ORIGINAL ARTICLE

Multiple Sclerosis Registry in Germany

Results of the Extension Phase 2005/2006

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SUMMARY

Introduction: In 2001, a nationwide multiple sclerosis (MS) registry was initiated in Germany under the auspices of the German MS Society, (DMSG Bundesverband e.V.). The project aimed at collecting epidemiological data and information on health care provision for MS patients in Germany.

Methods: After a 2-year pilot phase, the original entry mask was modified, and new centers were recruited, resulting in the registration of a total of 5821 patients in 2005 and 2006. Following a 2 stage quality control process, standardized data sets for 5445 patients (93.5%) were able to be analyzed.

Results: Mean duration from onset of disease to diagnosis was 3.5 years. More than 70% of patients received immunomodulatory drugs, whereas symptomatic treatments were less commonly administered. The number of participating centers as of 31 December 2006 was 57 (29 neurological hospitals, 11 rehabilitation units, 13 specialized practitioners, and 4 regional MS centers).

Discussion: The MS registry provides valuable data on patterns of care for MS patients in Germany, and may help to improve service provision and overall quality of life for these patients.

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) and is the most common disease to cause chronic disability in young adults. It has been estimated that some 120 000 to 140 000 patients are affected by MS in Germany, although the exact number is unknown. The distribution of the disease according to its different subtypes or severity is also unclear (1).

Despite the high economic burden of MS on society, with total annual costs of 40 000 euros per patient (2), there are still limited data on patterns of care for patients with this disease. A comprehensive multiple sclerosis registry is therefore highly desirable, both from a health economic perspective and to ensure the targeted use of limited resources. To date, there has been no systematic attempt to collect the necessary data in Germany. To address this deficit, a nationwide registry was initiated in 2001 under the auspices of the German MS Society (Deutsche Multiple Sklerose Gesellschaft Bundesverband e.V.) with the aim of providing cross-sectional data on the frequency of MS and its subtypes in Germany. Another objective was to obtain information on the distribution of disease severity, the effect of MS on patients' ability to work, and the use of immunomodulatory, symptomatic, and non-pharmacological treatments. Following the 2-year pilot phase, in which 3223 patients took part (3), we present here the results of the extension phase of the study.

Methods

During the pilot phase, all MS patients were included who were treated at participating centers between 7 January 2002 and 31 December 2003, and who provided written, informed consent that their data be evaluated centrally. Data were collected, stored, and evaluated according to the latest state legislation governing data protection. All five centers that participated in the pilot phase were specialized in the management of MS patients and were representative of different regions and hospital types throughout Germany (3).

Based on experience gained during the pilot phase, the input mask (3) was modified. Parameters were deleted if they were regarded as unnecessary, amended if incomplete, and reworded if they were unclear and could be easily misunderstood. This streamlined the

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Documentation
centers as of
15 March 2007.
Red = neurological
hospitals;
light blue
= rehabilitation
units;
dark blue
= specialized
practitioners;
green = regional
MS centers.

FIGURE 1

data sets, ensuring that they would be sufficiently precise and clear. The full questionnaire is available from the authors upon request. Documentation was performed on-site in the study centers by participating physicians.

Data sets were coded using pseudonyms and sent every three months on a digital storage medium to the non-profit organization MS Research and Project Development (MS-Forschungs- und Projektentwicklungs-gGmbH) in Hannover, Germany for quality control and evaluation. There, data sets were checked for completeness (age, gender, degree of disability, and reliability of diagnosis) and consistency, and those with missing data or inconsistencies were returned for completion or correction. Using a unique key, we were able to identify redundant data sets, which had been entered either multiple times at one center (longitudinal analysis) or consecutively at more than one center (e.g. acute inpatient treatment and subsequent rehabilitation therapy). For the cross-sectional analysis, only the most recent data set was used.

Results

In the 2-year pilot phase, 3458 standardized data sets were collected. Of these, 3223 (93.2%) passed quality control and were eligible for further analysis (3). Since 15 March 2005, the number of new centers participating in the registry has grown continuously, totaling 57 by the 31 December 2006 report date (figure 1). So far, a total of 5821 data sets have been collected from 35

centers (figure 2). Of these data sets, 5445 (93.5%) passed quality control and were eligible for further analysis. Data from the remaining centers were not delivered until after the report date and were thus not included in the evaluation. Because some of the data sets were not complete for all parameters, different bases for comparison were used for the individual evaluations.

Demographic data and clinical characteristics

At the time of data collection, patients' mean age ($\pm$ standard deviation) was 44.2 ± 11.5 years, and disease duration was 12.7 ± 9.2 years. Age at onset of disease was 31.4 ± 10.2 years (7 to 75 years). Onset occurred between the ages of 20 and 40 (70%) in the large majority of patients, but in 9 patients it occurred before age 10 (0.2%) and in 44 patients after age 60 (0.9%). A total of 4.9% patients manifested the disease after the age of 50.

At the time of diagnosis, patients were 34.8 ± 10.7 years old, which means that the mean duration between onset of disease and diagnosis was 3.4 ± 5.5 years. This duration remained virtually unchanged in patients newly diagnosed after 1999 (3.6 years). Women were 2.5 times more likely than men to contract MS (72% vs. 28%). In total, 55% of patients had relapsing-remitting MS, 32% secondary progressive MS, and 9% primary progressive MS (i.e. from the outset). In total, 1% of patients presented with their first MS event. In 16.9% of patients, the clinical condition was stable within the last year, whereas 17.1% of patients experienced more than one relapse or rapid progression. The majority of patients (56.0%) exhibited slow progression or less than one relapse per year.

Degree of disability

The Kurtzke Expanded Disability Status Scale (EDSS) is the international standard for quantifying a patient's degree of disability (4). The distribution of EDSS scores in our population can be seen in figure 3. The median EDSS score was 3.5. In total, 51% of patients were fully ambulatory (EDSS <4), 28% of patients required assistance (cane, crutch, brace) to walk 100 m (EDSS ≥ 6), and 6% were confined permanently to a wheelchair (EDSS ≥ 8). The likelihood of reaching an EDSS score of 4.0 or 6.0 in relation to age is shown in figure 4. As can be seen in the figure, 60% of patients aged 50 years, and 40% of patients aged 60 years, did not require assistance to walk 100 m.

Occupational status

Only 1183 patients were still working full-time (27.9%), 1671 patients (39.4%) were in early retirement, 6.0% were unemployed, and just 0.7% were taking part in occupational retraining programs due to MS symptoms. The percentage of patients in early retirement was strongly associated with age (table 1). The relationship between early retirement status and degree of physical disability can be seen in figure 5. Here it is interesting to note that a substantial number of patients in early retirement (14.8%) had an EDSS score ≤ 3.5 and were thus still fully ambulatory.

Immunomodulatory and symptomatic treatment

In total, 71% of patients received immunomodulatory treatment, primarily with interferons (*table 2*). Treatment escalation with mitoxantrone was also a comparatively frequent strategy. Other treatment options, including intravenous immunoglobulins, were used only infrequently. Altogether 670 patients (20%) did not receive immunoprophylactic treatment, especially those with secondary progressive MS and slow disease progression. However, 98 (14.9%) of the patients who did not receive immunoprophylactic treatment experienced rapid disease progression or frequent relapses. *Table 3* summarizes the different treatment options for the common MS symptoms. In particular, fatigue and cognitive disorders, although quite common, were left untreated in the large majority of patients. In contrast, pain and depression were managed comparatively frequently with pharmacological treatment. Finally, a considerable percentage of patients with spasticity or bladder disorders received neither pharmacological nor non-pharmacological treatment.

Discussion

After the successful completion of the 2-year pilot phase, data collection efforts were expanded as part of the extension phase of the project. In just under 2 years, a total of 5445 data sets were registered.

Course of MS and prognosis

MS is characterized by unpredictable relapses of symptoms (relapsing-remitting MS), with which 90% to 95% of cases begin. In 5% to 10% of cases, patients experience a progressive worsening of disease (primary progressive MS), especially with respect to ambulation. After approximately 10 to 15 years, 30% to 40% of patients with initial relapsing-remitting MS enter the chronic phase (secondary progressive MS) (5). The results of the present survey show a higher percentage of patients with progressive disease compared to the pilot phase (3), as well as a shift towards a greater degree of disability. These findings are likely due to the increased recruitment of rehabilitation centers, as well as of neurologists in practices. The results presented here correspond to those reported in population-based epidemiological studies (6–11) and indicate that the data are becoming increasingly representative as the registry expands.

Whereas earlier studies investigating the natural course of MS found that 50% of patients required a cane, crutch, or brace to walk 100 m (EDSS 6.0) after a disease duration of approximately 15 years (5, 9), more recent studies suggest a considerably more favorable prognosis, with a median duration of 20 or 29 years until an EDSS of 6.0 is reached (8, 11–13). Because the exact time of disease onset is often difficult to establish, it is often more helpful when counseling individual patients to approach the matter by considering the relationship between degree of disability and age.

In our study, 60% of patients aged 50 years and 40% of patients aged 60 years could still walk 100 m

FIGURE 2

Growth of the MS registry. Increase in the number of documentation centers (above) and data sets (below) over time. The total number of centers increased from 5 in the pilot phase (2002 to 2003), to 15 in 2005, 57 in 2006, and 74 as of 15 March 2007. By the end of 2006, a total of 5445 cumulative data sets had passed both stages of quality control. Data sets from the pilot phase were not eligible for inclusion, because the structure of the data sets was modified prior to the extension phase.

without assistance. These results are comparable to those reported in British Columbia, Canada (11).

Most of the patients in our MS registry had already received immunomodulatory treatment for many years, which means that these favorable figures do not reflect the natural course of MS, but rather the course of disease under current care with disease-modulating drugs and improved symptomatic treatment.

Duration from onset of disease to diagnosis

Despite improved testing methods and new diagnostic criteria that generally allow a diagnosis to be made within a month after disease onset (14), the mean duration from onset of disease to diagnosis was comparatively long in the pilot and extension phases of our study, amounting to 3.4 and 3.5 years, respectively. This also applies to patients diagnosed after 1999.

Disease frequency in relation to degree of disability as measured by the Expanded Disability Status Scale, or EDSS (4) (n = 5343).

It remains to be seen whether increased awareness about the course of disease and possibilities for early treatment, as well as the more widespread implementation of newer diagnostic criteria, will lead to earlier diagnosis, thus reducing prolonged diagnostic uncertainty. Indeed, just such a trend for other countries has been observed in data from the NARCOMS Registry, established by the Consortium of Multiple Sclerosis Centers in North America (15). Here it is, above all, the responsibility of general practitioners, ophthalmologists, orthopedists, and urologists to ensure that neurological testing is performed in young patients who present with a loss of neurological function that cannot be

attributed clearly to peripheral causes. Doing so can help ensure that the appropriate treatment is initiated early in cases of subclinical disease (16, 17).

Ability to work

After a disease duration of just under 13 years, almost 40% of patients (mean age: 44 years) in the registry were receiving pension benefits due to work-related disability. Only 28% of patients were still working full-time. Similar figures have been reported in other studies (2, 7, 18). As was to be expected in light of the higher percentage of MS patients with more severe disease in the extension phase, the results here are less favorable than those seen in the pilot phase (3).

Compared to unemployment rates of 10% to 12% in the general population, the percentage of unemployed MS patients in the extension phase was relatively low. This may reflect the fact that MS patients with more severe disease and disability are more likely to be eligible for early retirement and are thus not counted in unemployment statistics. Moreover, although the percentage of patients in early retirement increased with degree of physical disability (6, 19, 20), a full 15% of the patients in early retirement were still fully ambulatory.

This means that factors other than physical disability must be playing a role in patients' early retirement. Here it should be noted that the EDSS does not provide an adequate picture of cognitive impairments or fatigue, and it is precisely these two factors that are likely to contribute to impaired working capacity (19). It is, therefore, crucial that the symptoms responsible for changes in work status be identified and treatment strategies developed to help patients maintain their ability to work and quality of life (20).

Ambulatory ability in relation to age

Red = percentage of MS patients who had not reached EDSS 6.0 (i.e. still able to walk 100 meters without a cane, crutch, or brace); blue = percentage of MS patients who had not reached EDSS 4.0 (i.e. still able to walk more than 500 meters without a cane, crutch, or brace). The numbers above the x-axis indicate the number of patients in each decade of life (n = 5343).

Immunoprophylactic and symptomatic treatment

More than 70% of patients in our registry received disease-modifying treatment, which corresponds to the percentages seen in the pilot phase and in the NARCOMS Registry (21). Almost 50% of patients were given first-line immunomodulatory treatment with interferon beta and glatiramer acetate according to the treatment ladder developed by the German Multiple Sclerosis Treatment Consensus Group (Multiple Sklerose Therapie Konsensusgruppe; MSTKG) (17, 22, 23). In the extension phase, the percentage of patients on mitoxantrone or steroid pulse therapy was higher than in the pilot phase of the study. This is due to the larger number of patients in the extension phase who had progressive MS and for whom these types of treatment are the only available options. Natalizumab was not approved until mid-2006, and there are currently few documented cases of treatment with this agent. Other immunomodulatory treatments, including intravenous immunoglobulins, were used only rarely.

The type and frequency of treatments thus indicate that the evidence-based recommendations developed by the MSTKG, which have been adopted by the Germany Neurological Society in its own treatment guidelines

TABLE 1

Occupational status according to age of patients

	Total	< 25	25–34	35–44	45–54	55–64
Employed full-time	27.9 %	25.9 %	48.3 %	33.2 %	24.1 %	14.2 %
Employed part-time	8.9 %	2.5 %	9.7 %	11.1 %	10.5 %	5.0 %
Unemployed	6.0 %	15.2 %	8.4 %	7.6 %	4.8 %	2.1 %
Partial disability benefits or full disability benefits/early retirement	39.4 %	2.5 %	12.0 %	36.4 %	50.6 %	61.3 %
Others	14.7 %	48.0 %	19.1 %	11.7 %	10.0 %	17.4 %
Unknown	3.1 %	1.9 %	2.5 %	3.7 %	3.5 %	2.4 %
n	4 242	158	609	1 392	1 222	618

The percentages in the "Total" column refer to the 4242 patients for whom data on occupational status were available. The other columns give the percentage distribution of patients with a particular occupational status according to age group.

The column ">65 years" (243 patients) is not shown.

The "Other" category includes the categories "Housewife/househusband," "MS-related vocational retraining," and "training/school/college."

(16), are indeed being implemented in everyday clinical practice. Nevertheless, there are still many patients who do not receive immunoprophylactic treatment despite the presence of active disease (i.e. rapid progression and/or more than one relapse per year). Even more striking is the suboptimal use of symptomatic treatment in most patients, especially in those with cognitive impairments, fatigue, or ataxia. These findings clearly indicate that the care provided to MS patients in Germany is inadequate, both generally and with respect to symptom management (17, 22–25).

There are many possible reasons for these observations. For example, it may be that some patients who presented at the centers were seeking advice on appropriate treatments and underwent a change of regimens only after documentation had already taken place. Follow-up studies could shed more light on this issue.

Another possible explanation is that MS patients in Germany are more likely than patients in other European countries to decline or prematurely interrupt treatment, even in cases where treatment is clearly indicated. To address this possibility, physicians must ensure that all patients are provided with comprehensive counseling on the benefits and risks of therapy, and that realistic treatment goals are set (17).

Finally, with regard to MS symptoms such as cognitive impairments or fatigue, either there are no clearly effective treatments or the existing healthcare infrastructure is unable to provide services such as outpatient neuropsychological therapy. There is an urgent need not only for further clinical research on this point, but also for structural changes which will ensure that all MS patients receive proper care.

Limitations of the study

The survey included all patients who visited a participating center during the data collection period, and not only new cases of MS. This is a suitable approach when studying chronic diseases like multiple sclerosis,

which are characterized by high prevalence and relatively low incidence (1), precisely because of the diagnostic uncertainty and great psychological burden on patients at the onset of disease.

The survey was not population-based, relying instead on data provided by study centers, which may have led to selection bias. Though desirable, a comprehensive population-based study would require the participation of all individuals and organizations involved in providing care to MS patients, something that is only possible if participation is mandated by

FIGURE 5

Inability to work in relation to degree of physical disability. Percentage of MS patients in retirement according to Expanded Disability Status Scale (EDSS) score. Grey bars = old-age benefits; green bars = early retirement due to inability to work; red bars = early retirement due to impaired ability to work.

TABLE 2

Use of immunomodulatory treatments

Classification	Substance	n	Percentage
First-line treatment	rec. IFN-beta	1291	37.6 %
	Glatiramer acetate	305	8.9 %
Second-line treatment	Azathioprine	170	5.0 %
	IVIg	89	2.6 %
Treatment escalation	Natalizumab	10	0.3 %
	Mitoxantrone	358	10.4 %
	Cyclophosphamide	20	0.6 %
Other	Methotrexate	17	0.5 %
	Plasmapheresis	15	0.4 %
	Steroids (intravenous pulse)	293	8.5 %
	Steroids (long-term)	73	2.1 %
	Steroids (intrathecal)	66	1.9 %
Total immune treatment		2435	71.0 %
No immune treatment		670	19.5 %
		3431	

Classification according to the treatment ladder developed by the German Multiple Sclerosis Treatment Consensus Group (Multiple Sklerose Therapie Konsensusgruppe; MSTKG) (25)
 rec. IFN-beta = recombinant interferon-beta; IVIg = intravenous immunoglobulins;
 steroids (intravenous pulse) = regular intravenous steroid pulse therapy.
 The percentages refer to 3431 patients for whom data on immune therapy were available.
 The sum of the percentages given for the individual treatments (78.8%) is higher than the percentage indicated for "total immune treatment" (71%) because a (small) number of patients received combination therapy.
 A low percentage of patients (326 patients, or 9.5%) could not be classified.

law, as is the case in Denmark, for example. Nevertheless, the fact that the demographic data in the present study are comparable to those reported in population-based epidemiological studies indicate that our results are representative of the overall population of MS patients in Germany.

Finally, it must be noted that the MS registry was cross-sectional in design and can only describe patterns of care from this perspective; data on the course of disease before treatment are not available. As result, it is impossible to compare the effectiveness of the different treatment options. This will be possible only after data from the follow-up studies, currently under planning, have become available.

Despite these limitations, the MS registry provides valuable information on patterns of care for MS patients in Germany. This will help in the development of targeted approaches to addressing inadequate and inappropriate care and thus improve patients' quality of life. In addition, the German MS registry will serve as the basis for a Europe-wide MS register to be developed under the auspices of the European Multiple Sclerosis Platform (EMSP) and being supported by the European Union.

The project was conducted under the auspices of MS-Forschungs- und Projektentwicklungs-gGmbH together with DMSG Bundesverband e.V. The MS registry was financed by the German Multiple Sclerosis Foundation (Deutschen-Multiple-Sklerose-Stiftung), the official foundation of the DMSG. The German Multiple Sclerosis Foundation receives donations from private individuals, organizations, and the pharmaceutical industry. The substance of the projects is not influenced by these donations.

For further information about participating in the registry please contact:
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A list of the currently participating centers is available on the DMSG website (www.dmsg.de).

Conflict of interest statement

Prof. Haas reports receiving lecture and consulting fees, as well as research support, from Teva, Sanofi-Aventis, Bayer-Schering, Novartis, Biogen, Merck-Serono, Allergan, Octapharma, and Talekris.
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 Dr. Wolfgang Elias reports receiving financial support from Biogen, Bayer-Schering, Sanofi-Aventis, and Merck-Serono.
 Mr. Freidel has received lecture and consulting fees, research support, and travel expense reimbursement from Bayer-Schering, Merck-Serono, Biogen, and Teva, among others.
 Prof. Rieckmann reports receiving lecture fees from Bayer-Schering, Biogen, Novartis, Teva, Berlex, Merck-Serono, Sanofi-Aventis, and Almiral.

TABLE 3

Use of symptomatic treatments

Symptom	n	Frequency	Untreated	Pharmacological treatment	Non-pharmacological treatment	Combination*
Spasticity	2 419	1 599 (66 %)	31 %	38 %	18 %	13 %
Fatigue	2 230	1 431 (64 %)	79 %	14 %	7 %	0 %
Bladder disorders	2 296	1 423 (62 %)	45 %	36 %	14 %	5 %
Ataxia	2 142	988 (46 %)	62 %	8 %	29 %	1 %
Pain	2 199	858 (39 %)	44 %	47 %	7 %	2 %
Cognitive disorders	2 241	814 (36 %)	83 %	8 %	8 %	1 %
Depression	2 271	814 (36 %)	37 %	56 %	5 %	2 %
Rectal disorders	2 024	490 (24 %)	56 %	28 %	13 %	4 %

The "n" column shows the number of patients for whom data were available for each of the symptoms listed in the "Symptom" column.
 The "Frequency" column gives the absolute number and the percentage of patients with each symptom.
 The other columns show the percentage of patients with each symptom who received a particular form of symptomatic treatment or were untreated.
 *Combination of pharmacological and non-pharmacological treatment.

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Mrs. Pitschnau-Michel, M. A., Mrs. Stuke, Ph.D., Dipl.-Biol., and Dr. Schimrigk declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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