging, cerebrospinal fluids evaluation, and visual evoked potentials may aid in clarifying a diagnosis of MS. In some cases and clinical and radiographic monitoring over time may be necessary to confirm a diagnosis. In patients with confirmed MS, it is critical to distinguish functional neurological symptoms from inflammatory relapses to avoid risks associated with unnecessary treatment with corticosteroids.

Un-diagnosing MS, and Diagnosis and Treatment of Functional Neurological Disorders

Discussing a misdiagnosis can be challenging and some neurologists have even expressed hesitancy to disclose a suspected misdiagnosis of MS. Presumably in these situations these physicians perceive an ethical predicament surrounding concern for causing greater psychosocial, economic, or other harms to patients. While these considerations certainly complicate disclosure, they do not justify withholding information. Benefits of disclosure of misdiagnosis include ensuring patients are able to make autonomous decisions, maintenance of a trustworthy physician-patient relationship to facilitate shared-decision making, and the identification and treatment of a correct diagnosis which may better alleviate suffering. Numerous authors have discussed optimal communication strategies for the disclosure of medical errors.

Diagnosis of a functional neurological disorder, rather than MS, carries specific challenges but communication of the diagnosis should not differ from communication approaches commonly used for diagnosis of other disorders. Suboptimal and potentially harmful approaches include informing the patient they do not have a neurological disease, premature attribution of symptoms to psychological factors, and emphasis of negative neurological workup as basis for diagnosis. Instead, forthright discussion and validation of the diagnosis with an emphasis on the disruption of function of the nervous system is important. Furthermore, several authors have suggested that demonstration of positive physical signs suggestive of a functional neurological disorder can be particularly helpful as part of an explanation of how the diagnosis was reached. It is also important to explain why history, symptoms, or results of laboratory evaluation were not typical for MS or alternate suspected diagnoses prompting neurological referral.

Patients with functional neurological disorders may suffer more disability, and may have a poorer prognosis than patients with other disorders. Such patients may fear abandonment once a diagnosis is made, and ensuring follow up care is important. A variety of specific physical therapy and/or psychotherapy interventions may be particularly helpful in patients with functional neurological disorders and additional treatment modalities are currently under investigation.

Conclusions

- functional neurological disorders are likely frequently mistaken for MS
- overreliance on MRI findings in the setting of nonspecific or atypical clinical symptoms is likely a common cause of misdiagnosis
- strict adherence to MS diagnostic criteria with attention to clinical history and neurological exam findings may prevent misdiagnosis
- positive findings aid in the identification of a functional neurological disorder
- further evaluation is necessary to establish a diagnosis of MS in the setting of clinical presentations atypical for demyelination and/or with positive findings suggestive of a functional neurological disorder
