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Epidemiology of neuroimmunological diseases

Abstract This review gives an overview of various neuroimmunological diseases in terms of incidence and prevalence rates, age and sex distribution, and the frequency of subtypes, if applicable. The disorders selected for review are inflammatory muscle disorders (polymyositis, dermatomyositis and inclusion body myositis), myasthenia gravis, immune-mediated polyneuropathies (Guillain-Barré syndrome, chronic polyneuritis and vasculitic neuropathies), and multiple sclerosis.

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Introduction

Epidemiological studies reveal valuable data in terms of numbers of patients who were newly diagnosed with (incidence) or affected by (prevalence) a given disease, its sex and age distribution and the frequency of subclasses, if applicable. They may also provide important clues to the etiology and may thus be helpful in better understanding these disorders, in particular in those diseases in which the pathogenesis has not been elucidated. This review focuses on the epidemiology of several neuroimmunological diseases such as inflammatory muscle disorders (polymyositis, dermatomyositis and inclusion body myositis), myasthenia gravis, immune-mediated polyneuropathies (Guillain-Barré syndrome, chronic polyneuritis and vasculitic neuropathies), and multiple sclerosis.

Inflammatory myopathies

The idiopathic inflammatory myopathies comprise three major subsets: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) [8]. The hallmark of these disorders is a progressive muscle weakness, with retained reflexes and without sensory disturbances. Muscle pain occurs in approximately 50 % of patients and is more common in DM than in PM or IBM. Weakness of the diaphragm resulting in respiratory dysfunction is probably an underestimated manifestation of inflammatory myopathies [50]. Both PM and DM are characterized by proximal muscle weakness. Whereas DM is easily recognized due to the skin rashes that are DM specific and occur early in the course of the disease (heliotropic erythema, Gottron's sign and Keinig's sign), the diagnosis of PM remains a challenge. Most of the patients erroneously diagnosed as PM were eventually found to suffer from IBM, dystrophic, toxic or metabolic myopathies [8]. Moreover, among 165 patients with inflammatory myopathies, nine had been diagnosed with PM, 65 with unspecified myositis, and 32 with possible myositis; after a follow-up period of 6.5 years, five out of the nine patients initially diagnosed as PM were given a final diagnosis of IBM [52] indicating that PM is uncommon and that the newly described diagnostic criteria need to be adopted. In IBM, weakness and wasting are most profound in knee extensors, hip flexors, and long finger flexors [38]. Swallowing difficulties are present in about 50 % of patients, and subacute respiratory failure requiring mechanical ventilation was recently reported in one patient with IBM [56].

The incidence of PM, DM and IBM is approximately 1:100,000 patients per year, with IBM being the most

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common form [9]. In PM and DM, females are more commonly affected than males [2:1], whereas IBM occurs more often in males than in females [3:1]. The onset of the disease is age 18 or older in PM, has two peaks (5–15 and 45–65 years) in DM, and is 50 years or older in IBM. The prevalence of IBM has been estimated to be 4.9 per million population in the Netherlands [3], and 9.3 per million in western Australia which indicates that the prevalence of IBM is substantially higher than previously thought (Table 1) [41]. This disorder has attracted much interest not only because it is the most common acquired muscle disease in adults, but also because it combines features of inflammation and vacuolar degeneration with accumulation of pathological proteins similar to those changes seen in Alzheimer's disease, although the etiology remains unclear [38].

Myasthenia gravis

Myasthenia gravis (MG) is an antibody-mediated autoimmune disease of the neuromuscular junction. The pathogenetic role of autoantibodies directed against nicotinic acetylcholine receptors (AChR) was first demonstrated by passive transfer experiments [51] and later, indirectly, by the therapeutic efficacy of plasma exchange and antibody depletion [43]. The clinical hallmarks of MG are skeletal muscular weakness and fatigability caused by a decrease in the number of available acetylcholine receptors at the neuromuscular junction. This was found to be due to at least three mechanisms: functional blockade of acetylcholine binding sites, accelerated endocytosis and degradation, and complement-mediated damage [10]. The thymus gland has been implicated as a possible site of origin of the autoimmune response since approximately 75 % of patients showed thymic abnormalities ranging from thymic hyperplasia to thymoma [20].

Approximately 15 % of patients with generalized MG have no detectable antibodies to the AChR ("seronegative" MG, SNMG) although they are clinically indistinguishable from AChR antibody-positive patients. In 70 % of SNMG patients with generalized symptoms, autoantibodies against muscle-specific receptor tyrosine kinase (MuSK), which is expressed during early muscle development and crucial for the normal formation of the neuromuscular junction, have now been demonstrated underlining the assumption that SNMG is also an antibody-mediated disease [40].

MG has initially been thought to be a disease of the young, and some 50 years ago, it had begun to be considered not only a disease of young women but also of older men [45]. Onset of symptoms peaked in the third decade in females, whereas the male distribution was bimodal, with peaks in the third and sixth decades [32]. In thymoma-associated MG, the peak onset was at the fourth to fifth decade suggesting that this form of MG may represent a separate subtype [45]. With increasing life expectancy, the incidence of MG has increased from 2–5 per million to 9–21 per million population, and current estimates place the prevalence at a high value of about 20 per 100,000 (Table 1) [42]. Several reports during the last year indicate that these changes were due to an increasing incidence in the elderly for both males and females with an incidence rate being as high as 55.9 and 65.8 per million inhabitants in patients older than 65 years [1].

Table 1 Incidence and prevalence of selected neuroimmunological diseases in Western countries. Values are given per 100.000 population. For details, see text

	Incidence	Prevalence
Inflammatory myopathies	1	
Inclusion body myositis	0.5–0.9	
Myasthenia gravis	0.25–2	10–20
Immune-mediated neuropathies		
Guillain-Barré syndrome	1–2	
CIDP	3–7.7	
Multifocal motor neuropathy	1–2	
Multiple sclerosis*	3	54–127

* In Germany

Inflammatory neuropathies

Guillain-Barré syndrome

The Guillain-Barré syndrome (GBS) is an inflammatory demyelinating disorder of the peripheral nervous system which is assumed to result from aberrant immune responses directed against components of peripheral nerve [18]. The clinical features consist of acute or, more often, subacute symmetrical paresis with areflexia and mild sensory deficits [2]. It is considered a postinfectious disease as 60–65 % of patients report antecedent infectious diseases, most often upper respiratory tract infections (20–47 %), influenza (13–25 %), and gastrointestinal (11–21 %) infections [15]. *Campylobacter jejuni* is an important trigger factor occurring in 13–72 % in case-control studies, the strongest association being found in the epidemic form of the disease occurring in China [17]. Patients with *C. jejuni* infection are more likely to have pure motor GBS, with lack of sensory disturbances, antibodies to ganglioside GM1, and electrophysiological evidence of axonal degeneration, with more severe disability, slow recovery and poor outcome [17].

In the recent years, it has been recognized that GBS is a heterogeneous disorder (Table 2). The most common form is acute inflammatory demyelinating polyradiculoneuropathy (AIDP, "classical" GBS), and accounts for

Table 2 Subtypes of GBS

Acute inflammatory demyelinating neuropathy	AIDP	85–90 %
Acute motor axonal neuropathy	AMAN	
Acute motor sensory neuropathy	AMSAN	3–8 %
Miller-Fisher syndrome	MFS	6–7 %
Acute pandysautonomia		
Polyneuritis cranialis		

85–90 % of GBS cases in Western countries [46]. The axonal variants (acute motor sensory axonal neuropathy, AMSAN, and acute motor axonal neuropathy, AMAN) are most common in other parts of the world such as in China [15], and in these patients, AMAN was closely related to the presence of antibodies against the ganglioside GD1 [25]. Miller-Fisher syndrome (MFS) is characterized by the triad ophtalmoplegia, ataxia and areflexia. Population-based studies in Italy have found that MFS accounts for 6–7 % of total cases of GBS, whereas these numbers were as high as 18–19 % in Taiwan suggesting that there may be geographic differences [15]. Serum IgG anti-GQ1b antibodies were detected in 80–100 % of patients in the acute phase of MFS [58]. Other variants such as acute pandysautonomia and polyneuritis cranialis are less common forms of the disease.

After the virtual eradication of poliomyelitis, GBS has become the leading cause of acute flaccid paralysis in Western countries accounting for 50 % of cases in Finnish hospitals [21]. Most population studies during the last 40 years have shown that GBS seems to be evenly distributed throughout the world, with an annual incidence of approximately 1–2 per 100.000 population (Table 1) [15]. Although the reported incidence rates range between 0.2 and 4.0 per 100,000 population, these variations might be due to methodological differences such as small sample size, incomplete retrospective reviews and an underestimation of mild cases not referred to the hospital. Males are more often affected than females (1.5:1), which is unusual for an autoimmune disease and might imply a protective effect of estrogens. There is a more or less linear increase in incidence with advancing age, with a slight peak in late adolescence and young adulthood (coinciding with an increased risk of infections with cytomegalovirus and *C. jejuni*), and a second peak in the elderly [5]. Apart from the rural areas in northern China, where there is a large increase in incidence in the summer months due to summer epidemics of AMAN, there is no consistent seasonal pattern of incidence [12]. In some studies, GBS cases have more frequently been reported in the autumn and early winter, whereas others did not find any seasonal variation or an increase in June and most winter months (reviewed in [15]). Although it has been reported that the risk of GBS increases over time, the annual incidence remained stable from 1978 to 1993 in a large study in Sweden [24], and even declined from 1987 to 1996 in a large study in the Netherlands [54] indicating that the frequency of GBS is probably fairly stable over time.

GBS occurs sporadically, but rare small epidemics have been reported which could be attributed to epidemic enteritis [2]. In 1976/77, there was a sharp increase in incidence in vaccinees undergoing A/New Jersey swine influenza vaccination [48]. Although vaccines from four manufacturers were all associated with an increased risk of GBS, there was substantial variation among lots suggesting that some agent or factor in 1976 vaccines might be associated with an increased risk for GBS in the United States, but what the factor might have been remains completely unknown [2]. This study has widely been debated, but several re-analyses have corroborated the original findings. Many other studies performed during the following periods, however, did not confirm an increased risk after influenza vaccination: for example, in the periods 1992/93 and 1993/94, the adjusted relative risk for the two seasons combined was 1.7, which suggests that slightly more than one additional case of GBS per one million persons vaccinated against influenza has occurred [29]. In the most recent analysis, the reporting rates of GBS after influenza vaccination declined even more from a high of 0.17 per 100,000 vaccines in 1993/94 to 0.04 in 2002/2003 indicating that the risk of GBS after influenza vaccination is as low as one additional case per 2.5 million persons vaccinated [16].

Other immune-mediated neuropathies

The chronic immune-mediated neuropathies can be divided into chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), paraproteinemic neuropathy, and multifocal motor neuropathy (MMN). In general, CIDP is considered to be the chronic variant of GBS although there are obvious clinical and immunological differences [53]. The classical clinical features consist of a progressive symmetrical sensory-motor neuropathy that evolves over more than 8 weeks, with demyelinating features on electrophysiological studies, and an increased cerebrospinal fluid protein. The prevalence has been estimated to be 3–5 per 100,000 population, but these figures may be underestimated since a recent epidemiological survey in Norway found a prevalence rate of 7.7 per 100,000 inhabitants (Table 1) [36]. As in GBS, CIDP is not a homogeneous disorder: several subgroups can be distinguished such as the sensory ataxic group, a (sub)-acute motor-sensory demyelinating neuropathy, a chronic motor-sensory demyelinating neuropathy, multifocal motor-sensory neuropathy and a symmetric motor demyelinating neuropathy [4]. For these subtypes, the terms MADSAM (multifocal acquired demyelinating sensory and motor neuropathy)

and DADS (distal acquired demyelinating symmetric neuropathy) have been proposed, and diagnosis of these subtypes is based on clinical and electrophysiological characteristics [47].

Two thirds of patients with DADS neuropathy have IgM monoclonal gammopathy, a disorder that is characterized by the abnormal proliferation of a single clone of lymphoplasma cells. In 10 % of patients with peripheral neuropathy of unknown etiology, a monoclonal gammopathy is present, and 10–15 % of patients with either IgM monoclonal gammopathy of undetermined significance (MGUS) or Waldenström macroglobulinemia suffer from peripheral neuropathy [37]. Although serum proteins from the IgA, IgG and IgM type can be detected, an association could only be established for the IgM paraproteinemias. The prevalence of MGUS clearly rises with increasing age being 0.1 % in the third decade and more than 3 % in the eighth decade. In two long-term studies, the overall rate of progression of IgM MGUS into malignant forms averaged 1.3–1.5 % per year [37]. Men older than 60 years are most often affected by IgM neuropathy, which is characterized by a slowly progressive (70 %), relapsing (20 %), or chronic-relapsing (10 %), distal, symmetrical polyneuropathy with predominant sensory involvement.

In 1986, MMN was distinguished from other motor neuropathies and is characterized by slowly progressive, predominantly distal, asymmetric limb weakness and wasting, predominantly in the arms, with minimal or no sensory involvement [30]. The hallmarks of this disease are focal motor conduction block in electrophysiological studies, and serum IgM antibodies against the ganglioside GM1 which could be found in 30–80 % of patients [39]. MMN is a rare condition affecting no more than 1–2 per 100,000 population (Table 1), with men being more often affected than women (2.6:1). The mean age of onset is around 40 years, approximately 80 % of patients report their first symptoms between 20 and 50 years of age [30]. Currently it is not clear which degree of sensory impairment is acceptable for a diagnosis of MMN in contrast to MADSAM (also known as Lewis-Sumner syndrome) [47]. However, the differentiation between these two disorders is of practical importance because MMN does not respond to steroids, whereas 33 % of patients with the CIDP variant MADSAM improved after treatment with steroids [55].

Vasculitic neuropathy

Systemic vasculitis involving small-to-medium sized arteries commonly affect epineural vessels resulting in neuropathy. The most popular classification systems are those published by the American College of Rheumatology Subcommittee on the Classification of Vasculitis (that provides diagnostic criteria for seven types of vasculitis) [22], and by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis (that distinguishes vasculitis by the size and histopathology of involved vessels) (Table 3) [23]. The frequency of peripheral neuropathy substantially varies among different series: The vasculitides most commonly associated with peripheral neuropathy are polyarteritis nodosa, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, cryoglobulinemia-associated vasculitis, rheumatoid arthritis, systemic lupus erythematosus, and Sjörgen's syndrome (Table 3) [49]. In some patients, vasculitis remain restricted to the peripheral nervous system. For this condition, Dyck and collegues have coined the term "non-systemic vasculitic neuropathy" [11], which occurred in approximately one-third of patients with vasculitis.

The clinical characteristics are similar to those of systemic vasculitic neuropathy, with a mean age at diagnosis of 59 ± 16 years, and a female preponderance of 1.4:1 [6]. Three pattern of clinical involvement may be present: [1] multiple mononeuropathy or multifocal neuropathy, [2] asymmetric polyneuropathy, and [3] distal symmetric polyneuropathy. The distribution of these manifestations vary substantially among different studies, with 25–85 % for asymmetric polyneuropathy, 10–45 % for multifocal neuropathy, and 2–25 % for distal symmetric polyneuropathy [6, 27, 49]. These discrepancies may best be explained by the heterogeneous definition of discrete versus overlapping multifocal neuropathy. The classical presentation is that of a patient with acute pain, weakness and numbness in the distribution of a single peripheral nerve, followed by similar attacks involving other nerves, but more often, patients may develop slowly progressive,

Table 3 Vasculitic neuropathy. Frequency of peripheral neuropathy in primary and secondary vasculitides (according to [49])

Large vessels	
Takayasu arteritis	rare
Giant cell arteritis	14 %
Medium-sized vessels	
Polyarteritis nodosa	50–75 %
Kawasaki syndrome	rare
Small to medium-sized vessels (ANCA associated)	
Wegener granulomatosis	11–40 %
Churg-Strauss syndrome	50–75 %
Microscopic polyangitis	10–20 %
Small vessels	
Henoch-Schoenlein purpura	not reported
Leucoytoclastic cutaneous angitis	not reported
Cryoglobulinemia associated vasculitis	7–60 %
Vasculitis assciated with connective tissue diseases	
Rheumatoid arthritis	1–22 %
Systemic lupus erythematosus	6–21 %
Sjörgen's syndrome	10–23 %
Sclerodermia	14 %

asymmetric or multifocal neurological deficits, sometimes punctuated by acute events.

Multiple sclerosis

Multiple sclerosis (MS) is a chronic recurrent inflammatory disorder of the central nervous system (CNS) with presumed autoimmune etiology. The symptoms of MS vary, depending on the site of the plaques within the CNS. The most common symptoms include optic neuritis, motor symptoms particularly in the lower extremities resulting in walking difficulties, bladder and sexual dysfunction, sensory symptoms and ataxia [26]. Three main types of clinical courses have been defined [31]: In 85–90 % of patients, episodes of neurological deterioration evolve over days to weeks, with a recovery over the next weeks and months which is often but not always complete (relapsing-remitting MS, RR-MS). The second clinical course, primary progressive MS (PP-MS), is characterized by a steady decline of neurological function without acute attacks and occurs in approximately 5–10 % of patients. Secondary-progressive MS (SP-MS) begins with a relapsing-remitting course, but at some point, relapse frequency is reduced, and a steady progression unrelated to acute attacks occurs. After 10–15 years, up to 50 % of patients enter this phase of the disease [57].

With a lifetime risk of 1 in 400, affecting approximately 120,000 people in Germany, between 250,000 and 350,000 in the United States, and more than 1 million worldwide, MS is potentially the most common cause of neurological disability in young adults [7]. Most patients present between age 20 and 40, but sometimes, first symptoms are experienced before age 10 or after age 60, even in the eighth decade [13]. Women are at least twice as often affected than men. Ethnical factors play an important role in the development of the disease: The frequency of MS is more than 10 times higher in Caucasians than in Africans or Asians, and some ethnic populations such as the Norwegian laps, the Australian aborigines and the New Zealand maoris seem to be particularly resistant, whereas others are more susceptible to the disease. The highest prevalence has been found in Northern Europe and those countries that have been settled from this area, such as North America, Australia and New Zealand [33, 44].

Of particular interest is the geographical distribution of MS that is uneven, but not random. Hundreds of epidemiological investigations support the notion that the prevalence increases with latitude. High-risk regions (more than 30 cases per 100,000 population) are Europe, North America, and South Australia, for example, medium-risk regions (5–29 per 100,000) are Southeast Europe, North Africa, India, and the Southeast of the United States, and low-risk regions (less than 5 per 100,000) are Mexico, Brazil, South Africa, China and Japan [13]. The incidence rates range from 0.86 in Romania to 10.1–12.2 in Southeast Scotland; in most regions, the incidence was 3–5 MS cases per year and 100,000 inhabitants [34]. There is no clear evidence that the incidence increases over time, although some follow-up investigations from the same area report considerably higher rates than previously reported [13]. However, in a recently published study from Olmsted County, Minnesota, age-adjusted incidence rates rose from 1915 to 1975 but remained unchanged thereafter suggesting that at least during the last 25 years the frequency of MS remained stable over time [34]. An interesting phenomenon that is only incompletely understood are cyclic variations of the incidence in the Faroes, Iceland and the region of Rostock, suggesting an epidemic outbreak of the disease that might be due to an infectious agent [28, 35]. Based on these epidemiological studies, the presence of an environmental factor has been proposed, but what this factor might be, and why it is unevenly distributed throughout the world has yet to be defined and remains a matter of speculation [28].

In Germany, prevalence rates were 54–127 per 100,000 population (Fig. 1). Thus, estimates on the total

Fig. 1 Prevalence of MS cases (per 100,000 population) in Germany [19]

number range from 67,000 to 138,000, but the exact number of patients affected by the disease is not known [19]. In 2001, a nationwide epidemiological MS register was initiated under the auspices of the German MS Society (DMSG). This project aimed at collecting epidemiological data on the number of patients with MS, course of the disease, and the social situation in Germany. During the 2-year pilot phase, five MS centers (Berlin, general hospital; Bochum, university hospital; Hamburg, practice center; Rostock and Würzburg, both university hospitals) participated leading to a representative selection of patients. In December 2003, standardized data sets of 3,458 MS patients were available for evaluation. The demographics of the data were similar to those obtained from other epidemiological studies: 72 % of the patients were female, mean age was 42.9 ± 11.2 years, mean disease duration 12.6 ± 8.7 years, and 64 % suffered from the relapsing-remitting form of the disease. Median EDSS was 3.0, and 69 % of patients had an EDSS ≤ 4.0. The high impact of the disease was underscored by the fact that nearly one-third (32.7 %) of the patients were prematurely retired due to MS. Although the pilot phase of the MS register does not fulfill the criteria of an epidemiological study, an estimate of the "incidence" revealed that in the Rostock area, 3.0 MS cases per 100,000 inhabitants were newly diagnosed; an estimate that correspond to findings revealed in carefully designed epidemiological investigations, which were formerly done within the same area [14, 35]. For the future, the German MS register plans to recruit more and more centers, with 10 additional centers participating since the mid of 2005, and to document more than 10,000 data sets until 2009 in order to gather reliable data and thus serve as an important tool to improve the overall situation of MS patients in Germany.

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