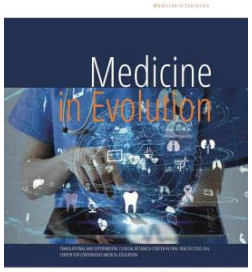
Multiple sclerosis in the context of rare diseases



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Abstract

The study focuses on highlighting the causes that determine the appearance of multiple sclerosis (MS) and on describing the general characteristics of the disease such as pathophysiology or symptomatology, but also on identifying its treatment. An important component of the study refers to the needs and services of the person diagnosed with MS, respectively of their companion. Last but not least, a circumscription of the phenomenon in the Romanian space is considered here.

Keywords: multiple sclerosis, demyelination, axons, immunology, genetics

1. EPIDEMIOLOGY AND ETIOLOGY

Multiple sclerosis is thought to involve an interaction between genetic and environmental factors leading to an immunologically mediated inflammatory response in the central nervous system (CNS). Although immunologic abnormalities have been systematically reported, the relative role of each component of the immune response in mediating tissue destruction and the extent to which these changes are the cause or consequence of myelin damage remain to be established. There is compelling evidence for a genetic susceptibility to MS, and environmental influence on MS is suggested by variations in disease incidence and prevalence across geographic areas.

There is a clear pattern of latitudinal variation in MS prevalence. Epidemiological studies indicate that the prevalence of MS is high (> 30 per 100,000) among young adults in northern Europe, North America and Australasia, moderate (5-30 per 100,000) in southern Europe, southern USA and northern Australia, and is less prevalent in the East, Africa, South America and India. Combined data from epidemiological studies in the USA, UK, Australia and New Zealand show a strong association between latitude and MS prevalence.

MS mainly affects the white race, although it is also known to affect black immigrants living in Europe and North America. In Australia and New Zealand, MS is rarely seen in Aboriginal or Maori people, but it does occur in white people. In South Africa the disease occurs more often among English-speaking whites than among Africans, and is not found among them. Incidence decreases in individuals of northern European descent as we approach the tropics, suggesting that certain environments may be relatively protective. For example, in Australians of Northern European descent and in English-speaking South Africans, the frequency of MS is only half that of Northern Europeans. Age is also a factor in immigrant populations. The risk of MS has been shown to be higher for white, English-speaking South Africans who migrated in adulthood rather than in childhood.

Other evidence supporting genetic susceptibility is provided by epidemiological studies conducted in that setting among ethnic groups. Results of a 1973 study of individuals with MS in Israel showed that the disease was common among immigrants from Europe, and rare among immigrants from Afro-Asian countries. Similarly, immigrants from areas with low MS risk arriving in areas with high MS risk retained the low risk of the area of origin. Familial aggregation studies have shown that approximately 15% of individuals with MS have an affected relative. This risk increases to 1:50 for children of affected individuals and to 1:20 for their siblings. MS is 20-40 times more common in first-degree relatives, decreasing rapidly with the degree of kinship.

Other potential environmental risk factors in MS include infections, vaccinations, stress, climate, and diet. Among these, infection is often considered a presumptive causative agent, especially childhood viral infections. It has been suggested that in countries where the disease is relatively rare, early contact with the causative agent, most likely a virus, protects the population by making it immune. On the other hand, there is some evidence that viral diseases such as measles, mumps, and rubella contracted relatively late in childhood may be a factor in those at risk of developing the disease. In the past decade, several studies have provided preliminary data indicating that environmental triggers that are perceived by the individual as stressful (ex: a broken relationship, job loss) are associated with MS relapses. Evidence for other risk factors such as climate and diet is less compelling [1].

It would therefore appear that MS does not have a single cause. New episodes of demyelination are more likely to follow viral infections or stressful events, but no single trigger may be involved, suggesting that in the context of genetic susceptibility/predisposition, environmental influence and priming immunologically,

demyelination is a physiological response to many pathogens. To summarize, the epidemiological evidence implicates environmental factors, including psychosocial triggers, acting in the context of a genetic predisposition or childhood resistance manifesting as an altered immune response.

2. DISEASE PROCESS

Review of large databases related to patients with MS has provided valuable information related to its natural history. The clinical signs and symptoms of MS are different and several patterns can be identified: benign; relapsing-remitting (RR); a secondary progressive form (SP) and a primary progressive form (PP). The clinical onset in 80 – 85% of MS patients is manifested by subclinical neurological symptoms, either multifocal or anatomically discrete, which may initially disappear completely. This manifestation is often known as clinically isolated syndrome (SCI). Among patients with SCI, approximately 20% had optic nerve lesions, 45% had long tract signs and symptoms, 10% had brainstem syndrome, and 25% had multifocal abnormalities. There are no differences in predictive value between unifocal and multifocal presentation but there is a longer time to second episode in optic neuritis presentation than in all other brainstem or spinal cord presentations. After the onset of SCI, 70% of patients experience new episodes in which MS symptoms worsen and then gradually decrease in severity until the next attack. Patients enter the RR phase. RR episodes usually occur with random frequency, and for unpredictable periods, involving the same or different regions of the CNS. Recovery from these relapses may be incomplete. Over time the symptoms can increase in severity and the disability becomes more pronounced. This RR phase lasts an average of 20 years, being shorter for men and for individuals with MS onset at an older age. The rate and severity of disease progression in the RR phase can vary considerably between patients, with 20–30% of patients continuing to work 20–25 years after disease onset and having minimal cognitive impairment. However, in cases with frequent relapses, the chronically progressive form of the disease may develop. The patient is in the SP phase. The age at which individuals enter the SP phase is independent of the initial course/trajectory of the disease [2].

A small percentage of MS patients (approximately 10%) experience a benign course of MS after SCI; i.e. subsequent episodes are delayed by 5 - 10 years where they have minimal signs and symptoms with each episode. A course of benign MS is significantly associated with female sex, younger ages of onset, and absence of motor symptoms at presentation. On the other hand, about 10% of patients experience a clinical course called primary progressive which is characterized by a progressive accumulation of neurological deficits from the onset without relapses or improvements. This group of patients generally has an older age at disease onset and a lower female predominance than in the general MS population.

In population studies, at any given time, about one-third of individuals are in a quiescent phase of the disease and without significant disability, another third are slowly deteriorating, and the remainder are stable but disabled because they have had the disease for many years. MS generally has a greater impact on the quality of life rather than its duration, with life expectancy decreasing very little in MS patients. However, severely disabled individuals are four times more likely to die than the general population [3].

3. CLINICAL SYMPTOMATOLOGY

3.1. Sensory-motor impairments

Weakness in MS can develop gradually in one or more limbs, increasing with use of that limb and often described as a feeling of heaviness or clumsiness. Depending on the

location of the lesion, signs of an upper motor neuron injury may be present, while involvement of the cerebellum and its connections produces ataxic symptoms that usually occur in combination with corticospinal damage. Spinal demyelination causes progressive weakness in both legs. In individuals with extensive demyelination adjacent to dorsal root entry areas, lower motor neuron signs may be present.

People with MS who experience loss of muscle activation and control often have difficulty taking part in activities of daily living and recreational activities. This fact, in turn, leads to a gradual decrease in physical activity. Physical limitations have been shown to be positively correlated with physiological changes in people with MS, a process similar to that which occurs in healthy people who have had prolonged periods of inactivity [4].

Spasticity (along with fatigue and weakness) is one of the three most common physical signs and symptoms experienced by MS patients. Epidemiological studies show that spasticity is a significant problem for approximately 60-80% of people with MS and is one of the major contributors to the disability of this population. The most widely used definition of spasticity is probably that of Lance (1980): a motor disorder characterized by a rate-dependent increase in stretch reflexes (muscle tone), with exaggerated tendon reflexes resulting from hyperexcitability of the stretch reflex as a component of upper motor neuron syndrome. Increasingly, a distinction is made between resistance to passive movement due to reflex hyperactivity, and resistance resulting from increased mechanical stiffness. The Ashworth scale is the instrument commonly used to measure spasticity, although this scale cannot differentiate between intrinsic muscle stiffness and reflex hyperactivity. The increased resistance to passive movement may be caused by an increase in passive soft tissue stiffness, an increase in stiffness mediated by the stretch reflex, or an increase in intrinsic stiffness that reflects the stiffness of the contractile properties of the involved bridges [5].

Furthermore, passive, intrinsic, and reflex-mediated stretch responses in the ankle extensors and flexors of MS and healthy subjects were measured. The results suggested that spastic muscles in individuals with MS have increased non-reflexive stiffness (passive and intrinsic) and that reflex-mediated stiffness in the ankle extensors during a sustained voluntary contraction did not differ significantly from that of healthy subjects. However, in this study the authors did not directly investigate the passive properties of the muscles because the stiffness measurements were obtained from electrically stimulated muscles – the muscles were not relaxed. Furthermore, the authors examined stiffness at the ankle joint. Ankle stiffness is partly due to stiffness in the muscles but also in other structures that cross the ankle, such as ligaments. A method has recently been developed that allows direct measurement of the passive properties of the relaxed human gastrocnemius muscle. Using this method, it was shown that the passive properties of the gastrocnemius in people with MS (patients are still ambulatory and have spasticity) are no different from those of healthy people [6].

Altered sensation occurs at one stage or another in all individuals with MS. Sensory symptoms such as paresthesia of a limb or face with numbness, tingling or burning sensation may be the first clinical signs. Due to the unpredictable nature of the disease, sensory impairments can affect one limb, one part of the body, or all four limbs. Involvement of the posterior columns of the spinal cord results in disturbances of position and sense of movement, sense of vibration and sense of touch. In MS, the sense of temperature can also be affected, causing the symptoms of sensitivity to heat or cold. Pain is also a common symptom in people with MS. Pain can be a direct result of demyelination and loss of axons (neurogenic pain) or a secondary consequence of other symptoms of MS (nociceptive pain). Several studies have determined that the incidence of pain in any one month period is between 60 – 80% of MS patients. Chronic pain, defined as pain lasting 3 months, is experienced by 65-70% of people with MS. Of these, 60% had chronic dysesthetic pain and 70% experienced episodic

pain. The prevalence of pain tends to increase with age and the number of years since the onset of the disease. Some studies have noted a higher prevalence of pain in women with MS and in people who have moderate to severe mobility restrictions as measured by the Expanded Disability Status Scale (EDSS). However, it is important to note that pain affects people with MS at all stages of the disease, including newly diagnosed people [7].

3.2. Cognitive and affective symptoms

The results of recent reviews suggest that the effect of MS on cognition is both general, all cognitive domains are affected, and specific, effects are greater for the domains of mood, motor functioning, memory or learning. It has been estimated that 40 – 60% of MS patients suffer from memory and learning deficits even in the early stages of the disease. Some clinical observations suggest that slowed mental processing makes it difficult for patients with attention deficits to understand all aspects of a verbal message, especially when it is long, complicated, and delivered quickly in a complex environment. When patients cannot remember what was said or what was happening around them, they and their families interpret this situation more as a memory problem rather than one of slowed information processing. Once patients, their families and professionals understand the nature of the problem, increased attention to how, when and where the information, message and organized activities are delivered can greatly improve patients' 'memory' [8].

3.3. Personality and psychosocial behaviour

In addition to cognitive and affective symptoms, MS can also be associated with a number of behavioral changes. For example, changes in personality, preferences and attitudes tend to accompany attention deficits and distractibility. Individuals with MS describe feelings of mental block, dissatisfaction with themselves, and diminished spontaneity in actions. Individuals with MS have been described as prone to 'euphoria'. Euphoria can be defined as a fixed state of well-being in which patients may express the belief that all is well and that they are physically fit and healthy despite the presence of considerable physical disability. The term euphoria is thus inappropriate when associated with individuals with MS who are trying to face the future with courage. Real euphoria is a relatively rare phenomenon, typically associated with advanced stages of the disease in forms involving the frontal lobes [9].

Depression is said to be more common in MS patients than in those with similar medical disorders. The lifetime risk of depression among people with MS has been estimated at 50%, compared to a risk of 10–15% in the general population. Although this fact is not surprising, and considering that depression is an appropriate reaction to what can be a devastating illness, the occurrence of depression does not appear to be related to the severity of the illness. Recent research suggests that depression develops after the onset of illness and is fairly stable longitudinally. Due to the stability of depression in MS and the fact that it is unlikely to go into remission without treatment, it can have devastating long-term consequences for the patient's daily functioning. Recent work has suggested that anxiety disorders are also common among MS patients, but are often overlooked and poorly treated. Risk factors include female sex, comorbidity of depression diagnosis and limited social support. Fortunately, anxiety disorders are a treatable cause of disability in MS [10].

On the other hand, stress can exacerbate symptoms and precipitate the onset. There is increasing evidence that stressful life events are associated with exacerbations in MS. A systematic meta-analysis of 14 studies identified consistent associations between stressful life events and subsequent exacerbations in MS but no link with specific stressors to exacerbations. From several clinical studies and animal models, it has been suggested that stress may be involved in the reduced sensitivity in glucocorticoid and beta-adrenergic modulation, which may exacerbate the overridden inflammation in MS. The roles of the two

major stress-response systems, the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, are topics of interest in current stress research [11].

3.4. Special senses

Involvement of the visual pathway is very common. The episodic visual blurring so often described by patients early in the disease can worsen later, with some patients losing vision in one eye or experiencing double vision. Deafness is observed more often in patients in whom the disease is stabilized. Acute vestibular symptoms with acute positional vertigo (an illusion of movement in the interaction between the person and the environment), vomiting, ataxia, and headache are common in cases with acute brainstem demyelination. Other senses such as taste and smell may also be involved.

Fatigue is one of the most common symptoms reported in MS, yet the least understood. It can be more debilitating than any of the milder symptoms because it compromises a person's efficiency and sense of well-being. Individuals with MS report that fatigue generally occurs daily, negatively impacts social function, and worsens with temperature. Individuals with MS, their families, and friends may misjudge the impact of fatigue, mistaking it for laziness. Working individuals complain that they have no energy for recreational activities because they need to rest on weekends. Furthermore, fatigue is one of the two major causes of unemployment among individuals with MS. Recent data from an ongoing longitudinal study (Multiple Sclerosis Society of Australia, 1990) involving more than 3,000 patients in Australia show that fatigue and mobility deficits are the main reasons for patients missing work. Many patients are unable to engage actively for more than a few hours without fatigue, and they tend to limit their activity to avoid fatigue and overheating. This creates a vicious circle, with low physical and social activity having a detrimental effect [12].

Four types of fatigue have been described: fatigue following physical exertion, experienced by the general population and disappearing after a period of rest; nervous impulse fatigue following extreme activity which, again, disappears with rest; fatigue related to depression, and associated with sleep disturbances, low self-esteem and mood swings; and malaise, or an abnormal feeling of tiredness of unknown etiology. All four types described can contribute to the fatigue shown in MS. However, the feeling of fatigue or malaise is poorly understood and people with MS seem to be particularly vulnerable to it. However, an additional cause of fatigue is the slowing of nerve impulse transmission on partially demyelinated axons.

Krupp and colleagues designed the Fatigue Severity Scale (FSS), a nine-item questionnaire in which patients rate agreement with statements that distinguish between fatigue in MS and healthy controls. This scale has been shown to have acceptable internal consistency, stability over time, and to reflect the effects of fatigue on daily functioning. Interestingly, Krupp and co-workers found that fatigue severity did not significantly correlate with depression in individuals with MS, suggesting that depression and fatigue are separate, albeit overlapping, entities. Another scale used to measure fatigue in MS is the Modified Fatigue Impact Scale or MFIS. This is a list of 21 statements developed by the National MS Society of the United States, derived from the original 40-item Fatigue Impact Scale. It has been classified as a multidimensional scale and is intended to analyse different aspects of fatigue, measuring the impact on physical, cognitive and psychosocial functioning [10].

Heat, in the form of hot water, overheated rooms, immersion in hot water, and body temperature after strenuous physical activity, increases the level of fatigue and other symptoms of MS, tending to weaken the individual. Increased temperature sensitivity, with reduced safety factor for conduction in partially demyelinated axons, may explain the temporary increase in severity of sensory symptoms immediately after exercise, but is unlikely to cause changes in the sense of fatigue and functional impairment. On the other

hand, the cold might help improve performance. In laboratory models and in a few small studies in people with MS, cooling nerve fibers has been shown to improve the speed at which messages are transmitted along the nerves, and as a result improve symptoms [13].

3.5. Autonomous involvement

Autonomic involvement occurs in most patients with MS. Bladder symptoms are more common in women than in men. Impotence may be prevalent in men. Sphincter control may be lost or impaired. Disinhibition causes the urgency and frequency that lead to incontinence. Bowel incontinence may also be present. Cardiovascular autonomic dysfunction is usually of minor clinical importance. However, orthostatic intolerance may be present in approximately 50% of patients and may be easily detected by routine measurements of resting or standing heart rate and blood pressure [14].

4. MEDICAL MANAGEMENT

There is currently no single laboratory-supported diagnostic test for MS. The diagnosis of MS requires the use of both clinical and paraclinical criteria. The latter involves information obtained by MRI, motor evoked potentials (MEPs) and cerebrospinal fluid (CSF) analysis. Investigations such as MRI, CSF analysis in individuals with MS are used to document the position and extent of lesions, to confirm the presence of intrathecal inflammation, and to rule out conditions that could mimic demyelinating disease. MRI is believed to have increased the accuracy of diagnosing MS from 60% to 90% and appears to be a more sensitive indicator of disease activity than clinical course or neurological examination [15].

New criteria for the diagnosis of MS, integrating MRI assessment with other clinical and paraclinical methods (McDonald criteria), were introduced in 2001. Since then, these criteria have been evaluated and used extensively. The 2005 revisions of the McDonald diagnostic criteria for MS are aimed at simplification and faster diagnosis while maintaining adequate sensitivity and specificity, and are now widely accepted by the neurological community.

Medical treatments in MS can be divided into several categories. The first category involves the use of drug treatments that have an impact on the underlying disease (disease-modifying therapies) that target a certain aspect of the inflammatory process of MS in order to prevent the inflammation that causes relapses. The second category involves drugs that help decrease the severity and duration of MS relapses (steroids) that aim to eliminate inflammation. The third category involves drugs that help alleviate many of the symptoms associated with MS, such as fatigue, spasticity, and pain, to name a few.

A larger body of experimental evidence implicating immunologically mediated processes in the activation of MS progression has led to the search for immunotherapies that not only eliminate acute relapses but also modify disease progression. Consequently, many extensively clinically tested disease-modifying drugs (DMDs) or immunomodulatory treatments for MS have been developed. To date, there is sufficient data to support that the use of DMDs may have an effect in slowing the accumulation of disability over time. Some of these drugs are interferon beta-1a (Avonex or Rebif), interferon beta-1b (Betaseron), glatiramer acetate (Cepaxone), and most recently natalizumab (Tysabri). Each of these drugs works to block different inflammatory pathways, and comparative studies have shown that none is more effective than the others. However, treatment may not be an option for every person with MS. DMDs are most effective in people with RR type MS, while there is no treatment for PP type. Additionally, drug resistance is another concern when using DMDs for long periods of time.

A short course of intravenous methylprednisolone is often used to treat relapses in MS. But there is still no evidence that it influences the final outcomes of the disease, although

it might speed up a stage of remission when given during a relapse. In many cases, after a series of intravenous methylprednisolone, oral prednisone is prescribed and gradually withdrawn. Recent observations suggest that oral prednisone after intravenous methylprednisolone treatment for MS relapse does not lead to an improved neurological outcome compared to intravenous methylprednisolone alone after 12 months [15].

Medicines such as baclofen and diazepam may be helpful in reducing hyperactive reflexes (spasticity). When administered to individuals suffering from severe flexor and abductor spasms associated with spinal cord injury, these agents may reduce hyperactivity sufficiently to allow the individual to stand or sit more comfortably, or be cared for more easily. However, oral medications like these, especially in high doses, can cause severe side effects such as general muscle weakness. Studies of botulinum toxin to relieve abductor spasms report improvement in spasticity in the lower extremities and a significant increase in passive range of motion in the wrists, allowing for easier care and rehabilitation, with no signs of significant side effects from the toxin.

5. MULTIPLE SCLEROSIS IN ROMANIA

According to specialists from the Quality of Life Research Institute, the concept of quality of life refers to the well-being of people in society and indicates the extent to which life is good for them. Being a multidimensional concept, it includes aspects of life such as material living conditions, health, housing, workplace, family life, balance between private and professional life, subjective well-being. Although it is fundamentally focused on the person and the circumstances of his life, the quality of life is closely correlated with the relationship of the person and the community/society in which he lives (e.g. trust in people, institutions), as well as with some elements of society as a whole (eg the quality of public services). Practically, the study of the quality of life gives people "a voice" through which they can evaluate aspects of their lives in the institutionalized framework of science [16].

As Zamfir C appreciates, the quality of life is ensured by all the conditions that offer the person the possibility of a harmonious development, of achieving a full, satisfying life. Starting from this context, we must mention the fact that the research carried out by us takes into account a series of indicators defined by Zamfir C such as: the person himself (health, the ability to establish relationships.); family (health, relationships, free time); the habitat (dwelling, neighborhood, city, neighborhood); work (profession, organization, colleagues); free time, possibilities for personal development (possibilities to develop knowledge, talents, accessibility of education); tone of life (cheerfulness, interesting life); human environment (trust, respect); economic resources; the social environment (the quality of the organization of social life, fairness, equity, safety, the functioning of institutions); economic services (transport, food supply, quality of goods); social services (education, healthcare, administration); participation (the possibility to change things, to have a say) [17].

An important tool for the present research, which is the basis for the construction of the questionnaire and the interview guide, is the Quality of Life Index (World Health Organization Quality of Life WHOQOL) developed by the World Health Organization. It includes six dimensions of quality of life: the physical dimension, the psychological dimension, the level of independence, social relations, the environment and the spiritual dimension [18].

Multiple sclerosis is an autoimmune disease that predominantly affects young adults (20-50 years old), especially women, characterized by chronic inflammation, demyelination and gliosis. The fundamental characteristic is the dissemination of lesions in time and space [19].

In Romania, statistically speaking, multiple sclerosis causes the greatest disability among young adults, affecting more than 7,500 patients in 2016, of which 5,000 accessed the public health system entering the national program. The specialized literature shows a significant reduction in the life span of MS patients between 6-13 years compared to a healthy person. (The "Impact of multiple sclerosis in Romania" study, carried out by EY Romania for Roche Romania)" In our country, there are 13 functional medical units distributed in seven university cities that provide treatment for MS patients:

Bucharest:

- Bucharest University Emergency Hospital - Neurology Clinic;
- Central Military Emergency Hospital "Dr. Carol Davila" Bucharest - Neurology Clinic;
- Colentina Clinical Hospital - Neurology Clinic;
- Elias University Clinical Hospital - Neurology Clinic;
- Fundeni Clinical Institute - Neurology Clinic;
- Clinical Hospital of Psychiatry "Prof. Dr. Alexandru Obregia" Bucharest;
- "Prof. Agrippa Ionescu" Emergency Hospital - Neurology Clinic.

Târgu Mureş:

- Târgu Mureş County Emergency Clinical Hospital.

Iaşi:

- Iaşi Clinical Recovery Hospital

Timiş:

- Timiş County Emergency Clinical Hospital - Neurology Clinic.

Cluj:

- Cluj County Emergency Clinical Hospital - Neurology Clinic.

Oradea:

- Oradea County Emergency Clinical Hospital

Dolj, Craiova:

- Clinical Neuropsychiatry Hospital" [20].

The main problems encountered by MS patients in Romanian society would be: the label placed on them, lack of medication, poor communication between doctors and patients, insufficient treatment centers, bureaucracy in the public health system, lack of useful information about the management of the disease, high financial costs, the reduced number of private providers of social services. The direct costs for 2016 are approximately 272 million RON (60 million EUR) in total or 56,500 RON (12,500 EUR) / year / per patient. The most important cost category is drug treatment, which represents 88% of the total direct costs. Products settled through the national program for MS represent 5.7% of the budget for drugs for high-risk chronic diseases, used in national programs with a curative purpose, reported by CNAS in the reference year of the study [21].

In addition to early detection of the disease and administration of treatment, therapies play a fundamental role in the lives of patients diagnosed with MS. Diagnosed young adults have completed their studies and most are working. After diagnosis, many continue their work at work until the disease progresses and as it progresses, the physical disabilities also increase, thus forcing them to retire. Patients require professional rehabilitation therapies such as physical therapy or occupational therapy in order to maintain dexterity and autonomy. Patients need to develop certain occupations with which to occupy their free time in a pleasant and useful way [22].

Both MS patients and their family need support and specialized social services provided by public or private institutions that have specialized equipment and trained specialists. When the motor disability advances, the MS patient needs services such as physiotherapy and kinesitherapy. Through these services, motor skills are regained, mobility and elasticity are maintained, muscle tone is maintained, fatigue is reduced, memory is

cultivated. Many sufferers have a permanent disability which in countless cases is severe. In this regard, occupational therapy is recommended, which ensures the increase of functional skills, well-being, restoration and gaining independence from household activities such as dressing, feeding, toileting. Psychological counseling of the patient and the family is very important. The adaptation of the family and the patient to the conditions of the disease can be improved by a specialist through group therapies or individual therapies. In training and counseling on the rights and facilities that people with disabilities have from the state, on treatment, information on disease management, procurement of assistive equipment plays an important role to improve the quality of life of the patient [22].

It has been statistically proven that patients who live with their family adapt much more easily to the conditions of the disease and present fewer physical disabilities compared to those who live alone or are isolated from their family. The necessary costs are high for the maintenance of a patient diagnosed with MS, and the family becomes burdened and certain problems arise. These costs increase according to the degree of disability. The first expenses occur with diagnosis, later expenses occur with medical care and recovery. It is very important for the sufferer's family how they manage their financial resources, and they must take into account both the medical costs and the subsequent benefits and improvement in health that result from them. Another dysfunction at the family level is the sufferer's loss of autonomy and partial or total dependence on a family member. Family members go through a mental imbalance alongside the one diagnosed and through a period of accommodation [22].

For this purpose, the Multiple Sclerosis Society of Romania, a non-governmental federation, was founded in 1995. The mission of the federation is to coordinate the national MS movement in order to facilitate certain laws to improve the quality of life of patients through the active involvement of NGOs and the development of partnerships and public policies at the national and international level. To improve collaboration with public authorities; non-governmental organizations; medical and social providers for early disease detection; for the provision of quality social services in order to maintain autonomy and information about the management of the disease and the rights of persons with disabilities; providing support groups for both the patient and the relative. Following the steps taken and following the collaboration with the Ministry of Health and CNAS, the number of patients included in the national program has increased substantially. Within the federation, local organizations and SM day centers were established in counties such as: Alba, Bihor, Năsăud, Botoşani, Bistriţa, Braşov, Constanta, Bucharest, Dolj, Ilfov, Hunedoara, Neamţ, Sibiu, Suceava, Prahova, Timiş, Dâmboviţa, Vâlcea [23].

"The causes of multiple sclerosis are unknown, but most experts agree that they are a combination of a person's genetic predisposition, an underactive immune system, and one or more environmental factors. Possible factors would be:

- Epstein-Barr virus, Chlamydia Pneumoniae;
- Infections in early childhood (measles, chicken pox, scarlet fever);
- Smoking;
- Low level of vitamin D early in life;
- Stress;
- Genetic background;
- Geographical area (the risk of developing MS is higher in regions further away from Ecuador - for example in northern USA, Canada and southern Australia).

A theory would be that individuals who grow up as close to the Equator as possible have more exposure to sunlight which stimulates the body to produce more vitamin D, which can had a protective effect" [22].

Because MS can cause inflammation and demyelination in the central nervous system, the list of possible symptoms is very long. Fortunately, however, most people never experience all of these symptoms, with many exhibiting only a few. Possible symptoms, which can range from mild to severe, include fatigue, vision problems, difficulty walking (caused by balance problems, weakness, stiffness, numbness in the legs), bowel and bladder changes, sexual problems, pain and other sensory changes, tremors, problems with speaking and swallowing, depression and other mood disorders, and problems with thinking and memory. Any of these symptoms can be the first sign of MS, and the challenge for patients is that it is impossible to predict which symptoms will appear, how long they will last or how severe they will be [19].

After the onset of the disease, patients experience a series of changes in cognitive functions and behavior. In MS, disturbances occur in the following aspects of mental life: neurocognitive function; resistance to effort (fatigue); emotions; personality.

A very relevant aspect in the present study is the social life of people diagnosed with MS. We considered that the respondents' social relationships represent important indicators of their quality of life. Our opinion is based on the fact that "(...) social means different types of association, of life in common, even if we are talking about different social groups in terms of size and typology, institutions, organizations or social communities. Any social unit involves a special network between members, status networks, social groups and a certain ranking and structure of component elements" [24].

CONCLUSIONS

Finally, an important component of the study refers to the needs and services of the person diagnosed with MS, respectively of their companion. Education, vocational training and access to the labor market are some aspects captured in the research instruments. From a theoretical perspective, our point of view is based on the fact that "equal opportunities in education means, first of all, equal access to educational resources, a characteristic with a direct effect on school results. This is an important area under the attention of educational policies, considering the fact that school failure is one of the fundamental sources of social exclusion and compromising the social cohesion and human capital of a nation.

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