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Neuroepidemiology

Epidemiology of multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is the most frequently seen demyelinating disease, with a prevalence that varies considerably, from high levels in North America and Europe (> 100/100,000 inhabitants) to low rates in Eastern Asia and sub-Saharan Africa (2/100,000 population). Knowledge of the geographical distribution of the disease and its survival data, and a better understanding of the natural history of the disease, have improved our understanding of the respective roles of endogenous and exogenous causes of MS. Concerning mortality, in a large French cohort of 27,603 patients, there was no difference between MS patients and controls in the first 20 years of the disease, although life expectancy was reduced by 6–7 years in MS patients. In 2004, the prevalence of MS in France was 94.7/100,000 population, according to data from the French National Health Insurance Agency for Salaried Workers (*Caisse nationale d'assurance maladie des travailleurs Salariés* [CNAM-TS]), which insures 87% of the French population. This prevalence was higher in the North and East of France. In several countries, including France, the gender ratio for MS incidence (women/men) went from 2/1 to 3/1 from the 1950s to the 2000s, but only for the relapsing–remitting form. As for risk factors of MS, the most pertinent environmental factors are infection with Epstein-Barr virus (EBV), especially if it arises after childhood and is symptomatic. The role of smoking in MS risk has been confirmed, but is modest. In contrast, vaccines, stress, traumatic events and allergies have not been identified as risk factors, while the involvement of vitamin D has yet to be confirmed. From a genetic point of view, the association between HLA-DRB1*15:01 and a high risk of MS has been known for decades. More recently, immunogenetic markers have been identified (*IL2RA*, *IL7RA*) and, in particular thanks to studies of genome-wide associations, more than 100 genetic variants have been reported. Most of these are involved in the immune response and often associated with other autoimmune diseases. Studies of the natural history of MS suggest it is a two-phase disease: in the first phase, inflammation is focal with flares; and in the second phase, disability progresses independently of focal inflammation. This has clear implications for therapy. Age may also be a key factor in the phenotype of the disease. In conclusion, France is a high-risk country for MS, but it only slightly reduces life expectancy. MS is a multifactorial disease and the implications of immunogenetics are major. Preventative approaches might be derived from knowledge of the risk factors and natural history of the disease (smoking, vitamin D).

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1. Introduction

Multiple sclerosis (MS) is the most common demyelinating disease seen in high-income countries, and has a heterogeneous prevalence worldwide: it is highest in North America (140/100,000 population) and Europe (108/100,000), and lowest in East Asia (2.2/100,000 population) and sub-Saharan Africa (2.1/100,000). The global median prevalence of MS has increased from 30/100,000 in 2008 to 33/100,000 in 2013, according to a report by the MS International Federation. In Europe in particular, a North-South prevalence gradient has been described for distribution of the disease (higher in the North, lower in the South). France is located in the middle of Western Europe between zones of high MS prevalence (such as the Scandinavian countries and United Kingdom) and areas of low MS prevalence (Italy, Greece, Spain), and also appears to reflect the European epidemiology of the disease rather well. Given this situation, MS mortality, incidence and prevalence data and their evolution over time in France are important in that they provide a pertinent view of the epidemiology.

Analyzing such data is an essential first step towards taking into account the considerable knowledge and numerous hypotheses regarding the cause(s) of MS and, above all, the environmental risk factors. Also, extensive databases for large groups of MS patients provide accurate information on the natural history of MS as a two-stage disease (first the focal inflammatory process, and then the second, which is independent of focal inflammatory markers). All of these descriptive and analytical epidemiological data will lead to a better understanding of the risk factors for MS, and may even have implications for therapeutic strategies.

2. MS mortality

To our knowledge, around 40 epidemiological studies of mortality have been conducted in patients afflicted with MS. According to one published series [1–13], 70–88% of patients are still alive 25 years after clinical onset, and the median time from onset to death ranges from 24 years to > 45 years. These differences can be explained by differences in study periods, geographical areas and methodology (such as study population, duration, statistical method used).

On the other hand, all of the studies [1,2,6–13], whatever their location, period or methods, showed excess mortality in MS patients compared with the general population matched for age, gender and follow-up duration. Life expectancy with MS seems to be reduced by 6 to 14 years. A large French study (SURVIMUS), which included 27,603 MS patients, showed that, during the first 20 years of the disease, survival was closely similar to that of the general population. The excess mortality was seen after this period and led to a reduction in life expectancy of about 6 to 7 years [14].

In fact, about 50–70% of deaths could be considered MS-related, with MS as either the main cause or a contributing one. Progressive disability leads to severe handicaps, which increase the risk of death, especially by increasing the risk of infection. The second cause of death is cardiovascular, and the proportion of these deaths correlates strongly with age distribution and therefore differs from one series to another. Deaths due to cancer are also frequent, although the risk of cancer in MS is not consistent between studies, being sometimes higher than and sometimes similar to that of controls [15]. Suicide also needs to be specifically mentioned as a cause of death in MS. Earlier studies demonstrated an elevated suicide rate among MS patients, ranging from 1.6 to 7.5 times that of the general population [2,12,13,16,17]; however, more recent studies do not support this trend and have reported suicide rates similar to or even below the expected rate [11,18,19], suggesting that an excess risk of suicide may no longer be a reality for MS patients.

In the literature, factors associated with a better vital prognosis [1–3,5,7,8,11,13] include a relapsing–remitting phenotype, MS clinical onset before 25 or 30 years of age, initial symptoms such as optic neuritis and sensory problems, a low level of disability during the first years of the disease, and a long time lag between the first and second neurological episodes.

Also, in recent decades, MS patients in the developed countries have experienced an increased life expectancy and decreased mortality. At the same time, however, the incidence of MS has increased, at least in women. These two phenomena have led to an increased prevalence of MS and, therefore, an increased number of patients in need of care for this chronic disease.

3. Risk factors of MS

The cause of MS is multifactorial: both genetic and environmental risk factors contribute to disease risk. Several factors have been assessed and are reviewed below. However, the specific causes of MS are still largely unknown and, at present, there are no well-established factors to assist disease prevention [20,21].

3.1. *Environmental factors*

The following data are largely derived from an umbrella review recently published by Belbasis et al. [21]. Indeed, they have provided a rigorous and systematic assessment of published reviews and meta-analyses, representing decades of research on environmental risk factors for MS (609 articles found in their search, 20 articles considered eligible). Of the 44 factors included in their analysis, only three showed strong, consistent evidence of an association with MS with no suggestion of bias: immunoglobulin G (IgG) seropositivity to Epstein-Barr virus (EBV) nuclear antigen; infectious mononucleosis; and smoking (Table 1). The three associations were statistically significant ($P < 0.001$) and based on > 1000 cases; the between-study heterogeneity was not large and the 95% prediction interval excluded the null value.

Indeed, the strongest known risk factor for MS is infection with EBV [22], as this led to consistent results, whatever the place, period or study design. Compared with non-infected individuals, the risk of developing MS is approximately 15 times higher among those infected with EBV in childhood and about 30 times higher among those infected with EBV in adolescence or later in life. Although the mechanisms