The Accuracy of Prevalence Rates of Multiple Sclerosis: A Critical Review

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Key Words

Multiple sclerosis · Disseminated encephalomyelitis · Neuromyelitis optica

Abstract

Review of the recent medical literature raises doubts about the reliability of reported prevalence rates of multiple sclerosis (MS). Many published prevalence rates are inflated. Some studies have shown that relying on clinical information and MRI interpretation leads to one third of incorrect MS diagnoses. The most important error is failing to distinguish between the clinical and MRI characteristics of MS and of disseminated encephalomyelitis (DEM) in both their acute and relapsing forms. The diagnostic criteria in current usage, including those relating to imaging, do not differentiate between MS and other recurrent inflammatory demyelinating diseases of the central nervous system. Considering a second demyelinating episode following a clinically isolated symptom or acute DEM, as confirming MS, is another major source of error. Another is including cases with onset before they entered the study group or moved to the geographic area. Neuromyelitis optica (NMO) has long been considered an MS variant and in Far Eastern countries it is counted as the

‘oriental’ form of MS, falsely inflating prevalence rates of MS in those areas. Recent immunologic and radiologic evidence shows that at least some NMO cases represent instances of DEM.

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Introduction

Both genetic and environmental factors play a role in the acquisition of multiple sclerosis (MS). Hundreds of epidemiologic studies measuring MS prevalence rates (PR) have been published all over the world. Comparative studies of different countries, families, populations and ethnic groups aim to delineate the relative importance of genetic and environmental factors in the genesis of MS.

Crude diagnostic criteria for MS were first proposed by Charcot. Subsequently, more sophisticated schemes appeared, progressively incorporating the results of para-clinical procedures, culminating in the incorporation of magnetic resonance imaging (MRI) in 1981. Although the more recent criteria stress the principle that the diagnosis of MS is and remains a clinical one, it has become abundantly clear that the interpretation of the MRI by a radi-

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Table 1. Responses of 108 neurologists on the diagnosis of 30 autopsied cases

Case No.	Age of onset, years	Sex	Probable %	Possible %	Unlikely %	Anatomy diagnosis	CSF colloidal gold curve	CSF γ -globulin, %
1	31	F	91.7	8.3	0	MS	not done	
2	22	F	25.0	38.0	36.0	MS	3333343311	
3	39	F	4.6	11.1	84.3	MS	not done	
4	47	M	4.7	24.0	71.3	non-MS ¹	0000000000	13
5	32	M	10.3	35.1	54.6	MS	not done	10
6	27	F	84.3	13.0	2.7	MS	0000000000	9
7	30	F	23.2	40.8	36.0	MS	2223322100	
8	40	F	47.2	29.2	23.2	MS ²	not done	
9	57	M	2.8	14.8	82.4	MS	1110000000	
10	31	F	43.5	32.5	24.0	MS	1233332100	
11	26	M	89.8	8.3	1.9	MS	0000000000	
12	32	M	42.6	32.4	25.0	MS	not done	
13	18	M	75.0	19.4	5.6	MS	not done	
14	31	M	88.9	11.1	0	MS	5554321000	
15	25	M	78.7	15.7	5.6	MS	not done	
16	27	F	31.5	29.6	38.9	MS	0000000000	
17	28	M	1.9	9.2	88.9	non-MS ¹	0000000000	
18	23	M	61.1	28.6	10.3	MS	4443322211	
19	22	M	80.6	17.6	1.8	MS	0000000000	
20	24	M	86.1	13.0	0.9	MS	0000000000	
21	33	M	65.7	26.0	7.4	MS	0000000000	
22	19	M	98.2	0.9	0.9	MS	0023111100	
23	15	F	14.8	25.9	59.3	non-MS ¹	0122110000	19
24	61	F	1.9	14.8	83.3	MS ³	0000000000	
25	38	M	68.5	27.8	3.7	MS	0000000000	13
26	28	M	81.5	13.9	4.6	MS	1122210000	
27	28	F	86.1	13.9	0	MS	5555432100	
28	26	F	13.9	29.6	56.5	MS ⁴	not done	
29	18	M	21.3	34.3	44.4	MS	4442210000	
30	23	F	54.6	30.6	14.8	MS	not done	

All the patients were Caucasians except No. 6, 7, 20 and 29 who were black. The anatomical diagnosis was the only information not provided. All clinical information, except the results of the autopsy, was furnished to the respondents.

¹ Brain tumor. ² MS + brain tumor. ³ MS + stroke. ⁴ MS + solitary lung tumor.

ologist, or less often by a neurologist, has become the principal, at times the exclusive, basis for the diagnosis of MS, at the expense of a thorough, probing clinical history and neurological examination. The commonly used diagnostic criteria of Poser et al. [1], McDonald et al. [2], and Polman et al. [3] are unable to differentiate between the two commonest forms of inflammatory demyelinating diseases, MS and disseminated encephalomyelitis (DEM).

It is the purpose of this paper to show that despite the availability of clinical criteria and paraclinical tests, the published PR data of MS patients are inaccurate and artificially inflated.

A Clinical Questionnaire Survey

In 1963, a collection of 30 complete clinical histories and examinations, including cerebrospinal fluid colloidal curves when available, was sent to prominent clinical neurologists around the world [4]. All the cases had been autopsied: 25 had classical MS, 1 patient had MS plus a brain tumor, another MS and a stroke, and 3 did not have MS but died because of brain tumors.

The respondents were simply asked to indicate for each of the cases if the diagnosis of MS was probable, possible or unlikely, according to their own diagnostic crite-

ria. One hundred and eight neurologists responded. The individual responses were scored as follows: each correct diagnosis (MS or non-MS) was given a rating of 2, cases marked as possible were given 1, while incorrect responses received a 0, 60 being the perfect score (27 MS and 3 non-MS). The variations in scoring for some of the individual cases were striking (table 1). The average score per respondent was 40. Thus, collectively, the 108 neurologists correctly identified two thirds of the cases, *but they were not the same cases*. Experience, country of training and of practice and 'specialization' in MS made no difference, the mean score for all these subgroups was still 40. This large clinical diagnostic error was unexpected. It is only fair to suggest that the errors might well have been smaller had the physicians been able to interview and examine the patients in person, since clinical intuition may play an important role in diagnosis.

An Australian Clinicoepidemiologic Study

Hankey and Stewart-Wynne [5] reviewed a 1981 pre-neuroimaging survey of 385 patients in Western Australia who had been told that they had or might have MS. Their review noted that only 264 (69%) of 385 cases could be classified as definite or probable MS using the criteria by Rose et al. [6]. The overall error for this 1981 survey, 121 out of 385, is 31%.

The Effect of Neuroimaging on the Diagnosis of MS

The diagnostic use of MRI for MS grew with incredible rapidity. By the mid 1990s, a patient was rarely diagnosed with the disease without having had one or more MRI scans. Erroneous diagnoses were still frequent. A total of 366 patients who had received the diagnosis of MS from their neurologists were referred for another opinion. All had had MRI films that were available for review. Out of the 366, 236 (64.5%) were observed to have clinically definite MS, an error of 35.5% [7]. The commonest misdiagnosis was DEM, but also included chronic fatigue syndrome and a variety of other conditions, resulting from a failure of obtaining a detailed clinical history, and misinterpretation of the MRI scans.

The similarity of the error rates of the three cited studies is striking. Some of the patients in the 1997 review [7] had participated in clinical trials for immunomodulatory drugs, and some were still being so treated, destined to receive a lifelong regimen of treatment.

The Effect of Immigration on PR

Epidemiologic studies measuring PR are designed to provide data about potential environmental etiological factors. The disease is generally believed to be acquired by most people at the time of puberty [8]; for this reason, surveys designed to determine the relevance of these etiological factors must take into consideration the geographic and environmental locations of the patients at the time of putative acquisition. Neither the dates of diagnosis nor of clinical onset have any biological significance, although the latter may occasionally suggest the effect of a triggering agent or mechanism. However, the true onset of the disease, such as transient numbness of an arm or a day's dimness of monocular vision, may be easily forgotten.

PR studies have traditionally focused on a defined geographic area or population group. In the case of the former, it would be logical to count only those MS patients whose disease started when they were living in the study area. However, some authors include patients who already had symptomatic MS when they moved to the study area. For example, in 1978 the PR of MS in Olmsted County, Minn., USA, was said to be 102 per 100,000, but this included 25 patients who already had MS when they moved there [9]. A corrected PR was 74 per 100,000. In another study of the same area in 1991 [10], the PR of 179 per 100,000 included 57 MS patients with prior onset, reducing the correct PR to 122 per 100,000.

Recurrent DEM and MS

There are two ways that the failure to distinguish between MS and recurrent DEM may result in inflation of the number of MS patients in surveys. The first is the continuing controversy about the distinction between a recurrent form of DEM and relapsing-remitting MS. This is in spite of the dozens of publications that have documented the reality of clinical and pathological recurrent DEM [11], in addition to the existence of an experimental model [12]. Traditionally, DEM has been considered a monophasic illness, occurring predominantly in children, and many neurologists believe that a second episode of neurological dysfunction confirms the diagnosis of MS, eliminating DEM from consideration and inflating the numbers of childhood MS. In 1931, McAlpine [13], in discussing the chronic stage of DEM, stated that 'should a relapse occur some months after the onset, then the case should be classified as disseminated

[multiple] sclerosis'. Similarly, in 1994, even after MRIs had become generally available, Caldemeyer et al. [14] excluded from their series patients with recurrent neurological deficits suggesting MS. In their review of adult DEM, Schwarz et al. [15] noted that they had made the diagnosis retrospectively: a case was counted as acute DEM if there was no evidence of a second clinical episode of central nervous system demyelination, a position also adopted by Bangsgaard et al. [16], who believe that only the absence of relapses would rule out MS. Hollinger et al. [17] declared that: 'If there is clear dissemination in time and space with regard to the clinical relapse, the diagnosis of MS should be considered.' Dale and Branson [18] stated: 'When there are relapses or progressive disease, the term MS is used.' Mikaeloff et al. [19] said: 'A second attack at least one month after the first attack qualified for conversion to MS.' It is remarkable that in addition to the strikingly different appearance of MRI lesions, the clinical characteristics of DEM, which are most often also very different from those of MS, are totally disregarded.

By contrast, Tenembaum et al. [20] reported a 10% relapse rate in their 84 patients with DEM, whereas Anlar et al. [21] found it to be 33%. Other recent publications also mention relapses of DEM [22–24]. A curious logical hiatus occurs when changing the diagnosis from DEM to MS after a recurrence, since the MRI lesion(s) is/are still atypical and similar to those of DEM. The use of the 'relapse equals MS' principle artificially inflates the number of MS patients, especially in children.

The second and more common problem is the persistent misinterpretation of MRI. The diagnostic criteria incorporated in the schemes by McDonald et al. [2] and Polman et al. [3] are purely quantitative and lack any qualitative descriptive features. It is the appearance, not the number, of plaques that distinguishes DEM from MS.

MRI has become important in diagnosing MS, but its value in excluding that diagnosis has largely been ignored, despite many publications illustrating what have now been recognized as typical lesions of DEM. In 1983, Lukes et al. [25] published the first MRI scans of acute DEM, followed by Atlas et al. [26] and Kappelle et al. [27] in 1986, and Epperson et al. [28] who reproduced the typical, very large, near-symmetrical MRI T₂-weighted images of acute DEM. Other landmark articles were those of Kesselring et al. [29] on the distinctions between MS and DEM, and of van der Meyden et al. [30], who demonstrated gadolinium enhancement of almost all the lesions seen in DEM, an important point in differentiat-

ing it from MS in which usually only one or two plaques enhance. The lesion load is often much greater than what is seen in MS [31]. Indeed a number of authors have stressed the unique importance of MRI to differentiate between MS and DEM [32, 33]. The failure to recognize the diagnostic significance of the typical MRI appearance of DEM, the lack of images of the spinal cord, and the scant attention to cerebrospinal fluid abnormalities have led to publications incorrectly labeling patients as having MS.

Neuromyelitis Optica and MS

Neuromyelitis optica (NMO) has long been considered a variant of MS, although Miller and Evans [34] as far back as 1953 suggested that it might be a form of DEM. The diagnostic criteria for NMO by Wingerchuk et al. [35] required an elongated spinal cord T₂-weighted MRI lesion, equal to or greater than three vertebral bodies, a feature that was mentioned 8 years previously in the criteria by McDonald et al. [2] as excluding MS. The discovery of antibodies against aquaporin 4, the so-called NMO-IgG [36], seemed to differentiate between NMO and MS. Finally, Pittock et al. [37] have shown by means of MRI that at least some, if not all, cases of NMO are instances of DEM. These new discoveries also verified the long-suspected identity of Oriental opticospinal MS with NMO, although such cases are still included in series of MS in the Far East: a good example is the incomprehensibly confusing review of both anti-aquaporin-antibody-positive and -negative cases of 'MS' in Japanese patients, a mixture of MS, opticospinal MS, NMO and DEM [38].

Clinically Silent MS

The exact number of persons with asymptomatic MS is unknown. Four studies [39–42] have reported finding unexpected, asymptomatic MS lesions at autopsy with an overall prevalence of 100 per 100,000. Typical MS plaques have been seen when MRI scans are performed for various complaints in patients who are not suspected of having MS, and in the siblings of MS patients. It is probable that the disease is far more common than suspected. Conceivably, some neurologists might be tempted to initiate immunomodulatory treatment of these persons, but we believe that this would not be warranted at this time.

How Prevalent Is MS in the United States?

The most recent estimate by Hirtz et al. [43] based on published PR studies was a total of 266,000, with a PR of 100 per 100,000, a figure that presumably applies only to symptomatic MS patients. This prompted an e-mail (dated February 2, 2007) from the National MS Society stating 'The Society currently has over 300,000 people in its data base *who have identified themselves as having MS* [italics added]. Based on previous research, the Society estimates MS prevalence to be about 135 per 100,000 in the US, for a total population of approximately 400,000.' It is probable that both figures are somewhat exaggerated.

Conclusions

Comparisons between geographic areas and ethnic-racial groups are essential to determine the influence of environmental and genetic factors on the etiology and acquisition of MS. They are dependent on the accuracy of prevalence studies, thus on the reliability of the diagnosis. Clinical as well as MRI diagnostic criteria have so far failed to reasonably ensure such outcomes. The need to recognize the clinical and imaging differences between MS and other inflammatory demyelinating diseases, in particular between relapsing-remitting MS and recurrent DEM, is imperative.

Accurate data are essential for epidemiological studies not only for the purpose of seeking etiological factors and mechanisms, but also as the bases for socioeconomic decisions.

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