New data in the epidemiology of multiple sclerosis in Hungary

Ph.D. Thesis

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I. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system characterized by inflammation, demyelination and axonal degeneration (Trapp et al., 1998). At young age, in the caucasian race, it is the third of the most frequent neurological diseases in the temperate zone (Compston & Coles, 2008).

The name of multiple sclerosis comes from the plaques, which are visible at several different places of the nervous system (multiple). The touch of the plaques is stiffer than that of the normal brain tissue (sclerosis).

I.1. History of MS

The first case in the history of MS was described in Augustus d'Esté's diary (1794-1848) (Landtblom et al., 2010). He was the grandson of King George III of England. Augustus d'Esté's first symptoms appeared after an infection of rubeola in 1822. He reported transient failure of vision, which was most likely a bilateral optic neuritis. Later he felt weakness and numbness in his legs for several weeks. Few years later, he got paraparesis, sphincter incontinence, urinary problems and impotence. Just by looking at his diary, it is obvious that Augustus d'Esté's handwriting was barely readable in 1848 due to his intention tremor. Few weeks later, his hand got palsy, and he died.

The first medical description of MS is associated with Jean-Martin Charcot's name (1825-1893) (Clanet, 2008). Charcot was a French neurologist and a professor of anatomical pathology. By the integration of previous reports and his own clinical and pathological observations, he dubbed the disease *sclérose en plaques* in 1868. Charcot observed cognition symptoms, too. He described his patients as having a "marked enfeeblement of the memory" and "conceptions that formed slowly".

I.2. Epidemiology of MS

Since MS is a rare disease in the whole population, the common mortality and morbidity data are not useable for the examination of its epidemiology and for the determination of its geographical distribution. There are two factors which describe the frequency of the disease: prevalence and incidence. Prevalence is the number of cases with a disease per 100,000 people in a certain place and time. Incidence is the number of new cases with a disease within a year.

In the world, approximately 2.5 million people have MS. The disease has a north-south gradient (Simpson et al., 2011). Close to the equator, MS occurs at extremely low level. Earlier studies showed that in case of certain ethnic groups, the prevalence of MS is markedly low, despite they are living in countries, in which MS is common. These ethnic groups include the Sami or the Lapps of northern Scandinavia, the Inuits in Canada, and the Maoris of New Zealand. The higher prevalence of MS in Northern Europe, North America, Australia and New Zealand (Alla & Mason, 2014) suggests that MS may have been carried around the world by the European colonists. The origin of the disease is suggested to be in the Viking populations.

As regards the prevalence of MS, Hungary is a medium-risk country. The first epidemiological study in Hungary on MS was conducted in 1961 by Lehoczky & Halasy-Lehoczky. According to this study, the crude prevalence of MS was 20/100,000. Pálffy et al. reported that the prevalence of MS in Baranya County was 37/100,000 (Pálffy, 1983). In Csongrád County, the crude prevalence of MS was found to be 62/100,000, reported by Bencsik et al. in 2001 (Bencsik et al., 2001).

I.3. Pathomechanism of MS

The etiology of MS is unknown. The damage of the central nervous system (CNS) is caused by an inflammatory process, which leads to the impairment of the myelin coating of the axons and thus axon degenerations. This demyelination process is influenced by genetic,

environmental, infectious and other agents.

The role of genetic factors in MS susceptibility was confirmed by several cross-sectional studies of patients with MS and their families, as well as by twin studies (Sadovnick & Baird, 1988; Ebers et al., 1986). Studies of adoptive relatives, half-siblings and offsprings of conjugal pairs also supported these data (Ebers et al., 1995; Sadovnick et al., 1996; Robertson et al., 1997). In 1975, a relationship between MS and the major histocompatibility complex (MHC) was confirmed (Jersild et al., 1975). Furthermore, through a genomwide linkage study, it was confirmed that the HLA DRB1*15:01 allele is linked to MS susceptibility (GAMES Study, 2003). In subsequent years, several MHC- and other loci were confirmed as susceptibility factors for MS (ANZgene Consortium, 2009; De Jager et al., 2009, Hafler et al., 2007; Sawcer et al., 2011). Ebers et al. in 1995 showed that the family risk is 300 times higher in monozygotic twins, and 20-40 times higher in biological first-degree relatives than in the normal population. They estimated the familial prevalence of MS between 5 and 10% (Ebers et al., 1995). Lately, numerous studies on the recurrence risk of MS managed to define several associated loci, which can explain the heritability of MS, or to estimate the potential influence of environmental factors. According to the data of the International Multiple Sclerosis Genetics Consortium (IMSGC), over 100 associated genes were confirmed (IMSGC et al., 2013).

In Hungary, the APOE gene and the tumor necrosis factor alpha gene-376 polymorphisms were examined in patients with the primary progressive form of MS by Losonczi et al. (Losonczi et al., 2009; Losonczi et al., 2010). Their data confirmed that certain alleles of APOE gene ($\epsilon 2$ and $\epsilon 4$) play a role in the development of MS, and the G allele of the TNF-alpha gene-376 polymorphism may be one of the factors responsible for the progression in primary progressive MS.

The principal environmental factors are the viral infections, such as Epstein-Barr virus (Handel et al., 2010), polio virus, HSV and rubeola. Besides these, smoking (Hawkes, 2007), stress and the relative deficiency of vitamin D (Islam et al., 2007; Munger et al., 2004) are the susceptibility factors of MS.

The damage of the myelin, the oligodendrocytes and the axons are caused by immune-

mediated processes involving both the innate and the adaptive immune system. (Koch et al., 2013). The innate immune system plays a role both in the initiation and progression of MS, and also modulates the adaptive immune system. Due to antigene presentation, CD4+ lymphocytes and CD8+ lymphocytes are activated in the peripheral lymph tissues (Viglietta et al., 2004). In people with MS, the pro-inflammatory lymphocytes, such as the Th1 and Th17 lymphocytes get activated and start to proliferate. (Lubetzki & Stankoff, 2014; Durelli et al., 2009). These cells secrete pro-inflammatory cytokines and matrix metalloproteinases, which disrupt the blood brain barrier (Obermeier et al., 2013). Through the blood brain barrier damage, T and B cells, monocytes and macrophages migrate into the central nervous system. A damaging inflammatory cascade starts up in the central nervous system involving the T and B cells, monocytes, macrophages and microglial cells (Babbe et al., 2000).

Futher studies demonstrated that free radicals and reactive oxygen species may cause mitochondrial damage, and the iron deposition may contribute to demyelination and oligodendrocytes damage. Nitrous oxide may also have an important role in these process (Haider et al., 2011; Witte et al., 2014; Trapp & Stys, 2009).

I.4. Natural history of MS

MS occurs in four clinical forms (Lublin & Reingold, 1996; Lublin et al., 2014). These are the relapsing-remitting (RRMS), the secondary progressive (SPMS), the primary progressive (PPMS) and the progressive-relapsing (PRMS) clinical courses. The relapsing-remitting form is the most common disease course. In this case, patients have relapses or exacerbations, during which their neurological functions worsen. After each relapse, a partial or complete recovery period takes place, which is called remission.

SPMS occurs in people who earlier had a relapsing-remitting clinical form of MS. At the first relapses, the disability level does not increase, but with time, the damage and the loss of the axons become dominant. From this time on, the disease turns into its progressive phase, either with or without relapses.

Patients with the primary progressive clinical form are characterized by a continuous

worsening of neurological function without relapses (Lassmann et al., 2012). This disease course differs from RRMS in several factors: the female-male ratio in PPMS is approximately equal and the disease begins around ten years later than in the case of RRMS. The lesions of the central nervous system are also different from those in the clinical form with relapses. Furthermore, in case of the primary progressive clinical form, there are more lesions in the spinal cord than in the brain, and the lesions contain fewer inflammatory cells than in patients with RRMS.

The relapsing-progressive clinical form of MS is very rare. It is characterized by worsening of the neurological function and relapses from the beginning of the disease.

A relatively new term, the „clinically isolated syndrome” (CIS) (Miller et al., 2012), describes the first episode of the neurologic symptoms that goes on at least for 24 hours and is caused by inflammation and demyelination in one place or several places in the central nervous system. In CIS, it is obligatory to follow up the patients by MRI. If CIS is combined with MRI detected lesions, which are similar to MS lesions, patients belong to the high risk for MS group. By these patients, it is suggested to begin the treatment with a disease-modifying medication to delay the second relapse, which is the onset of MS (Comi et al., 2009; Kappos et al., 2006; Comi et al., 2001; Jacobs et al., 2000).

Benign MS is an obsolete term for patients having only mild disability for more than 15 years in their case history. The term is no longer used as it was shown that 45% of the patients with „benign MS” have cognitive impairment, 49% of them have fatigue and 54% of them have depression (Amato et. al., 2006).

I.5. Symptoms of MS

If there is evidence for at least two areas of CNS damage that occurred at different times, the diagnosis of MS can be adjudged. The symptoms and signs of MS are very diversified, they may also mimic other diseases. Furthermore, the symptoms of two individuals may be very different from each other.

The most common symptoms are numbness or tingling of the face, the body or the

extremities, weakness and vision problems. The latter is often the first symptom of MS, which evaluates promptly and manifests as blurred or doubled vision, possibly poor contrast or color vision, and often pain during eye movement. The other frequent symptoms of MS are dizziness, spasticity, bladder dysfunction or constipation caused by bowel problems. Walking difficulty is also a characteristic symptom of people with MS caused by weakness, spasticity, loss of balance or sensory deficit. Symptoms of cerebellar damage, such as ataxia or intention tremor, are also typical for MS.

The above mentioned symptoms can be examined in the course of the routine neurological examinations, which we performed every three months in case of our patients at the Department of Neurology in Szeged. With physical examination, the patients' rate of disability can be determined by the neurologist.

The generally used score to define the level of disability of patients with MS is the Expanded Disability Status Scale (EDSS) score, which was developed by John F. Kurtzke (Kurtzke, 1983). This is a scale from zero to ten points. The steps from 1.0 to 4.5 belong to those patients who are fully ambulatory. From 5.0 points disability impairs daily activity, therefore the patients need aid for walking. The highest score, EDSS 10.0 indicates death caused by MS.

However, several aspects of MS are not detectable by EDSS. These aspects are fatigue, depression, pain, sexual dysfunction and cognitive dysfunction.

I.6. Fatigue

Fatigue, which can be described as a lack of energy, sense of exhaustion or an abnormal feeling of trouble, fundamentally influences the patients' daily activity. Fatigue is found as an early symptom in 20% of the patients, while in chronic cases, its frequency can be as high as 80% (Lerdal et al., 2003). Fatigue limits the personal interactions of patients, impairs their quality of life, and also hinders the patients in their jobs. This symptom is the most crippling symptom of MS according to the majority of the patients. In certain cases, fatigue is the only manifestation of an acute MS relapse (Flachenecker & Meissner, 2008).

Three forms of fatigue were described: physical, cognitive and social fatigue (Bakshi, 2003; Vucic et al., 2010).

In case of physical fatigue, the patients need to rest to continue their activity, because due to the function of the muscles, the patients' extremities transitionally paralyse, and a rest is necessary for their proper function. It was proven that a conduction block stands in the background of this phenomenon (Braley & Chervin, 2010). Under demyelination, the Na channels free up in the axons, and therefore, the conduction of the impulse gets slower. By muscle activity, the demyelinated motor nerves warm up, which increases the rate of impairment, and induces conduction block. By the rest, the temperature decreases, so the muscles can move again.

The diagnosis of social and cognitive fatigue is not as obvious as physical fatigue. Patients with cognitive fatigue are not able to concentrate for longer times, and have difficulties with counting or reading. Patients with social fatigue may get isolated from people, since they cannot participate in a long conversation.

To determine whether or not a patient has fatigue, questionnaires are used widely. Although questionnaires are somewhat subjective, they yield useful information about the patients' everyday life. The most frequently used questionnaires are the Fatigue Severity Scale (FSS) (Krupp et al., 1989), the Fatigue Impact Scale (FIS) (Fisk et al., 1994), and the Modified Fatigue Impact Scale (MFIS) (Achiron et al., 2015). While the FSS is one-dimensional, measuring only physical fatigue, the FIS and MFIS assess all three aspects of fatigue. The completed FIS questionnaire contains 40 statements, the MFIS is a 21-item scale, each with a score ranging from 0 to 4 points, giving information on the last 4 weeks of the patients. The Hungarian version of the FIS was validated in 2011 (Losonczy et al., 2011).

Based on its pathomechanism, primary or secondary fatigue are distinguished. Recent studies confirmed that primary fatigue is a result of the malfunctioning immune system and of the damage of central nervous system in MS. Proinflammatory cytokines, such as interferon-gamma and TNF-alfa were proven to play a role in fatigue (Sharief & Hentges, 1991; Hirsch et al., 1985). A study showed that the level of TNF-alfa and interferon-gamma is significantly higher in fatigued patients with MS compared to patients without fatigue (Heesen et al., 2006;

Flachenecker et al., 2004).

The other possible cause of fatigue may be the endocrine dysfunction. Several studies examined the ACTH level in fatigued patients with MS (Gottschalk et al., 2005). The gained results were not definitive, but it was shown that the corticosteroid therapy increases the patients' level of energy in the MS relapse.

The third group of primary fatigue causes include axonal loss and altered cerebral activation. A decreased glucose metabolism in the frontal cortex and basal ganglia of fatigued patients was confirmed with positron emission tomography (PET) (Roelcke et al., 1997). The reduction of N-acetylaspartate/creatine (NAA/Cr) ratios in several brain areas detected by magnetic resonance spectroscopy (MRS) in patients with fatigue suggests axonal loss in the brain, which may lead to fatigue (Tartaglia et al., 2004; Tellez et al., 2008).

Frequent causes of secondary fatigue include sleep disorders, depression and several medicaments used to treat MS. The most common sleep disorders among patients with MS are: restless legs syndrome, periodic limb movement disorder, chronic insomnia, and circadian rhythm disturbances (Kaynak et al., 2006; Kaminska et al., 2011; Veauthier et al., 2013; Veauthier & Paul, 2014).

Drugs, which can cause fatigue, include antispasmodics, such as cyclobenzaprine and benzodiazepines, as well as pain medications and anxiolytics. An immunosuppressive therapy with interferon beta agents can also cause fatigue, because interferon beta therapy often causes flu-like symptoms and fever (Plosker, 2011).

Depression can be a symptom of MS, but, on the other hand, it can also cause secondary fatigue (Patrick et al., 2009). Depression in MS is very common, major depression occurs in 15.7% of patients, which means a 2.3 times higher risk than in the normal population (Patten et al., 2003). It is suggested by several studies that only a small proportion of patients with MS receive effective treatment for their depression. Depression can lead to interruption of immunomodulatory therapy, to more severe fatigue and to the failure of the health-related quality of life in case of patients with MS. (Sadovnick et al., 1996).

I.7. Health-related quality of life

According to the definition of World Health Organization (WHO), health is a state of complete physical, mental, and social well-being, not merely the absence of disease. The measurement of the quality of life is used as an assessment of the well-being in a social, emotional and physical sense. The health-related quality of life expresses how these parameters change over time due to a disease or its treatment (Vickrey et al., 1995; Hadgkiss et al., 2013).

Over the last decades, there was an expansion of studies examining health-related quality of life in patients with MS. To measure this factor, questionnaires are the most adequate tools. Three types of questionnaires are used: general, specific and combined ones. Combined questionnaires contain general, health-related, as well as disease-specific questions. General questionnaires are used in population-based studies with large number of cases, while specific questionnaires are the most competent to analyze patients with a certain disorder. With the use of a combined questionnaire, the quality of life of patients having different disorders with the healthy population can be compared.

The most frequently utilized questionnaire in MS to estimate quality of life is the Multiple Sclerosis Quality of Life Questionnaire (MSQoL-54), which is a combined questionnaire. This was developed for English-speaking patients, and contains general questions regarding the quality of life (Short Form-36) and 18 specific questions for patients with MS (Vickrey et al., 1995). The total of 54 questions can be divided into 14 groups: Physical health, Role limitations due to physical problems, Role limitations due to emotional problems, Pain, Emotional well-being, Energy, Health perceptions, Social function, Cognitive function, Health distress, Overall quality of life, Sexual function, Satisfaction with sexual function and Change in health.

The MSQoL-54 was validated in Hungary in 2008 (Füvesi et al., 2008). The first multicentre survey with this questionnaire was performed in Hungary in 2010 (Füvesi et al., 2010). The questionnaire was given to more than 400 patients. It was confirmed that 62.1% of the patients had at least one comorbid disease besides MS. Furthermore, Füvesi et al. proved

that the quality of life of patients with depression was significantly lower than that of the patients without depression.

I.8. Diagnostic criteria for MS

MS is characterized by the signs of multiple neurological dysfunctions followed by remission and increasing functional disability. MS cannot be diagnosed with a simple test. The diagnosis is based on the neurological examination of the patient, laboratory tests and MRI data. These results, together with anamnestic data, allow us to prove the dissemination of neurological symptoms in space and time.

Earlier epidemiological studies used the Poser Committee Criteria for the diagnosis (Poser et al., 1983). The diagnostic criteria by Poser are based on the number of relapses and several additional tests, such as the measurement of visual evoked potential (VEP) and the analysis of the cerebrospinal fluid for increased number of oligoclonal bands and/or elevated IgG level. On the basis of the results, four categories can be distinguished: clinically definite MS, laboratory-supported definite MS, clinically probable MS and laboratory-supported probable MS.

For the diagnosis of MS, the McDonald criteria and their new versions were introduced in 2001, 2005 and 2010 (McDonald et al., 2001; Polman et al., 2005; Polman et al., 2011). Using these new criteria, which are based on MRI data, the patients can receive a diagnosis of MS or possible MS. As compared to the Poser criteria, the McDonald criteria enables the diagnosis of MS in a much shorter time after the recognition of the first symptoms. The period between the first relapse and the diagnosis of definitive MS became notably shorter.

I.9. Treatment of MS

A curative therapy for MS is not yet available, however, to alleviate the symptoms of MS, three types of medications exist. The first type modifies the course of the disease, the

second treats relapses, and the third manages the symptoms of MS.

With the use of disease-modifying agents, the disease activity can be reduced. The latest available first-line disease-modifying drugs are the interferon beta-1a 30 µg weekly intramuscular injection, the interferon beta-1a 44 µg subcutaneous injection three times weekly, the interferon beta-1b 250 µg subcutaneous every other day, the glatiramer acetate 20 mg daily subcutaneous injection, the dimethyl fumarate 240 mg twice daily oral medicament and the teriflunomid 14 mg daily oral drug (Jacobs et al., 1996; PRISMS Study Group, 1998; The IFNB Multiple Sclerosis Study Group, 1993; Johnson et al., 1995; Gold et al., 2012; Fox et al., 2012; O'Connor et al., 2011). All first-line immunomodulatory agents reduce the activity of MS, and slow down the progression of disability at around a similar rate, however, the mechanism of their action and their side effects are different.

In fact, the major difference between interferon beta agents and glatiramer acetate is that interferon beta therapy can cause flu-like symptoms, inflammation next to the injection-site, hepatic abnormalities and depression while these side effects are not typical in glatiramer acetate therapy (Plosker, 2011).

I.10. Glatiramer acetate

Glatiramer acetate (GA), known as copolymer 1, is a mixture of synthetic polypeptides composed of four amino acids, was approved for use in Hungary in 1999. This synthetic molecule is very similar to the myelin basic protein. Since it was very effective in preventing the experimental autoimmune encephalomyelitis, the animal model of MS, it was later tested in different clinical studies. The mechanism of its effect is complex. Glatiramer acetate binds strongly to major histocompatibility complex molecules and competes with various (myelin) antigens for their presentation to T cells (Fridkis-Hareli et al., 1994). Glatiramer acetate therapy not only changes the frequency and the pattern of cytokine secretion *in vivo*, but also modulates the effector function of GA-specific CD4⁺ and CD8⁺ T cells (Karandikar et al., 2002). Glatiramer acetate affects the properties of antigen-presenting cells, such as monocytes and dendritic cells. It promotes the differentiation of T cells to Th2 and T-regulatory cells,

which then migrate to the brain (Duda et al., 2000; Vieira et al., 2003). This leads to *in situ* bystander suppression of the inflammatory process in the brain. Furthermore, in the brain, these cells release neurotrophic factors, such as the brain-derived neurotrophic factor (BDNF) and anti-inflammatory T helper 2-like cytokines (Graber et al., 2010).

II. Aims

The aims of our studies were to:

1. determine the age- and sex-specific crude and standardized prevalence of MS according to the McDonald criteria in Csongrád County on the prevalence day (1 January 2013);
2. determine the prevalence of familial MS in Hungary;
3. determine the prevalence of fatigue and depression in glatiramer acetate-treated patients in Hungary;
4. compare the health related quality of life in fatigued and non-fatigued patients;
5. analyze the correlation of fatigue, depression, clinical disability and the disease duration with the health-related quality of life in case of patients with MS.

III. Patients and methods

III.1. Prevalence of MS in Csongrád County

Csongrád County is located in the south-eastern region of Hungary. Its climate is humid continental. The Hungarian Central Statistical Office performed the latest census in 2011. According to the available data, at that time, 421,827 people lived in Csongrád County: 199,388 males and 222,439 females. Hungarians were accounting for 85% of the population (source: ksh.hu).

At the Department of Neurology, University of Szeged, an MS outpatient unit functions for the inhabitants of Csongrád County. Since 1996, this outpatient unit has maintained an MS register containing regularly updated patient records. From the region of the Southern Great Plain, all suspected MS cases are investigated at the MS Centre of the University of Szeged to confirm the diagnosis. Until 2001, the diagnosis was established by neurology specialists according to the Poser criteria. Since the introduction of the McDonald criteria, the neuroradiologist is responsible for the medical record.

Patients are examined every 3 months for their neurological status, the Expanded Disability Status Scale (EDSS) score and the clinical form of MS are also checked. For the diagnosis of MS, brain MRI and, if necessary, spinal cord and optic nerve MRI examinations are required. In our accredited laboratory (ISO 9002), we analyze the cerebrospinal fluid samples. We perform laser nephelometry for the quantitative analysis of proteins, isoelectric focusing and IgG immunoblotting to detect oligoclonal bands. According to the McDonald criteria, in case of patients with clinically isolated syndrome (CIS), we perform control MRI examinations 3 and 6 months after the appearance of the first symptom. If we do not detect new lesions, we control MRI examinations every 3 months. Patients with clinically definitive MS undergo MRI examination yearly. Patients who receive with disease modifying therapy undergo MRI examinations yearly in the first two years of the treatment, and in case of a new relapse. In case of a relapse, we have an unscheduled visit, at which we record the neurological status and the EDSS score of the patient.

Patients, who had earlier been presumed to have MS, but whose diagnosis is not relevant after the revision of the hospital archives, are excluded by three independent neurology specialists. In case of a relevant diagnosis, the patient's medical history is recorded in the MS registry. The medical history contains the patient's relapse rate, EDSS score, paraclinical examinations data, the clinical form and the date of onset of MS. Deaths due to MS are identified from the pathological records and the certificates of death.

In our prevalence study, we included the patients with clinically isolated and clinically definitive MS living in Csongrád County on the prevalence day. The patients with relapsing-remitting clinical form had to be in a stable neurological state and in remission at the prevalence day. The duration of the disease was counted from the onset of the first symptom.

We documented the female/male ratio, the proportion of each clinical form, the number of new patients and the number of patients who moved away from the county during the study period. We also monitored the different disease-modifying treatments (DMTs).

Age- and sex-adjusted prevalence of MS was calculated by the direct method of standardization using the European Standard Population as reference. The study was approved by the Human Investigation Review Board of the University of Szeged (approval number 3267) in accordance with the Helsinki Declaration.

III.2. Familial aggregation of MS in Hungary

In 2004, with the contribution of five MS centers in Hungary, we collected MS cases implying familial aggregation. Altogether, 1500 patients were treated in the MS centres. The distribution of patients between the five centres is shown in Table 1. The patients participating in the study were diagnosed by the McDonald criteria. The patients showed relapsing-remitting, secondary progressive and benign clinical forms. The distribution of the patients and the families with MS among the five MS centres is shown the Table 1.

MS centres	Number of patients	Number of MS families	
		Cases	Families
Szeged	700	14	6
Debrecen	200	4	2
Budapest 1.	150	6	3
Budapest 2.	300	7	3
Kecskemét	150	2	1

Table 1. Number of examined patients with MS in the five MS centres in Hungary

III.3. Prevalence of fatigue and its effect on HRQoL in MS

III.3.1. Participants and measures

For the quality of life study, data of 428 patients with MS from 19 Hungarian multiple sclerosis centres were collected. The patients had the relapsing-remitting clinical form, and were treated with glatiramer acetate. The relevant socio-demographic and disease-related data were collected from the multiple sclerosis registers at the centres. The diagnosis was confirmed according to the 2005 modification of the McDonald criteria (McDonald et al., 2001; Polman et al., 2005). The distribution of the patients among the multiple sclerosis centres is shown in Table 2.

	Centres	No. of patients
1.	Dept. of Neurol., F. Jahn Hosp. of South-Pest, Budapest, Hungary	48
2.	Dept. of Neurol., Hungarian Military Hosp., Budapest, Hungary	3
3.	Dept. of Neurol., St. István Hosp., Budapest, Hungary	4
4.	Dept. of Neurol., Univ. of Debrecen, Debrecen, Hungary	25
5.	Dept. of Neurol., Gy. Kenézy Hosp., Debrecen, Hungary	18
6.	Dept. of Neurol., A. Petz County Hosp., Győr, Hungary	11
7.	Dept. of Neurol., M. Kaposi Hosp., Kaposvár, Hungary	24
8.	Dept. of Neurol., Bács-Kiskun County Hosp., Kecskemét, Hungary	25
9.	Dept. of Neurol., BAZ County Hosp., Miskolc, Hungary	21
10.	Dept. of Neurol., A. Jósza Hosp., Nyíregyháza, Hungary	19
11.	Dept. of Neurol., Univ. of Pécs Med. School, Pécs, Hungary	40
12.	Dept. of Neurol., Univ. of Szeged, Szeged, Hungary	74
13.	Dept. of Neurol., Tolna County Hosp., Szekszárd, Hungary	9
14.	Dept. of Neurol., St. György Hosp., Székesfehérvár, Hungary	16
15.	Dept. of Neurol., G. Hetényi County Hosp., Szolnok, Hungary	18
16.	Dept. of Neurol., L. Markusovszky Hosp., Szombathely, Hungary	22
17.	Dept. of Neurol., K. Vaszary Hosp., Esztergom, Hungary	6
18.	Dept. of Neurol., Uzsoki St. Hosp., Budapest, Hungary	38
19.	Dept. of Neurol., Zs. Bajcsy Hosp., Budapest, Hungary	7

Table 2. Hungarian multiple sclerosis centres participating in the study

The inclusion criteria of the study were the following: the patients had a relapsing-remitting form of MS, the glatiramer acetate treatment period was longer than one year, the patients were in remission for at least 30 days, the patients were off steroid therapy for more than 30 days, the patients had an EDSS score between zero and 5.5, and the patients were more than 18 years old.

The patients completed the Hungarian versions of the MSQoL-54, the FIS and the Beck Depression Inventory (BDI) questionnaires for the assessment of QoL, fatigue and depression. The BDI provides 21 grouped assertions on how the patient has been feeling during the week before. Each question has a set of at least four possible answers. With a total score above 21 points, the patient is regarded to have depression (Beck et al., 1961).

III.3.2. Ethics

The personal data of the patients were subject to strict confidentiality. All participants received appropriate information about the study both in written form and orally. They gave their written consent to statistical evaluation of their answers. The study was approved by the Science and Research-ethics Committee of the Medical Science Council in Hungary (3462-0/2010-1018EKU (197/PI/10)) and was in full accord with the Declaration of Helsinki. The same, ethically approved information sheet and consent form were given to the participating patients at each centre.

III.3.3. Statistical analysis

Statistical analysis was carried out with the Statistical Package for Social Sciences (SPSS 19.0, SPSS Inc., <http://www.spss.com>); the level of significance was predefined at $p < 0.05$. For determination of the prevalence of fatigue and depression, we used frequency analysis. Correlation coefficients and partial correlation coefficients were applied to assess the influence of the EDSS score, depression, fatigue and the disease duration on the quality of life. The predictors of the quality of life were determined by linear regression. The data on the fatigued and the non-fatigued patients were compared with the independent samples t-test. Our study is an exploratory pilot study, therefore no correction for multiple comparisons was made.

IV. Results

IV.1. Prevalence of MS in Csongrád County

In Csongrád County, 1999, our MS register listed 249 patients. Between 1999 and 2013, the number of new MS cases was 259. In that fourteen years, 86 patients died, and 30 moved away from the county. Thirteen patients were misdiagnosed, in their case, the longitudinal follow-up eventually ruled out MS (seven patients had neuromyelitis optica, 6 patients had autoimmunity-related vasculitis).

According to data of the Hungarian Central Statistical Office, in 2013, 421,827 people lived in Csongrád County (199,388 males, and 222,439 females). On the day of prevalence determination, January 1, 2013, 379 patients were registered in our MS register. On the basis of these data, the crude prevalence of MS was 89.8/100,000 (46.6/100,000 among males and 128.6/100,000 among females). The standardized prevalence was 83.7/100,000 for the overall MS population (42.3/100,000 for men and 122.6/100,000 for women). The age- and sex-adjusted prevalence data are detailed in Table 3. The female/male ratio was 3.08 in the MS population and 1.12 in the overall county population.

Age groups (years)	Men		Women		Total	
	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence
15>	0	0.0	0	0.0	0	0.0
15-19	0	0.0	2	16.4	2	8.0
20-24	3	20.4	9	62.8	12	41.4
25-29	14	92.1	22	147.0	36	119.3
30-34	9	50.4	24	141.3	33	94.7
35-39	10	60.4	38	238.0	48	147.6
40-44	15	103.6	37	259.5	52	180.9
45-49	5	41.5	27	214.8	32	130.0
50-54	9	68.3	41	276.5	50	178.6
55-59	14	97.4	32	187.4	46	146.3
60-64	9	76.5	29	193.0	38	141.9
65-69	2	21.0	15	114.8	17	75.2
70<	3	17.0	10	0.0	13	25.7
Crude	93	46.6*	286	128.6*	379	89.8*
Age-sex- adjusted		42.3#		122.6#		83.7#

* Crude prevalence per 100,000 population.

Standardized prevalence per 100,000 population (The European Standard was used as reference population in the direct standardization).

Table 3. Sex- and age specific prevalence of MS in Csongrád County on 1 January 2013

The distribution of the clinical forms was the following: clinically isolated syndrome (CIS): 11% (n=44), relapsing-remitting form: 69% (n=260), secondary progressive form: 14% (n=52) and primary progressive form: 6% (n=23).

The demographic data of the patients in the different clinical forms of MS are shown in Table 4.

	CIS	RRMS	SPMS	PPMS
Mean duration of MS (years)	4.7 ± 4.0 (range: 0-55)	12.9 ± 9.1 (range: 0-55)	21.7 ± 9.4 (range: 4-47)	8.5 ± 5.9 (range: 1-23)
Mean age at the onset of MS (years)	31.4 ± 9.6 (range: 19-61)	31.7 ± 9.1 (range: 5-59)	35.4 ± 12.0 (range: 13-64)	47.3 ± 8.8 (range: 20-61)

Table 4. Demographic data of patients in the different clinical forms of MS

The mean EDSS score in the group of patients with clinically isolated syndrome was 0.4 ± 0.6 . In the relapsing-remitting group, 91.9% of the patients (n=239) had EDSS scores in the range between 0 and 4. The EDSS of 8.1% of the patients in this group (n= 21) was between 4.0 and 6.5. In the secondary progressive group, 53.8% (n=28) of the patients had EDSS scores between 4.0 and 6.5, and 46.2% of SPMS patients (n=24) had scores higher than 7. In the primary progressive group, 26.1% of patients (n=6) had EDSS scores between 2 and 3.5, 13% (n=3) had a score of 4, 34.8% (n=8) had scores between 4.5 and 6.5, 26.1% (n=6) had scores of seven or higher.

We confirmed that 73.1% of the MS population received some sort of disease-modifying therapies (DMTs). Those who received any kind of DMTs in the first 5 years after the established diagnosis had a mean EDSS score of 1.1 ± 1.0 (range: 0-3.5), and those who received it between 5 and 10 years after the diagnosis had a mean EDSS score of 1.8 ± 1.3 (range: 0-5.5). The mean EDSS score among the patients, who spent 10 years or longer without disease-modifying therapy after the MS diagnosis was 2.1 ± 1.1 (range: 0-4).

IV.2. Familial aggregation of MS in Hungary

In 2006, with the collaboration of five Hungarian MS centres, we found 33 patients from 15 families among 1500 patients. This number includes a monozygotic twin pair, of which one patient showed the secondary progressive form (EDSS score of 8) of MS, and the other had benign MS. We also found a dizygotic twin pair, whose father had died of MS 20 years before. In another family, MS affected three generations (mother, son and granddaughter). In the remaining cases, the first-degree relatives affected by MS were the followings: mother-daughter, father-son, sister-sister, brother-sister and three sisters. Based on our data, which represented 25% of all MS patients in Hungary, we estimated a 2% familial rate of MS.

IV.3. Prevalence of fatigue and its effect on HRQoL in MS

IV.3.1. Demographic and clinical measures

The demographic data of the patients with relapsing-remitting form of MS were the followings: the average age of the patients was 43.6 years (95% confidence interval [CI] 42.6–44.6), the male to female ratio was 1:2.8, the mean disease duration of MS from the date of diagnosis was 11.2 years (95% CI 10.6–11.9), the mean duration of glatiramer acetate treatment was 6.6 years (95% CI 6.2–6.9) and the median EDSS score was 2.0 (95% CI 2.2–2.5). The percentage of the married respondents was 60.7%, and 83.8% had one or two children. Around 66% had participated successfully in secondary education, and about 33% had done so in higher-level education.

IV.3.2. Main outcome measures

In our multicentre study, from 428 patients with relapsing-remitting MS treated with glatiramer acetate, 402 and 381 patients answered all questions in the FIS and BDI questionnaires, respectively. In case of the MSQoL-54 questionnaire, in each question group, an average of 60 of the questionnaires could not be evaluated due to missing data. In the question groups relating to the sexual function and the satisfaction with the sexual function this rate was higher, with more than 80 cases.

Based on the data used the FIS questionnaire, the prevalence of fatigue was 62.4% (251 of 402 patients). Using the BDI, we confirmed the prevalence of depression in 13.4% of the patients (51 of 381 patients). Both questionnaires were filled out completely by 278 patients, among whom no one had depression without fatigue. However, 35 of the 168 fatigued patients (20.8%) had depression as well. We compared the health-related quality of life of patients with fatigue to that of the patients without fatigue and found that non-fatigued patients assessed their health-related quality of life significantly higher than patients with fatigue in all question groups of the MSQoL-54 questionnaire (Table 5).

		<i>t</i> -test for equality of means										
		N	Mean	St. dev.	St. err. mean	<i>t</i>	df	Sig. (2- tailed)	Mean diff.	St. error diff.	95% CI of the diff.	
											Lower	Upper
„Overall, how would you rate your own quality of life?“	NF	131	7.69	1.608	0.14	12.386	323	0.001	2.326	0.188	1.957	2.696
	F	194	5.36	1.695	0.122	12.514	288.797	0.001	2.326	0.186	1.96	2.692
„Which best describes how you feel about your life as a whole?“	NF	131	5.39	1.113	0.097	10.513	325	0.001	1.379	0.131	1.121	1.637
	F	196	4.01	1.194	0.085	10.661	291.742	0.001	1.379	0.129	1.124	1.634
Overall quality of life scale%	NF	131	75.013	14.852	1.298	13.144	325	0.001	23.014	1.751	19.57	26.459
	F	196	51.998	15.943	1.139	13.331	291.92	0.001	23.014	1.727	19.617	26.412
General health scale%	NF	131	65.473	20.318	1.775	15.132	325	0.001	31.441	2.078	27.353	35.528
	F	196	34.032	17.021	1.216	14.613	244.674	0.001	31.441	2.152	27.203	35.679
Cognitive function scale%	NF	130	85.692	17.239	1.512	11.423	323	0.001	26.923	2.357	22.286	31.56
	F	195	58.769	22.888	1.639	12.074	318.167	0.001	26.923	2.302	22.536	31.31
Sexual function scale%	NF	128	88.997	16.367	1.447	8.192	311	0.001	24.973	3.049	18.975	30.972
	F	185	64.024	31.68	2.329	9.108	290.671	0.001	24.973	2.742	19.577	30.37
Bodily pain scale%	NF	131	82.924	21.171	1.85	12.938	323	0.001	32.913	2.544	27.908	37.918
	F	194	50.01	23.347	1.676	13.185	296.503	0.001	32.913	2.496	28.001	37.826

Table 5. Health-related quality of life of patients with or without fatigue (NF=no fatigue, F=fatigue)

In our study, we examined the correlation of the EDSS score, depression, the three dimensions of fatigue and the disease duration with the health-related quality of life, as examined with the MSQoL-54, by correlation analysis. Depression and the three dimensions

of fatigue influenced all the subscales of the MSQoL-54 questions significantly negatively. The EDSS score correlated significantly negatively with all aspects of the MSQoL-54, except for the cognitive function scale. The disease duration had a significant negative correlation with the quality of life, with the exception of the mental health, the cognitive function and the satisfaction with the sexual function (data can be seen in Table 6).

		EDSS	Cognitive fatigue	Physical fatigue	Social fatigue	Depression	Duration of disease
Physical Functioning	r	-0.541	-0.455	-0.707	-0.651	-0.423	-0.201
Scale	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Role-Physical Scale	r	-0.422	-0.516	-0.655	-0.66	-0.452	-0.209
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Role-Emotional Scale	r	-0.241	-0.581	-0.578	-0.643	-0.523	-0.153
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.003
Bodily Pain Scale	r	-0.315	-0.567	-0.66	-0.655	-0.478	-0.138
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.008
Pain Scale (Vickrey)	r	-0.304	-0.581	-0.666	-0.674	-0.526	-0.145
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.005
Mental Health Scale	r	-0.181	-0.556	-0.569	-0.649	-0.716	-0.047
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.367
Vitality Scale	r	-0.328	-0.578	-0.723	-0.721	-0.591	-0.125*
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.016
Energy Scale (Vickrey)	r	-0.294	-0.577	-0.695	-0.705	-0.591	-0.134
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.01
General Health Scale	r	-0.358	-0.59	-0.698	-0.712	-0.563	-0.135
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.009
Social Functioning	r	-0.272	-0.57	-0.643	-0.705	-0.58	-0.11*
Scale	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.033
Social Function Scale	r	-0.352	-0.605	-0.685	-0.739	-0.588	-0.151
(Vickrey)	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.003
Cognitive Function	r	-0.084	-0.764	-0.528	-0.648	-0.603	-0.057*
Scale	p	0.106	0.0001	0.0001	0.0001	0.0001	0.276
Health Distress Scale	r	-0.292	-0.56	-0.649	-0.701	-0.617	-0.1*
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.053
Overall Quality of Life	r	-0.369	-0.545	-0.617	-0.675	-0.674	-0.133
Scale	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.01
Sexual Function Scale	r	-0.224	-0.442	-0.517	-0.549	-0.486	-0.122*
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.022
Reported Health	r	-0.262	-0.273	-0.412	-0.387	-0.317	-0.143
Transition Scale	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.006
Satisfaction with	r	-0.211	-0.406	-0.426	-0.471	-0.525	-0.097*
Sexual Function Scale	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.071

Correlation is significant at the 0.01 level (2-tailed).

*Correlation is significant at the 0.05 level (2-tailed).

Table 6. Correlation of the level of disability, fatigue, depression and the duration of MS with HRQoL

By regression analysis, we confirmed that the overall quality of life was significantly predicted by the EDSS score, depression and social fatigue (Table 7). By examination of the patients separately on the basis of the presence of depression, we founded that in patients with depression, social fatigue was the only factor that predicted the quality of life (Table 8).

	Coefficients ^a				
	Unstandardized coefficients		Standardized coefficients		
	B	Std. error	Beta	<i>t</i>	Sig.
(Constant)	18.184	0.306		59.46	0.0001
EDSS	-0.394	0.108	-0.155	-3.654	0.0001
Cognitive fatigue	0.057	0.029	0.152	1.947	0.052
Physical fatigue	0.032	0.033	0.094	0.996	0.320
Social fatigue	-0.148	0.023	-0.785	-6.329	0.0001
Depression	-1.742	0.478	-0.152	-3.643	0.0001

^a Dependent variable: overall quality of life scale (N=349, R²=0.519)

Table 7. Predictors of the overall quality of life scale by linear regression

		Coefficients ^a				
		Unstandardized		Standardized		
		coefficients		coefficients		
		B	Std. error	Beta	<i>t</i>	Sig.
No depression	(Constant)	18.287	0.312		58.698	0.0001
	EDSS	-0.436	0.114	-0.186	-3.843	0.0001
	Cognitive fatigue	0.058	0.031	0.157	1.875	0.062
	Physical fatigue	0.023	0.034	0.069	0.661	0.509
	Social fatigue	-0.143	0.025	-0.768	-5.780	0.0001
Depression	(Constant)	14.996	2.238		6.702	0.0001
	EDSS	-0.102	0.384	-0.046	-0.264	0.793
	Cognitive fatigue	0.05	0.094	0.133	0.529	0.600
	Physical fatigue	0.115	0.116	0.275	0.998	0.325
	Social fatigue	-0.177	0.081	-0.707	-2.200	0.034

^a Dependent variable: overall quality of life scale (N=305 and 44, $R^2=0.448$ and 0.170 , respectively)

Table 8. Predictors of the overall quality of life scale among patients without or with depression by linear regression

At question 54 of the MSQoL-54, the patients evaluate their quality of life verbally (Terrible (1) - Unhappy (2) - Mostly dissatisfied (3) – Mixed (about equally satisfied and dissatisfied) (4) - Mostly satisfied (5) - Pleased (6) - Delighted (7)). By regression analysis, we confirmed that the verbal characterization of the quality of life was predicted by the EDSS score, depression, social and cognitive fatigue ($R^2=0.389$, $p<0.05$).

In case of the cognitive and the sexual quality of life, we found significant effects of depression and cognitive fatigue (Tables 9, 10).

	Coefficients ^a				
	Unstandardized		Standardized		
	coefficients		coefficients		
	B	Std. error	Beta	<i>t</i>	Sig.
(Constant)	85.468	2.060		41.499	0.0001
Depression	-10.716	3.389	-0.142	-3.162	0.002
EDSS	1.344	0.744	0.082	1.806	0.072
Cognitive fatigue	-27.332	2.988	-0.55	-9.147	0.0001
Physical fatigue	-2.642	3.693	-0.051	-0.715	0.475
Social fatigue	-6.473	3.891	-0.13	-1.663	0.097

^aDependent variable cognitive function scale % (N=276, R²=0.527)

Table 9. Predictors of the cognitive quality of life by linear regression

	Coefficients ^a				
	Unstandardized		Standardized		
	coefficients		coefficients		
	B	Std. error	Beta	<i>t</i>	Sig.
(Constant)	91.62	3.077		29.774	0.0001
Depression	-16.605	5.130	-0.182	-3.237	0.001
EDSS	-1.705	1.121	-0.086	-1.521	0.129
Cognitive fatigue	-14.892	4.468	-0.249	-3.333	0.001
Physical fatigue	0.511	5.503	0.008	0.093	0.926
Social fatigue	-11.049	5.799	-0.185	-1.905	0.058

^aDependent variable: sexual function scale % (N=271, R²=0.273)

Table 10. Predictors of the sexual quality of life by linear regression

V. Discussion

The aim of an epidemiological study on the prevalence of a disease is to give comparable, standardized data from a certain region. The differences in the methodology, the ethnic origins, the geographical areas and the age distributions in the different study groups can cause discrepancies. To solve this problem, sex- and age adjustment for a standard population has to be used (Bauer, 1987).

In 1999, Bencsik et al. conducted an epidemiological study of MS in Csongrád County, which revealed a crude prevalence of 62/100,000 (Bencsik et al. 2001). This study was based on the diagnostic criteria by Poser (Poser et al., 1983). The novel diagnostic criteria by McDonald and its revisions by Polman were introduced in 2001, 2005 and 2011 (McDonald et al., 2001, Polman et al., 2005, 2011). In our study, we examined the prevalence of MS diagnosed by these novel criteria. The crude prevalence in Csongrád County was 89.8/100 000, the standardized prevalence of MS was 83.7/100,000.

Our results are in line with the data of other prevalence studies based on the McDonald diagnostic criteria. In these studies, data were adjusted to the European standard population. The standardized prevalence of MS was 203.4/100,000 in UK, in 2010; 74/100,000 in Osana, Spain in 2008; 96/100,000 in Verona, Italy, in 2001 and 94.7/100,000 in France, in 2004 (Mackenzie et al., 2014; Otero-Romero et al., 2013; Gajofatto et al., 2013; Fromont et al., 2010).

In Scandinavia, several prevalence studies were conducted. These studies included all probable and possible MS cases according to the diagnostical criteria of Poser, and used the European population as a reference. In Oppland County, Norway, the age-adjusted prevalence of MS was 185.6/100,000 in 2002; in Vest-Agder County, Norway, in 2007 it was 186/100,000 (Risberg et al., 2011; Vatne et al., 2011). The latest prevalence study in Norway was performed in 2013. The crude prevalence, based on the Norwegian Patient Registry, was 208/ 100,000 (Grytten et al., 2015).

In 1990, Sundström et al. performed a prevalence study, in which the patients with probable MS diagnosis were excluded. According to this study, the age-adjusted prevalence to

the European standard population in Västerbotten County, Sweden was 126/100,000 (Sundström et al., 2001). The prevalence increased over time. On the 31st of December 2010, it was 215/100,000 (Svenningsson et al., 2015). Our prevalence results are lower than those gained from the northern areas of Europe. This finding is in line with the known geographical distribution of MS.

An epidemiological study using the Poser criteria was performed in Belgrad in 1996, and the prevalence was found to be 41.5/100,000 adjusted to the world population (Pekmezovic et al., 2001).

In 1999, a prevalence study, which was conducted in Croatia and Slovenia, using the criteria of Poser and the European population as standard, found that age-adjusted prevalence of MS was 156.1/100,000 (Peterlin et al., 2006). This value is almost the double of the prevalence value found in our study.

In western Hercegovina in 2003, the prevalence of MS based on the McDonald criteria was 26.9/100,000. The European population was used as the standard population (Klupka-Sarić et al., 2007). The prevalence value found in our study is higher than this, which may be a result of the ten years that have passed since that time.

Prevalence data from the Republic of Moldova were submitted this year. According to these data, the standardized prevalence is 20.2/100,000. The patients with MS were diagnosed by the McDonald criteria (Marcoci et al, 2016).

The ratio of males to females was 1:2.75 in the MS population of Csongrád County, reported by Bencsik et al. in 2001. This ratio was 1:1.09 in the whole population of the county (Bencsik et al., 2001). In our study, we found the male:female ratio in the MS population to be 1:3.08, and 1:1.12 in the population of the whole county. These findings are in line with the literature data, which suggests that MS is more frequent among women, and this difference between the genders shows an increasing tendency (Orton et al., 2006).

We examined the proportion of patients with different clinical forms. 68.6% of the patients with MS showed the relapsing-remitting clinical form. Disease-modifying therapies have been applied in Hungary since 1996. 73.1% of the patients with the relapsing-remitting form of MS are treated with one of these drugs. Our study revealed that 91.9% of the patients

with relapsing-remitting form have either no or only mild symptoms. The average disease duration in the group of patients with RRMS was 12.9 years, which is four years longer than it was in 1999, found by an earlier prevalence study in Csongrád County (Bencsik et al., 2001). This indicates that the progression of MS became slower, which delays the shift to the secondary progressive form. Due to the disease-modifying therapies, the patients with MS stay in good physical condition for a longer time.

Our findings were supported by an epidemiological study performed in Poland. This study showed that in 2004, 40% of the patients with MS were in the severe secondary progressive form, and after the introduction of disease-modifying treatments, in 2010, this value decreased to 16% (Kulakowska et al., 2010; Obińska et al., 2004).

We found that the percentage of the primary progressive form of MS is lower (6.1%) than it was reported previously (11%) by Bencsik et al. in 2001. This reduction may be caused by the death of the older patients with a severe state. This change of the patients' proportion between the different stages of the disability is significant. While in 2001 more than 80% of patients with primary progressive form of MS had an EDSS score higher than 4.5, which means that they could not walk without aids, in 2013, only the 60% of patients with PPMS belonged to this group (EDSS: 4.5-9). 26% of patients with PPMS have even better functional status with an EDSS between 2 and 3.5. This change happened due to the new diagnostic criteria of MS by Polman, which enabled us to diagnose PPMS at the onset of the disease (Polman et al., 2005).

There are several factors – both environmental and genetic - which contribute to the etiology of MS. According to data of the International Multiple Sclerosis Genetics Consortium (IMSGC), there are over a hundred associated genetic loci confirmed that contribute to MS (IMSGC et al., 2013). It is also known that the disease shows a geographical distribution from the Equator to the north (Simpson et al., 2011). Hungary is a middle-risk area for MS. In high-risk regions, the relative risk of first-degree relatives in familial cases is between 5 and 10% (Ebers et al., 1995).

In 1996 in the United Kingdom, a cross-sectional study was performed, in which 19% of the patients with MS were reported to have effected relatives. The age-adjusted risks for

first-, second- and third-degree relatives of patients were 2.77%, 1.02% and 0.88% respectively (Robertson et al., 1996).

In France, the crude overall MS recurrence risk was lower than in the UK or in Canada examined with a similar methodology. According to these data, 9.8% of patients had a relative with MS (Sazdovitch et al., 2000).

Two studies examined the familial recurrence of MS in Sardinia, which is characterized by high disease incidence and prevalence of MS. Here, the age-adjusted recurrence risk for relatives of patients with MS was 1.9% (Marruso et al., 2002; Prokopenko et al., 2003). Nielsen et al. (2005) estimated the lifetime risk of patients with MS to 2.9% in female and to 2.8% in male first-degree relatives of patients with MS.

In Argentina, where the prevalence of MS ranged from low to intermediate, 10% of the patients with MS were reported to have at least one relative with MS (Farez et al., 2014). Another study on the familial accumulation of MS from the southern hemisphere was performed in Australia. The familial recurrence risk of MS was found to be lower than that in the northern hemisphere, which may be related to the lower population prevalence of MS. The age-adjusted risk for siblings was 2.13%, however, the overall genetic susceptibility was similar to that on the northern hemisphere, which can be explained with the different environmental factors (O'Gorman et al., 2011).

A meta-analysis of more than 500 studies on the familial risk in MS was conducted by O'Gorman et al. in 2013. The overall recurrence risk was 18.2% for monozygotic twins, and 2.7% for siblings. These data show a significantly higher recurrence risk for dizygotic twins compared to siblings. This may suggest either an environmental risk factor, or an intrauterine effect. In addition, they concluded that the known 57 MS loci are responsible for only quarter of the familial cases. This meta-analysis demonstrated that there is a consistent evidence for the latitudinal gradient in the recurrence risk in case of all relatives at adult ages. This latitudinal gradient is absent in the recurrence risks of younger generations, which suggests that the emergence of disease has a stronger genetic determination in these cases. This is also supported by the results of an earlier study, which demonstrated, that the younger age at the onset of MS is related to the HLA DRB1*15:01 allele (Hensiek et al, 2002).

In Sweden, thanks to the Swedish Multiple Sclerosis Registry, a nationwide hospital registry, the national Multi-Generation Registry and the Swedish Twin Registry, there was an opportunity to conduct a comprehensive study on familial MS recurrence risk based on about 15 million people living in Sweden (Westerlind et al., 2014). The age-adjusted risk was 17.26% for monozygotic twins, 1.69% for dizygotic twins and 2.29% for siblings. The relative risk was 23.62 for monozygotic twins, and 7.13 for siblings. These data show a lower familial relative risks in MS than previously reported.

Our study involved 1500 patients with MS, which is almost 25% of all Hungarian patients with MS. The ratio of the familial cases was 2%, which is significantly lower than data in the literature. This difference can be explained by the lower prevalence rate in this region. The different frequency and inheritance of susceptibility and resistance alleles may provide an alternative explanation for this low number of familial cases. In our study, we examined first-degree relatives only. Due to the low number of patients, we could not perform a subgroup analysis based on the degree of relatedness. Despite this fact, we believe that our study was important, since this was the first study on the familial risk of MS in a middle-risk population.

The researches of the last ten years pointed out the importance of the unseen symptoms of MS, such as fatigue and depression, as well as their effects on the patients' health-related quality of life. In 2012, we started a multicentre, cross-sectional study in Hungary to estimate how frequent the fatigue and the depression are among patients with the relapsing-remitting form of MS and how these factors influence the patients' health-related quality of life. We selected patients treated with glatiramer acetate, since the chance of secondary fatigue is much lower in case of this treatment, than in patients treated with interferon beta treatment. Furthermore, unlike in the case of interferon beta, the side-effects of glatiramer acetate do not include depression (Plosker, 2011).

Considering the data of our prevalence study (the standardized prevalence of MS in Csongrád County is 83.7/100,000, 69% of the patients have RRMS and 78% of the patients with RRMS are treated with disease-modifying therapy), the 428 patients examined in our study represent almost 10% of the Hungarian MS patients treated with disease-modifying

therapy, and more than 50% of the Hungarian MS patients treated with glatiramer acetate.

Our data on the prevalence of fatigue (62.4% after a mean disease duration of 11.23 years) are in line with the literature data (Lerdal et al., 2003). According to data gained by previous studies, the prevalence of depression among patients with MS is between 36% and 54% (Ziemssen, 2009). The risk factors for depression in MS include the female gender, an age under 35 years, a family history of major depression and stress (Patten et al., 2000). Chwastiak et al. (2002) showed that depression correlates with a lower level of education, a younger age and the absence of social support. However a study in Sarajevo, Bosnia and Herzegovina confirmed that depression is more frequent among younger and middle-aged patients with a higher educational level and an unmarried status (Alajbegovic et al., 2011). In the general population, depression is 1.7 to 2 times more frequent in females than in males (Kessler et al., 1993). The above-mentioned studies did not support this ratio in patients with MS.

Surprisingly, in our study, the prevalence of depression was significantly lower (13.4%) than found by previous studies. The low prevalence of depression in our study may result from several factors. The majority of the respondent patients lived in family, with one or two children. However, about 70% of the patients did not answer the questions on their family status. In Hungary, there is a freely available phone service with the contribution of multiple sclerosis nurses. This, together with the usual medical examinations ensure stable and well-functioning medical support for patients with MS. The participants in this study suffered from a low level of disability (low median EDSS score). Furthermore, glatiramer acetate treatment is known not only to reduce the activity of MS, but also to have an antidepressant effect (Tsai, 2007; Johnson, 2012). Due to these facts, it is very important to introduce this therapy as soon as possible after the onset of MS.

The diagnosis and effective therapy of depression are extremely important, since depression significantly worsens the patients' health-related quality of life, and can also mask the effects of the other factors, such as fatigue, the disability, as well as the duration of MS on quality of life, as demonstrated by our correlation analysis. Depression is also an important factor in the choice of disease-modifying therapy, since depression is listed among the adverse

events of interferon beta therapy (Plosker, 2011). Finally, due to the ineffective treatment of depression, the level of the patient's compliance may decrease, which may lead to the cessation of disease-modifying therapy. Despite these facts, recent studies showed that depression in MS is not diagnosed and treated effectively (McGuigan, & Hutchinson, 2006; Marrie et al., 2009).

In the past decade, several studies showed that fatigue and depression together with the disability and the disease duration significantly influence the health-related quality of life of patients with MS (Miller et al., 2003; Pittion-Vouyovitch et al., 2006). Furthermore, recent studies from Iran and Poland yielded results on the influence of fatigue and depression on the health-related quality of life in MS which are similar to those found in our study (Kargarfard et al., 2012; Papuc, & Stelmasiak, 2012).

Several previous studies confirmed that fatigue decreases the health-related quality of life significantly (Benedict et al., 2005; Janardhan & Bakshi, 2002; Lobentanz et al., 2004; Mitchell et al., 2005). In these studies, fatigue was examined as a one-dimensional factor. In our study, we used a new approach to examine the three dimensions of fatigue separately. Our partly contradictory and surprising results which indicate that physical fatigue does not predict the health-related quality of life of patients with MS, can be explained by this new approach.

However, social and cognitive fatigue have significantly negative effects on the quality of life. We believe that our results are important, since these factors cannot be measured by EDSS, and the patients do not talk willingly about their social and cognitive difficulties, as they do not find this important. However, decreasing their social or cognitive fatigue may lead to the improvement of their quality of life.

VI. Conclusions

In our studies, we investigated the prevalence of MS in Csongrád County, the familial rate of MS in Hungary and the prevalence of fatigue and depression, as well as their effects on the patients' health-related quality of life. Knowing the number of patients with MS in a geographical area allows us to estimate their number in the country. This helps to estimate the treatment costs, the effect of the different therapies on the natural history of the disease, as well as the conditions of the patients. To estimate the prevalence, a precise diagnosis and a well-defined geographical location are essential. Earlier, the diagnosis of MS was based on the Poser criteria. Our prevalence study was the first in Hungary to apply the McDonald criteria. We found that the standardized prevalence was 83.7/100,000, which means that Hungary is one of the medium-risk countries.

The onset of MS happens mostly at a young age. The question of heritability is very important for the patients. MS is a complex disease, its cause is unknown. Currently, more than 100 genetic loci and several environmental risk factors are confirmed to be related to the susceptibility for MS. In our familial epidemiological study, we involved 1500 patients with MS in Hungary, which was almost 25% of all the patients with MS in the country. The ratio of the familial cases was 2%. Due to the low number of patients, it was not possible to perform a subgroup analysis, however, in a middle-risk region, our study was the first that investigated familial risk in MS.

In our study, the prevalence of fatigue was 62.4%, which is in line with the data in the literature. The prevalence of depression was 13.4%, which is lower than it was found by earlier studies. The explanation for this may be the supporting medical and familial milieu, which surrounds the patients with MS in Hungary. We confirmed that the health-related quality of life of non-fatigued patients with MS is better than that of fatigued patients. We found that depression may escalate the negative effects of the other factors on the quality of life. Our study drew attention to the importance of the social and cognitive fatigue, which can be hidden in the common medical examinations, however, besides the level of disability, these factors significantly worsen the patients' health-related quality of life in case of MS.

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List of abbreviations

ACTH: adrenocorticotrophic hormone
APOE: apolipoprotein E
BDI: Beck depression inventory
CIS: clinically isolated syndrome
CNS: central nervous system
DMTs: disease-modifying treatments
EDSS: expanded disability status scale
FIS: fatigue impact scale
FSS: fatigue severity scale
GA: glatiramer acetate
HSV: herpes simplex virus
HRQoL: health-related quality of life
MFIS: modified fatigue impact scale
MHC: major histocompatibility complex
MRI: magnetic resonance imaging
MRS: magnetic resonance spectroscopy
MS: multiple sclerosis
MSQoL-54: multiple sclerosis quality of life instrument
PET: pozitron emission tomograph
PPMS: primary progressive multiple sclerosis
PRMS: progressive-relapsing multiple sclerosis
RRMS: relapsing-remitting multiple sclerosis
SPMS: secondary progressive multiple sclerosis
TNF-alpha: tumour necrosis factor-alpha
VEP: visual evoked potential
WHO: World Health Organization

Appendix

I.

Epidemiology of familial multiple sclerosis in Hungary

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The prevalence of familial aggregation of multiple sclerosis (MS) is estimated between 5 and 10%. Studies emphasize the effect of genetic factors over the environment of the patients in the development of the disease. We investigated familial accumulation of MS in the cases of 1500 patients in five Hungarian MS centers. According to our data, the risk of familial MS in Hungary is lower than in other countries for which literature data are accessible. The literature does not contain any data for the prevalence of familial MS in Hungary and middle-eastern Europe.

Multiple Sclerosis 2007; 13: 260–261. <http://msj.sagepub.com>

Key words: familial aggregation; first-degree relatives; genetic factors; multiple sclerosis; prevalence

Introduction

Multiple sclerosis (MS) is a demyelinating autoimmune disease of the central nervous system, caused by interplay of environmental and genetic factors. Numerous studies examined the role of these factors in familial aggregation of MS [4]. These findings indicate that familial aggregation is very largely determined by genetic background. Increased family risks range from 300-fold for monozygotic twins to 20- to 40-fold for biological first-degree relatives [7]. This great difference supports the idea of oligo/polygenic inheritance with epistatic interactions among susceptibility loci [6]. Ebers *et al.* [7], estimate the familial prevalence of MS between 5 and 10%, while data from the Mediterranean area show a greater prevalence of the disease (13–14%) [1]. The literature does not contain any data for the prevalence of familial MS in Hungary and middle-eastern Europe.

Patients and methods

We collected the cases implying familial aggregation of MS from the data of 1500 patients treated in five MS centers of Hungary in 2004. The data gained from the five centers are shown in Table 1.

The examined patients were diagnosed by the criteria of McDonald's, showing relapsing-remitting (RR), secondary progressive (SP) and benign form of MS. We found familial aggregation of the disease in 15 families involving 33 patients. Of the 33 patients, 24 were female and nine were male. The male/female ratio was 1:2.75, which is similar to the data of Hungarian epidemiological studies [2,3].

Results

Among 1500 patients in five MS centers of Hungary, we diagnosed 33 patients from 15 families. This number includes a monozygotic twin pair.

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Table 1 Number of examined patients with MS in the five MS centers of Hungary

MS centers	No. of patients	No. of MS families	
		Cases	Families
Szeged	700	14	6
Debrecen	200	4	2
Budapest 1.	150	6	3
Budapest 2.	300	7	3
Kecskemét	150	2	1

One patient of this twin pair showed SPMS (EDSS score of 8), while the other showed the benign form of the disease. We also found a dizygotic twin pair, whose father had died of MS 20 years previously. In another case, the disease affected three generations of the family (mother, son, and granddaughter). In the remaining cases, the affected family members were mother-daughter, father-son, sister-sister, brother-sister, and three sisters. In our group of patients (representing 25% of all MS patients in Hungary), we observed a 2% familial rate.

Discussion

MS disease risk shows a geographical distribution; the risk of MS decreases from the north to the south [5]. In Hungary, the prevalence of MS is 62/100 000, which indicates that Hungary is in the middle-risk area [3]. In high-risk areas, the risk of MS is estimated about 0.1%, while the relative risk of first degree relatives in familial cases is between 5 and 10% [7]. According to data published by Nielsen [8], the lifetime risk of MS patients was calculated to be 2.9% in female and 2.8% in male first-degree relatives of MS patients. Our study involved 1500 cases, which is almost 25% of all MS patients in Hungary. In this group of patients, the ratio of the familial cases was 2%.

This shows that, in Hungary, the risk of familial MS is 50% lower than data in the literature [7,10]. However, the familial rate may increase after a generation of observation, and is very likely to stay significantly lower than the data above. The lower rate of familial MS can be an effect of the lower prevalence rate in the region. This hypothesis

is also supported by the finding that penetrance in twins appears to correlate with MS prevalence [9].

The differential frequency and inheritance of susceptibility and resistance genes may give an alternative explanation for this low rate of familial cases. Higher frequency of resistance genes might cause a lower familial rate even in higher-risk regions, depending on the pattern of inheritance of resistance and susceptibility genes.

We examined the ratio of the first-degree relatives, but due to the low number of patients, we were unable to perform a subgroup analysis (regarding the degree of relatedness). To date, no other middle-risk population was examined for risk data. In the future, we plan to study the role of genetic factors in these familial cases.

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II.

Prevalence of multiple sclerosis in Csongrád County, Hungary

Zsiros V, Fricska-Nagy Z, Füvesi J, Kincses ZT, Langane É, Paulik E, Vécsei L, Bencsik K. Prevalence of multiple sclerosis in Csongrád County, Hungary.

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Objective – Recent epidemiological studies were mainly based on the Poser or other diagnostic criteria. There have been no previous data from Hungary, which were assessed with the more up-to-date McDonald criteria and which give comparable standardized data from the region. **Materials and Methods** – Data were collected from the MS Register of the Department of Neurology at the University of Szeged. All possible and definitive patients with MS living in the county on the prevalence day were included in the study. Direct standardization was based on the European standard population. **Results** – On 1 January 2013, 379 registered patients with MS were alive in the county, that is, a crude MS prevalence of 89.8/100,000, 46.6/100,000 in males and 128.6/100,000 in females; standardized prevalence: 83.7/100,000 (42.3/100,000 for males, 122.6/100,000 for females). The distribution of the clinical forms: 11% clinically isolated syndrome, 69% relapsing–remitting form, 14% secondary progressive form, 6% primary progressive form. Patients with no or only mild symptoms comprised 91.9% of the relapsing–remitting population.

Conclusions – This is the first standardized epidemiological study based on the McDonald criteria in Central Europe. Hungary is a medium-risk country as concerns the prevalence of MS. The crude prevalence appears to have increased relative to previous reports from the county.

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Key words: epidemiology; Hungary; multiple sclerosis; prevalence

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Introduction

Multiple sclerosis (MS) is the most common autoimmune, demyelinating and neurodegenerative disease of the central nervous system among young adults. Epidemiological studies not only reveal the number of patients, but also draw attention to aetiological factors. Previous studies have presumed the roles of a genetic predisposition, infections and vitamin D deficiency in the development of MS (1–4). The disease has a north–south gradient in Europe, decreasing towards the equator. The improved diagnostic facilities and longer survival of patients with MS also probably explain to some extent the increasing prevalence in the past 60 years (5).

The diagnosis of MS is still a clinical diagnosis, which is then confirmed via paraclinical

examinations. A precise diagnosis and a well-defined geographical location are essential as concerns epidemiological studies. Comparison of the findings of different epidemiological studies is limited because of the use of different diagnostic criteria and methodologies; moreover, the majority of these studies provide crude estimates (6). Recent epidemiological studies have focused on solving the discrepancies caused by diversities in age, sex and ethnic attribution of different populations to explore a global image of the epidemiology of MS.

Most studies of the epidemiology of MS have been carried out with the Poser or earlier diagnostic criteria (7). The various McDonald criteria, based on MRI findings, were introduced in 2001, 2005 and 2010 (8–10). Thanks to these criteria, the diagnosis of MS can be made

immediately after the recognition of the first symptom, and the time between the first relapse and the definitive diagnosis is therefore shorter. Research involving the McDonald criteria is not common (7). There has been no epidemiological study in Hungary in which the McDonald diagnostic criteria were used. The aim of this study was to determine the age- and sex-specific crude and standardized prevalence of MS in Csongrád County on the chosen prevalence day (1 January 2013) according to the McDonald criteria to obtain comparable data from the region.

Materials and methods

Study area

Csongrád County is located in the south-eastern region of Hungary between latitudes 46° 1' and 46° 8' and longitudes 19° 6' and 20° 7', in the temperate zone, with an area of 4262.68 km² (Fig. 1). The climate is humid continental. According to the latest census performed by the Hungarian Central Statistical Office in 2011, 421,827 people lived in Csongrád County: 199,388 males and 222,439 females, Hungarians accounting for 85% of the population (source: ksh.hu).

Patients

The Department of Neurology at the University of Szeged has an MS outpatient unit for the inhabitants of Csongrád County, which has maintained an MS register containing regularly updated patient records since 1996. All suspected MS cases are referred to the MS Centre at the University from the region of the Southern Great

Plain to confirm or exclude the diagnosis. The diagnosis was established by neurology specialists, who applied the criteria of Poser until 2001, but subsequently the criteria of McDonald were introduced and the medical records on MRI are the responsibility of a neuroradiologist (8–10). All patients with diagnoses of MS (ICD-9 code 340) according to Poser were reviewed according to the McDonald criteria. The patients are examined every 3 months, with checks on their neurological status, their Expanded Disability Status Scale (EDSS) score and the clinical form of the disease (11). All patients participate in brain MRI and, if necessary, spinal cord or optic nerve MRI examination. Cerebrospinal fluid samples are analysed in our accredited laboratory (according to ISO 9002) by means of laser nephelometry for the quantitative determination of proteins, isoelectric focusing and IgG immunoblotting to detect oligoclonal bands. Since 2001, patients with the clinically isolated syndrome (CIS) participate in control MRI examinations 3 and 6 months after the appearance of the first symptom. As long as the MRI does not indicate new lesions, control examinations are carried out every 3 months. Patients with clinically definitive MS take part in neurological control examinations every 3 months and brain MRI examinations yearly. Disease-modifying-treated patients have brain MRI examinations yearly in the first 2 years of the therapy, and subsequently only if a new relapse occurs. Unscheduled visits are made in the event of a relapse, and the neurological status and EDSS score are recorded. Three neurology specialists independently excluded those who had earlier been presumed to have MS, but whose diagnosis was ruled out during the revision

Figure 1. Csongrád County, located in the south-eastern region of Hungary.

of the hospital archives. Once the diagnosis was established, the patient's medical history, containing their relapse rate, EDSS score, paraclinical examinations data, clinical form and date of onset, was recorded in the MS registry. Deaths were identified from pathological records and certificates of death.

In this cross-sectional study, we included all patients with clinically isolated and clinically definitive MS living in the area on the prevalence day. To allow a well-defined, unified epidemiological study, only patients living in the county on the prevalence day were included.

The patients with the relapsing–remitting form were in a stable neurological state and in remission on the chosen prevalence day. The duration of the disease was calculated from the time of appearance of the first symptom.

The female/male ratio, the proportion of each clinical form, the number of new patients, the number of patients who migrated from this geographical area during the intervening period and the frequency data relating to the various disease-modifying treatments (DMTs) were also documented. Age- and sex-adjusted prevalence was calculated by the direct method of standardization with the use of the European Standard Population as reference (12). The study was approved by the Human Investigation Review Board of the University of Szeged (approval number 3267) in accordance with the Helsinki Declaration.

Results

The MS register listed 249 patients with MS in 1999. Between 1999 and 2013, 259 new MS cases were diagnosed. In that period, 86 patients died and 30 moved away from the geographical area. The diagnosis of 13 patients was revised, as the longitudinal follow-up eventually ruled out MS (seven patients had neuromyelitis optica, and six patients had autoimmunity-related vasculitis).

The most recent Hungarian Central Statistical Office data indicated that 421,827 people lived in Csongrád County (199,388 males and 222,439 females), and 379 patients with MS were registered as being alive on the day of prevalence determination, 1 January 2013. On the basis of these data, the crude prevalence of MS was 89.8/100,000, 46.6/100,000 among males and 128.6/100,000 among females. The standardized prevalence was 83.7/100,000 for the overall MS population, 42.3/100,000 for men and 122.6/100,000 for women. The age- and sex-adjusted prevalence data are detailed in Table 1. The

Table 1 Sex- and age-specific prevalence of multiple sclerosis in Csongrád County on 1 January 2013

Age groups (years)	Men		Women		Total	
	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence
15>	0	0.0	0	0.0	0	0.0
15–19	0	0.0	2	16.4	2	8.0
20–24	3	20.4	9	62.8	12	41.4
25–29	14	92.1	22	147.0	36	119.3
30–34	9	50.4	24	141.3	33	94.7
35–39	10	60.4	38	238.0	48	147.6
40–44	15	103.6	37	259.5	52	180.9
45–49	5	41.5	27	214.8	32	130.0
50–54	9	68.3	41	276.5	50	178.6
55–59	14	97.4	32	187.4	46	146.3
60–64	9	76.5	29	193.0	38	141.9
65–69	2	21.0	15	114.8	17	75.2
70<	3	17.0	10	0.0	13	25.7
Crude	93	46.6*	286	128.6*	379	89.8*
Age-sex-adjusted		42.3†		122.6†		83.7†

*Crude prevalence per 100,000 population.

†Standardized prevalence per 100,000 population (The European Standard was used as reference population in the direct standardization).

female/male ratio was 3.08 in the MS population and 1.12 in the overall county population.

The documented distribution of the clinical forms was 11% ($n = 44$) with the CIS, 69% ($n = 260$) with the relapsing–remitting form, 14% ($n = 52$) with the secondary progressive form and 6% ($n = 23$) with the primary progressive form (Fig. 2).

The average duration of the disease for the CIS cases was 4.7 years ± 4.0 (range: 0–17), for the relapsing–remitting cases was 12.9 years ± 9.1 (range: 0–55), for the secondary progressive cases was 21.7 years ± 9.4 (range: 4–47) and for the primary progressive cases was 8.5 years ± 5.9 (range: 1–23). The average age at the onset of the disease was 31.4 years ± 9.6 (range: 19–61) in the CIS group, 31.7 years ± 9.1 (range: 5–59) in the relapsing–remitting group, 35.4 years ± 12 (range: 13–64) in the secondary progressive group and 47.3 years ± 8.8 (range: 20–61) in the primary progressive group.

The average EDSS score in the CIS group was 0.4 ± 0.6 . In the relapsing–remitting group, 91.9% ($n = 239$) had EDSS scores in the range 0–4, and 8.1% ($n = 21$) had scores of 4.0–6.5. In the secondary progressive group, 53.8% ($n = 28$) of the patients had EDSS scores of 4.0–6.5 points, and 46.2% ($n = 24$) had scores of ≥ 7 . In the primary progressive group, 26.1% ($n = 6$) had EDSS scores of 2–3.5, 13% ($n = 3$) had a score of 4, 34.8% ($n = 8$) had scores of 4.5–6.5, and 26.1% ($n = 6$) had scores of ≥ 7 (Table 2).

Figure 2. Distribution of clinical forms of MS in Csongrád County. CIS, clinically isolated syndrome; R-R, relapsing–remitting; SP, secondary progressive; PP, primary progressive.

Table 2 Distribution of patients in Csongrád County by EDSS scores in the clinical forms of the disease on the day of prevalence determination

Clinical form	EDSS scores	Number of patients	Percentage within the clinical form (%)
Relapsing–remitting	0–4	239	91.9
	4.5–6.5	21	8.1
	≥7	0	0
Secondary progressive	4–6.5	28	53.8
	≥7	24	46.2
Primary progressive	2–3.5	6	26.1
	4	3	13
	4.5–6.5	8	34.8
	≥7	6	26.1

The patients with the relapsing–remitting form comprised 73.1% of the MS population who regularly received DMTs. Those who received any kind of DMTs in the first 5 years after the diagnosis was established had an average EDSS score of 1.1 ± 1.0 (range: 0–3.5), and those who received it between 5 and 10 years after the diagnosis had an average EDSS score of 1.8 ± 1.3 (range: 0–5.5). The average EDSS score among the patients who spent 10 years or more without therapy after the diagnosis was 2.1 ± 1.1 (range: 0–4).

Discussion

Recent epidemiological studies focusing on the prevalence of the disease have attempted to solve the discrepancies in terms of the differences in the methodologies used, the ethnic origins, the geographical areas and the age distributions in the various study populations. One possibility to solve some of these differences and obtain uniform comparable results is sex and age adjustment for a standard population (13).

As regards the occurrence of MS, Hungary is one of the medium-risk countries. The first epidemiological study in Hungary, by Halasi in 1961, revealed a crude prevalence of 20/100,000. The crude prevalence in Baranya County in 1983 was reported by Pálffy et al. (14) to be 37/100,000, and the epidemiological study by Bencsik et al. (15) in Csongrád County in 1999 revealed a crude prevalence of 62/100,000. Our present study indicated a crude prevalence in Csongrád County of 89.8/100,000 and a standardized prevalence of 83.7/100,000.

Prevalence studies based on the McDonald criteria adjusted to the European standard population have been published from Osona, Spain, where in 2008 it was 74/100,000, from Verona, Italy, where it was 96/100,000 in 2001, and from France, where it was 94.7/100,000 in 2004. Our data are in line with these reports (16–18).

Prevalence data from areas closer to Hungary are not common. An epidemiological study from Belgrade, Yugoslavia, in 1996 revealed a prevalence of 41.5/100,000, but it was performed according to the Poser diagnostic criteria and adjusted to the world population (19). A study from western Herzegovina in 2003, based on the McDonald criteria and standardized to the European population, revealed a prevalence of 26.9/100,000 (20). Our result is higher, probably because those data were published more than 10 years previously. In 1999, a study from Croatia and Slovenia with the European population as standard indicated that the age-adjusted prevalence was 156.1/100,000 according to the Poser diagnostic criteria; this is much higher than we reported (21).

Epidemiological studies from Scandinavia are relatively common. In 2002 in Oppland County, Norway, the age-adjusted prevalence was 185.6/100,000; in Vest-Agder County, Norway, in 2007, it was 186/100,000 (22, 23). All Scandinavian studies took into consideration all probable and possible MS cases according to the Poser criteria and the standardized data to the European population as reference. In 1990, in Västerbotten County, Sweden, with use of Poser diagnostic criteria, the age-adjusted prevalence to the European standard population was 126/100,000, but patients with a diagnosis of only probable MS were excluded (24). As expected, our data are lower than those reported from the northern region of Europe, which is in line with the geographical distribution of the disease described by Dean, and the introduction of national registries in these countries may lead to better and more precise case assessment (25).

In our own study, the female/male ratio was 1:3.08 in the MS population and 1:1.12 in the county population, while the standardized prevalence was 122.6/100,000 among women and 42.3/100,000 among men. In 1999, Bencsik et al. (15) reported that the female/male ratio was 1:2.75 in the MS population of the county and 1:1.09 in the overall county population. These results are in accordance with the literature finding of a higher occurrence of MS in women and with those that show an increasing tendency (26, 27).

Among patients with the relapsing–remitting form, who accounted for 68.6% of the overall MS population, the average disease duration was 12.9 years, and 91.9% had no or only mild symptoms. DMTs were introduced in Hungary in 1996. In fact, 73.1% of the patients with the relapsing–remitting form receive some type of DMTs. The progression of the disease is slower; the proportion of patients in good physical condition increases and the quality of life improves in consequence of the therapy. The change to the secondary progressive form shifts to an older stage of life, and the patients can remain at work for a longer time, which is important because MS tends to affect young people. Similar results have been reported from Poland, where, without the disease-modifying therapy, 40% of the patients suffered from the severe secondary progressive form in 2004, whereas the number had decreased to 16% by 2010, after the introduction of immunomodulatory treatment (28, 29).

The frequency of the primary progressive form was 6.1%, which is lower than previously reported. This may be due to the death of older patients with severe disability. However, it should be mentioned that the patients with a better functional status in this clinical form (EDSS scores of 3.0–3.5) comprise 26% of the population. The earlier lack of a protocol meant that the definitive diagnosis of the primary progressive form usually took years. The application of the diagnostic criteria system of Polman et al. (9) allows the diagnosis to be established at the beginning of the illness, when the impairment is milder. The importance of the earlier diagnosis resides in the future possibility of the medication of this clinical form.

An important limitation of the study is that the population of Csongrád County with 421,827 inhabitants is a low population number, but it comprised 4.2% of the whole population of Hungary (9,985,722 persons according to the latest census performed by the Hungarian Central Statistical Office in 2011).

We conclude that, as regards the occurrence of MS, Hungary is one of the medium-risk countries.

The current study appears to have been the first in Hungary that was performed with the McDonald criteria and that has provided standardized prevalence data from the region and the opportunity to establish prospective follow-up studies to identify the real pattern of MS.

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Conflict of interest

There is no conflict of interest.

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III.

The effects of fatigue, depression and the level of disability on the health-related quality of life of glatiramer acetate-treated relapsing-remitting patients with multiple sclerosis in Hungary[☆]

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ABSTRACT

Background: The common symptoms of multiple sclerosis are fatigue, depression, cognitive dysfunction, pain and sexual dysfunction, which influence the health-related quality of life of the patients.

Objective: We aimed to determine the correlations between the health-related quality of life, the level of disability, fatigue and depression in glatiramer acetate-treated patients with multiple sclerosis in Hungary.

Methods: The Hungarian versions of the Multiple Sclerosis Quality of Life-54, Fatigue Impact Scale and Beck Depression Inventory questionnaires were completed by 428 relapsing-remitting multiple sclerosis patients treated with glatiramer acetate from 19 Hungarian centers.

Results: The prevalence of fatigue was found to be 62.4%. The prevalence of depression was lower (13.4%) than that described in previous studies (36–54%) among patients with multiple sclerosis. Significant differences in the health-related quality of life were found between fatigued and non-fatigued patients. The level of disability, fatigue, depression and the duration of the disease correlated significantly with the quality of life. However, linear regression analysis indicated that the quality of life was predicted by the level of disability, depression, social and cognitive fatigue, but not by physical fatigue.

Conclusions: Decreasing the disease activity in multiple sclerosis with immunomodulatory therapy, together with improvements of the diagnostics and treatment of the accompanying depression and fatigue are of high priority to improve the health-related quality of life of patients with multiple sclerosis.

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1. Introduction

Multiple sclerosis (MS) is a chronic disease, which, via its various symptoms, impairs the patients' ability to move and work, as

well as their level of well-being. Although the Expanded Disability Status Scale (EDSS) is generally used to determine the level of disability of patients with multiple sclerosis, several aspects of multiple sclerosis are not measurable with this scale (Kurtzke, 1983). In recent years, measurement of the health-related quality of life (HRQoL) became a useful tool to assess the burden of MS. HRQoL is a multidimensional parameter which relates to physical, mental and social health, and which is estimated by using general, combined and specific questionnaires (Hadjgkiss et al., 2013). The common symptoms of multiple sclerosis are fatigue, depression, cognitive dysfunction, pain and sexual dysfunction, which synergistically influence the health-related quality of life (Crayton et al., 2004).

Fatigue is found in 40–90% of patients with multiple sclerosis

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(Lerdal et al., 2003), and fundamentally influences their daily routine. The patients' capability of moving is better during the morning hours, but they need resting periods during longer activities. Fatigue also limits the patients' personal interactions; moreover, it can even lead to losing their jobs. A patient with multiple sclerosis was reported, who presented fatigue as the only manifestation of an acute MS relapse (Flachenecker and Meissner, 2008). Furthermore, in another study, the correlation of fatigue and a cognitive sign of MS, alertness, was confirmed (Weinges-Evers et al., 2010). Three forms of fatigue have been described: physical, cognitive and social fatigue (Bakshi, 2003; Vucic et al., 2010).

The diagnosis and treatment of depression are essential in multiple sclerosis cases. Patten et al. concluded that major depression occurs in 15.7% of individuals with multiple sclerosis, which means a 2.3 times higher risk than in the normal population (Patten et al., 2003). A survey by Ziemssen et al. suggested that major depression may occur in approximately 50% of patients with multiple sclerosis (Ziemssen, 2009). Only a small proportion of patients with multiple sclerosis receive effective treatment for their depression, and this situation, besides putting their uninterrupted immunomodulatory therapy at risk, can lead to more severe fatigue, with a resulting negative influence on their health-related quality of life (Sadovnick et al., 1996).

Among the various modes of immunomodulatory therapy, the interferons can cause flu-like symptoms and fever, which can lead to secondary fatigue (Plosker, 2011). Sleep disorders can also cause secondary fatigue. Studies showed that sleep medical therapy may improve MS related fatigue (Veauthier et al., 2013; Veauthier and Paul, 2014). Furthermore, one of the adverse events of interferon beta treatment is depression. It was suggested that interferon beta induces secondary depression due to inhibition of serotonin production, however, long-term studies did not prove this hypothesis (Loftis and Hauser, 2004; Reder et al., 2014). For our study, we selected a group of glatiramer acetate-treated patients with multiple sclerosis, since the adverse events of glatiramer acetate (depression, flu-like symptoms, fever) are less common than those of interferon beta.

The aim of our study was to determine the prevalence of fatigue and depression in glatiramer acetate-treated patients with multiple sclerosis. Since we expected that fatigue negatively influences the health-related quality of life, we compared this parameter in fatigued and non-fatigued patients. We analyzed the correlation of fatigue, depression, clinical disability and the disease duration with the health-related quality of life.

2. Methods

2.1. Participants

Data on 428 relapsing-remitting patients with multiple sclerosis treated with glatiramer acetate were collected from 19 Hungarian multiple sclerosis centers. The relevant socio-demographic and disease-related data were obtained from the multiple sclerosis registers at the centers. The diagnosis was confirmed according to the 2005 modification of the McDonald criteria for relapsing-remitting multiple sclerosis (McDonald et al., 2001; Polman et al., 2005). Patients were included in the study according to the following inclusion criteria: the patients had a relapsing-remitting form of multiple sclerosis, glatiramer acetate treatment period was longer than one year, the patients were in remission for at least 30 days, the patients were off steroid therapy for more than 30 days, the patients had an EDSS score between zero and 5.5, and the patients were more than 18 years old.

2.2. Ethics

The personal data on the patients were subject to strict confidentiality. All participants received appropriate information about the study both in written form and orally. They gave their written consent to statistical evaluation of their answers. The study was approved by the Science and Research-ethics Committee of the Medical Science Council in Hungary (3462-0/2010-1018Eku (197/PI/10)) and was in full accord with the Declaration of Helsinki. The same, ethically approved information sheet and consent form were given to the participating patients at each center.

2.3. Measures

The most frequently utilized questionnaire in multiple sclerosis to measure quality of life is the Multiple Sclerosis Quality of Life Questionnaire (MSQoL-54), which is a combined questionnaire, developed for English-speaking patients. It contains general questions regarding the quality of life (Short Form-36) and 18 specific questions for patients with multiple sclerosis (Vickrey et al., 1995). The MSQoL-54 enables the comparison of the quality of life of patients with multiple sclerosis with that of the general population and with that of patients with other diseases. The total of 54 questions can be divided into 14 groups: Physical health, Role limitations due to physical problems, Role limitations due to emotional problems, Pain, Emotional well-being, Energy, Health perceptions, Social function, Cognitive function, Health distress, Overall quality of life, Sexual function, Satisfaction with sexual function and Change in health. The MSQoL-54 was validated for the Hungarian language (Füvesi et al., 2008), and the first survey with this questionnaire was performed in Hungary in 2010 (Füvesi et al., 2010). Apart from determining the health-related quality of life of multiple sclerosis patients, the survey demonstrated that 62% of the patients had at least one concomitant disease. Depression was found in 20.3% of the patients with multiple sclerosis.

The pathophysiology of fatigue is not well understood, and the objective characterization of fatigue is difficult. Recently, it was shown that fatigue is associated with the alterations of basal ganglia functional connectivity and with altered parameters of saccade like ocular motor movements, therefore testing these may lead to a better quantification of fatigue (Finke et al., 2012, 2015). However, questionnaires are widely used for this purpose. Although they are somewhat subjective, they yield useful information about the patients' everyday life. The most frequently used questionnaires are the Fatigue Severity Scale (FSS) (Krupp et al., 1989), the Fatigue Impact Scale (FIS) (Fisk et al., 1994), and the Modified Fatigue Impact Scale (MFIS) (Achiron et al., 2015). While the FSS is one-dimensional, measuring only physical fatigue, the FIS and MFIS assess all three aspects of fatigue. The completed FIS questionnaire contains 40 statements, the MFIS is a 21-item scale, each with a score ranging from 0 to 4 points, giving information on the last 4 weeks. The Hungarian version of the FIS was validated in 2011 (Losonczai et al., 2011).

The Beck Depression Inventory-First Edition (BDI-I.) provides 21 grouped assertions on how the patient has been feeling in the last week. Each question has a set of at least four possible answers. With a total score above 21 points, the patient is regarded to have depression (Beck et al., 1961).

2.4. Statistical analysis

Statistical analysis was carried out with the Statistical Package for Social Sciences (SPSS 19.0, SPSS Inc., <http://www.spss.com>); the level of significance was predefined at $p < 0.05$. For determination of the prevalence of fatigue and depression, we used frequency

analysis. Correlation coefficients and partial correlation coefficients were applied to assess the influence of the EDSS score, depression, fatigue and the disease duration on the quality of life. The predictors of the quality of life were determined by linear regression. The data on the fatigued and the non-fatigued patients were compared with the independent samples *t*-test. Our study is an exploratory pilot study, so no correction for multiple comparisons was made.

3. Results

3.1. Demographic and clinical measures

The average age of the patients was 43.6 years (95% confidence interval [CI] 42.6–44.6), the male to female ratio was 1:2.8, the mean disease duration of multiple sclerosis from date of diagnosis was 11.2 years (95% CI 10.6–11.9), the mean duration of glatiramer acetate treatment was 6.6 years (95% CI 6.2–6.9) and the median EDSS score was 2.0 (95% CI 2.2–2.5). The percentage of the married respondents was 60.7%, and 83.8% had one or two children. Around 66% had participated successfully in secondary education, and about 33% had done so in higher-level education. The distribution of patients among the multiple sclerosis centers is shown in Table 1.

3.2. Main outcome measures

As concerns the responses to the MSQoL-54, FIS and BDI questionnaires by the 428 glatiramer acetate-treated relapsing-remitting patients with multiple sclerosis in this multicentre study, 402 and 381 patients answered all questions in the FIS and BDI questionnaires, respectively. In each question group of the MSQoL-54, an average of 60 of the questionnaires could not be evaluated because of missing data. An exception was the question group relating to the sexual function and the satisfaction with the sexual function, which were incomplete in more than 80 cases.

The FIS scores indicated that the prevalence of fatigue was 62.4% (251 of 402 patients). The prevalence of depression was

13.4% (51 of 381 patients). Among the 278 patients who filled in both questionnaires completely, no one had depression without fatigue. However, 35 of the 168 fatigued patients also had depression (20.8%). Non-fatigued patients assessed their health-related quality of life significantly higher than patients with fatigue in all question groups of the MSQoL-54 questionnaire (Table 2).

By means of correlation analysis, we examined the correlation of the EDSS score, depression, the three dimensions of fatigue and the disease duration with the health-related quality of life, as examined with the MSQoL-54. Depression and the three dimensions of fatigue influenced all the subscales of the MSQoL-54 questions significantly negatively. The EDSS score correlated significantly negatively with all aspects of the MSQoL-54, except for the cognitive function scale. The disease duration had a significant negative correlation with the quality of life, with the exception of the mental health, the cognitive function and the satisfaction with the sexual function (Table 3).

Regression analysis revealed that the overall quality of life was significantly predicted by the EDSS score, depression and social fatigue (Table 4). When the patients were grouped on the basis of the presence of depression, it emerged that in patients with depression, social fatigue was the only factor that predicted the quality of life (Table 5). At question 54 of the MSQoL-54, the patients verbally evaluate their quality of life (terrible (1)–unhappy (2)–mostly grumbler (3)–mixed (4)–mostly satisfied (5)–satisfied (6)–happy (7)). Regression analysis showed that the verbal characterization of the quality of life was predicted by the EDSS score, depression, social and cognitive fatigue ($R^2=0.389$, $p < 0.05$). As concerns the cognitive and the sexual quality of life, we found significant effects of depression and cognitive fatigue (Tables 6, 7).

4. Discussion

The standardized prevalence of multiple sclerosis in Csongrád County, Hungary is 83.7/100,000, 69% of the patients show the relapsing-remitting clinical form (Zsíros et al., 2014), and 78% of the relapsing-remitting patients is treated with immunomodulatory therapy. The 428 patients examined in our study represent almost 10% of the Hungarian MS patients treated with immunomodulatory therapy, and more than 50% of the Hungarian MS patients treated with glatiramer acetate.

In this multicentre, cross-sectional study of Hungarian, relapsing-remitting multiple sclerosis patients treated with glatiramer acetate, we found a considerable prevalence of fatigue and depression. We also showed that these factors significantly contribute to the health-related quality of life of our patients. The 62.4% prevalence of fatigue after a mean disease duration of 11.23 years is in line with the literature data (Lerdal et al., 2003). Many international studies found that glatiramer acetate therapy may improve fatigue (Jongen et al., 2010, 2014; Metz et al., 2004; Ziemssen et al., 2008).

In previous studies, the prevalence of depression among patients with multiple sclerosis was found to be 36–54% (Ziemssen, 2009). Surprisingly, in our study, the prevalence was significantly lower (13.4%). The risk factors for depression in multiple sclerosis include the female gender, an age under 35 years, a family history of major depression and stress (Patten et al., 2000). Chwastiak et al. reported that depression correlated with a lower level of education, a younger age and the absence of social support, while a survey in Sarajevo, Bosnia and Herzegovina indicated that depression is more frequent among younger and middle-aged patients with a higher educational level and an unmarried status (Chwastiak et al., 2002; Alajbegovic et al., 2011). In the general population, depression is 1.7–2 times more frequent in females than in males (Kessler et al., 1993), however, the above-mentioned

Table 1
Hungarian multiple sclerosis centers participating in the study.

Centers	No. of patients
1. Dept. of Neurol., F. Jahn Hosp. of South-Pest, Budapest, Hungary	48
2. Dept. of Neurol., Hungarian Military Hosp., Budapest, Hungary	3
3. Dept. of Neurol., St. István Hosp., Budapest, Hungary	4
4. Dept. of Neurol., Univ. of Debrecen, Debrecen, Hungary	25
5. Dept. of Neurol., Gy. Kenézy Hosp., Debrecen, Hungary	18
6. Dept. of Neurol., A. Petz County Hosp., Győr, Hungary	11
7. Dept. of Neurol., M. Kaposi Hosp., Kaposvár, Hungary	24
8. Dept. of Neurol., Bács-Kiskun County Hosp., Kecskemét, Hungary	25
9. Dept. of Neurol., BAZ County Hosp., Miskolc, Hungary	21
10. Dept. of Neurol., A. Jósza Hosp., Nyíregyháza, Hungary	19
11. Dept. of Neurol., Univ. of Pécs Med. School, Pécs, Hungary	40
12. Dept. of Neurol., Univ. of Szeged, Szeged, Hungary	74
13. Dept. of Neurol., Tolna County Hosp., Szekszárd, Hungary	9
14. Dept. of Neurol., St. György Hosp., Székesfehérvár, Hungary	16
15. Dept. of Neurol., G. Hetényi County Hosp., Szolnok, Hungary	18
16. Dept. of Neurol., L. Markusovszky Hosp., Szombathely, Hungary	22
17. Dept. of Neurol., K. Vaszary Hosp., Esztergom, Hungary	6
18. Dept. of Neurol., Uzsoki St. Hosp., Budapest, Hungary	38
19. Dept. of Neurol., Zs. Bajcsy Hosp., Budapest, Hungary	7

Table 2
Health-related quality of life of patients with or without fatigue.

		N	Mean	Std. deviation	Std. error mean	t-test for equality of means		t-test for equality of means				
						t	df	Sig. (2-tailed)	Mean difference	Std. error difference	95% CI of the diff.	
											Lower	Upper
“Overall, how would you rate your own quality of life?”	No Fatigue	131	7.69	1.608	0.14	12.386	323	0.001	2.326	0.188	1.957	2.696
	Fatigue	194	5.36	1.695	0.122	12.514	288.797	0.001	2.326	0.186	1.96	2.692
“Which best describes how you feel about your life as a whole?”	No fatigue	131	5.39	1.113	0.097	10.513	325	0.001	1.379	0.131	1.121	1.637
	Fatigue	196	4.01	1.194	0.085	10.661	291.742	0.001	1.379	0.129	1.124	1.634
Overall quality of life scale %	No fatigue	131	75.013	14.852	1.298	13.144	325	0.001	23.014	1.751	19.57	26.459
	Fatigue	196	51.998	15.943	1.139	13.331	291.92	0.001	23.014	1.727	19.617	26.412
General health scale %	No fatigue	131	65.473	20.318	1.775	15.132	325	0.001	31.441	2.078	27.353	35.528
	Fatigue	196	34.032	17.021	1.216	14.613	244.674	0.001	31.441	2.152	27.203	35.679
Cognitive function scale %	No fatigue	130	85.692	17.239	1.512	11.423	323	0.001	26.923	2.357	22.286	31.56
	Fatigue	195	58.769	22.888	1.639	12.074	318.167	0.001	26.923	23.02	22.536	31.31
Sexual function scale %	No fatigue	128	88.997	16.367	1.447	8.192	311	0.001	24.973	3.049	18.975	30.972
	Fatigue	185	64.024	31.68	2.329	9.108	290.671	0.001	24.973	2.742	19.577	30.37
Bodily pain scale %	No fatigue	131	82.924	21.171	1.85	12.938	323	0.001	32.913	2.544	27.908	37.918
	Fatigue	194	50.01	23.347	1.676	13.185	296.503	0.001	32.913	2.496	28.001	37.826

Table 3
Correlation of the level of disability, fatigue, depression and the duration of MS with the HRQoL.

		EDSS	Cognitive fatigue	Physical fatigue	Social fatigue	BDI	Duration of disease
Physical functioning scale	r	−0.541	−0.455	−0.707	−0.651	−0.423	−0.201
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Role-physical scale	r	−0.422	−0.516	−0.655	−0.66	−0.452	−0.209
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Role-emotional scale	r	−0.241	−0.581	−0.578	−0.643	−0.523	−0.153
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.003
Bodily pain scale	r	−0.315	−0.567	−0.66	−0.655	−0.478	−0.138
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.008
Pain scale (Vickrey)	r	−0.304	−0.581	−0.666	−0.674	−0.526	−0.145
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.005
Mental health scale	r	−0.181	−0.556	−0.569	−0.649	−0.716	−0.047
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.367
Vitality scale	r	−0.328	−0.578	−0.723	−0.721	−0.591	−0.125*
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.016
Energy scale (Vickrey)	r	−0.294	−0.577	−0.695	−0.705	−0.591	−0.134
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.01
General health scale	r	−0.358	−0.59	−0.698	−0.712	−0.563	−0.135
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.009
Social functioning scale	r	−0.272	−0.57	−0.643	−0.705	−0.58	−0.11*
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.033
Social function scale (Vickrey)	r	−0.352	−0.605	−0.685	−0.739	−0.588	−0.151
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.003
Cognitive function scale	r	−0.084	−0.764	−0.528	−0.648	−0.603	−0.057*
	p	0.106	0.0001	0.0001	0.0001	0.0001	0.276
Health distress scale	r	−0.292	−0.56	−0.649	−0.701	−0.617	−0.1*
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.053
Overall quality of life scale	r	−0.369	−0.545	−0.617	−0.675	−0.674	−0.133
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.01
Sexual function scale	r	−0.224	−0.442	−0.517	−0.549	−0.486	−0.122*
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.022
Reported health transition scale	r	−0.262	−0.273	−0.412	−0.387	−0.317	−0.143
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.006
Satisfaction with sexual function scale	r	−0.211	−0.406	−0.426	−0.471	−0.525	−0.097*
	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.071

Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

studies did not detect this ratio in patients with MS.

The low prevalence of depression in our study may result from the interaction of a number of factors. The majority of the respondent patients were married with one or two children. However, most of the patients (about 70%) declined to answer questions about their family status. The freely available phone service of multiple sclerosis nurses may also significantly influence the occurrence of depression among patients. This ensures stable and

well-functioning medical support for patients with multiple sclerosis. The participants in this study had a relatively low median EDSS score, indicating a low level of physical disability. If introduced within a few years after the onset of multiple sclerosis, glatiramer acetate not only reduces the activity of the disease, but may also have an antidepressant effect (Tsai, 2007; Johnson, 2012).

Our correlation analysis also demonstrated that depression significantly influences the health-related quality of life.

Table 4
Predictors of the overall quality of life scale by linear regression.

Coefficients ^a					
	Unstandardized coefficients		Standardized coefficients	<i>t</i>	Sig.
	<i>B</i>	Std. error			
(Constant)	18.184	0.306		59.46	0.0001
Depression	−0.394	0.108	−0.155	−3.654	0.0001
EDSS	0.057	0.029	0.152	1.947	0.052
Cognitive fatigue	0.032	0.033	0.094	0.996	0.320
Physical fatigue	−0.148	0.023	−0.785	−6.329	0.0001
Social fatigue	−1.742	0.478	−0.152	−3.643	0.0001

^a Dependent variable: overall quality of life scale (*N* = 349, *R*² = 0.519).

Depression has a strong influence on all aspects of the quality of life, and it can also mask the effects of fatigue, the EDSS score or the duration of the disease on quality of life.

Our results suggest that it is important to diagnose depression among multiple sclerosis patients, since depression can worsen their health-related quality of life, and its presence can influence the choice of immunomodulatory therapy. For patients with multiple sclerosis, who are susceptible to depression, glatiramer acetate is to be recommended since depression may occur as an adverse event of interferon beta therapy.

Depression in multiple sclerosis is often not well-diagnosed, and is not effectively treated (Marrie et al., 2009). The diagnosis is missed in around 23–30% of the cases, and around 20–36% of the patients are claimed to receive inadequate treatment of depression (McGuigan and Hutchinson, 2006). The effective treatment of depression is essential since, if left untreated, it may decrease the level of patient compliance, which may result in the cessation of immunomodulatory therapy.

According to several previous studies, fatigue can decrease the health-related quality of life significantly (Benedict et al., 2005; Janardhan and Bakshi, 2002; Lobentanz et al., 2004; Mitchell et al., 2005). In these studies, fatigue was examined as a one-dimensional factor. Our results are partly contradictory to these findings, which may be explained by our different approach. We examined the three dimensions of fatigue separately, and found that physical fatigue does not predict the quality of life of multiple sclerosis patients. Social and cognitive fatigue, however, exerts significantly negative effects on the health-related quality of life. We cannot measure these with the EDSS, and it is not sure that the patients

Table 5
Predictors of the overall quality of life scale among patients without or with depression by linear regression.

Coefficients ^a					
		Unstandardized coefficients		Standardized coefficients	
		<i>B</i>	Std. error	Beta	<i>t</i>
No depression	(Constant)	18.287	0.312		58.698
	EDSS	−0.436	0.114	−0.186	−3.843
	Cognitive fatigue	0.058	0.031	0.157	1.875
	Physical fatigue	0.023	0.034	0.069	0.661
	Social fatigue	−0.143	0.025	−0.768	−5.780
Depression	(Constant)	14.996	2.238		6.702
	EDSS	−0.102	0.384	−0.046	−0.264
	Cognitive fatigue	0.05	0.094	0.133	0.529
	Physical fatigue	0.115	0.116	0.275	0.998
	Social fatigue	−0.177	0.081	−0.707	−2.200

^a Dependent variable: overall quality of life scale (*N* = 305 and 44, *R*² = 0.448 and 0.170, respectively)

Table 6
Predictors of the cognitive quality of life by linear regression.

Coefficients ^a					
	Unstandardized coefficients		Standardized coefficients	<i>t</i>	Sig.
	<i>B</i>	Std. error			
(Constant)	85.468	2.060		41.499	0.0001
Depression	−10.716	3.389	−0.142	−3.162	0.002
EDSS	1.344	0.744	0.082	1.806	0.072
Cognitive fatigue	−27.332	2.988	−0.55	−9.147	0.0001
Physical fatigue	−2.642	3.693	−0.051	−0.715	0.475
Social fatigue	−6.473	3.891	−0.13	−1.663	0.097

^a Dependent variable: cognitive function scale % (*N* = 276, *R*² = 0.527).

Table 7
Predictors of the sexual quality of life by linear regression.

Coefficients ^a					
	Unstandardized coefficients		Standardized coefficients	<i>t</i>	Sig.
	<i>B</i>	Std. error			
(Constant)	91.62	3.077		29.774	0.0001
Depression	−16.605	5.130	−0.182	−3.237	0.001
EDSS	−1.705	1.121	−0.086	−1.521	0.129
Cognitive fatigue	−14.892	4.468	−0.249	−3.333	0.001
Physical fatigue	0.511	5.503	0.008	0.093	0.926
Social fatigue	−11.049	5.799	−0.185	−1.905	0.058

^a Dependent variable: sexual function scale % (*N* = 271, *R*² = 0.273).

are willing to talk about their social difficulties or about their inability to lead a social life due to multiple sclerosis. We have to consider and strive to decrease the level of social fatigue, and thereby raise the patients' quality of life perceptibly.

In the past decade, various surveys have emphasized the importance of depression and fatigue in multiple sclerosis, showing that these parameters, together with the EDSS score and the disease duration, significantly influence the health-related quality of life of patients with multiple sclerosis (Miller et al., 2003; Pittion-Vouyovitch et al., 2006). Recent studies in Iran and Poland on the

influence of fatigue and depression on the health-related quality of life in multiple sclerosis yielded data that are in line with our results (Kargarfard et al., 2012; Papuc and Stelmasiak, 2012).

5. Conclusions

Our study draws attention to the importance of estimation and follow-up of both social and cognitive fatigue and depression in multiple sclerosis. Besides the determination of the EDSS score, it is necessary to consider these symptoms as parameters, which influence the health-related quality of life. Their treatment adds further values to immunomodulatory therapy, and hence provides a better life for patients with multiple sclerosis.

Competing interests

The authors declare that there is no competing of interest.

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