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The epidemiology of multiple sclerosis, the potential factors causing and affecting the course of the disease.

Epidemiologia stwardnienia rozsianego, potencjalne czynniki wywołujące i wpływające na przebieg choroby.

Summary
Multiple sclerosis (Lat. sclerosis multiplex MS) is a chronic, inflammatory and autoimmune disease of the central nervous system. However, the etiologic factor that initiates the inflammatory and immune response leading to demyelination and, consequently, to the onset of MS still remains unknown. The disease usually begins between 20 and 40 years old, although there are cases among children and elderly. The disease occurs mainly in white race. MS affects nearly two times more women than men. The largest number of cases occurs in the central part of North America, northern Europe, New Zealand and South - Eastern Australia. Poland belongs to the zone of high risk disease.
The etiology of MS is complex and may involve many different factors. The causes of the disease are sought in genetic factors as well as in environmental factors such as viral infections, bacterial infections. Observations indicate that the occurrence of MS is related to latitude, exposure to sunlight, vitamin D, place of birth and migration. It is possible that MS can be affected by factors such as pollution, geological structure, diet, smoking cigarettes. The paper presents the epidemiology of MS and potential factors causing MS and affecting the course of the disease.

Key words: multiple sclerosis, epidemiology, genetics, environmental factors

Streszczenie
Stwardnienie rozsiane (sclerosis multiplex, SM) jest przewlekłą, zapalną, autoimmunologiczną chorobą ośrodkowego układu nerwowego. Nadal jednak pozostaje nieznany czynnik etiologiczny, który zapoczątkowuje reakcję zapalno-immunologiczną prowadzącą do demielinizacji, a w konsekwencji do wystąpienia objawów SM. Choroba najczęściej rozpoczyna się między 20 a 40 rokiem życia, choć zdarzają się przypadki zachorowań już w wieku dziecięcym, a także w wieku późnym. Choroba występuje głównie u rasy białej. Kobiety chorują prawie dwa razy częściej od mężczyzn. Największa liczba zachorowań ma miejsce na obszarze środkowej części północnej Ameryki, północnej części Europy, Nowej Zelandii i południowo – wschodniej Australii. Polska należy do strefy wysokiego zagrożenia chorobą.
Etiologia SM jest złożona i może wiązać się z wieloma różnymi czynnikami. Przyczyn choroby poszukuje się w czynnikach genetycznych, badane są również czynniki środowiskowe takie jak infekcje wirusowe, bakteryjne. Obserwacje

wskazują, że wpływ na występowanie SM ma szerokość geograficzna, ekspozycja na światło, witamina D, miejsce urodzenia i migracje. Możliwe, że na SM mają wpływ też takie czynniki jak zanieczyszczenie środowiska, budowa geologiczna, diety, palenie papierosów. W pracy przedstawiono epidemiologie SM oraz potencjalne czynniki wywołujące SM i wpływające na przebieg choroby.

Słowa kluczowe: stwardnienie rozsiane, epidemiologia, genetyka, czynniki środowiskowe

Introduction

Multiple sclerosis (Lat. multiple sclerosis, MS) is a chronic, inflammatory disease of the central nervous system (CNS) with the demyelination - degenerative substructure and still unexplained (Peterson, et al, 2007). The essence of the disease is multifocal damage to the nervous tissue and destructive multi-phase process, with periods of exacerbation and remission, which is clinically manifested by diverse neurological symptoms.

Currently, there are four types of the course of MS that can be distinguished:

- relapsing-remitting (R-R)
- primary progressive (PP)
- secondary progressive (SP)
- progressive – relapsing (P-R)

Approximately 85% of MS patients begins with relapsing - remitting form (Zakrzewska-Pniewska, 2010). It is characterized by the occurrence of clinically distinctive moves, which are defined as a new neurologic deficit lasting less than 24 hours. At the end there is total or partial relief of symptoms. There is not seen any exacerbation in the remission of that distinctive moves.

Relapses occur with very individual rate, approximately 1 or 2 per year. There are also long periods of remission, when relapses do not occur but can also occur in a few throws per year (Selmaj, 2005).

Approximately 30% of patients have secondary progressive course of MS. In the analysis of the natural history of the disease it has been shown that in about half of patients the initial R - R course changes into SP. This form of MS is characterized by decay of relapses and constant progression of the disease.

The progressive relapsing type of MS occurs simultaneously with its clear progression between relapses (Zakrzewska-Pniewska, 2010). A separate course has a primary progressive type, in which the onset of the disease has no throws and neurological deficit of the disease gradually increases. This form of MS involves 20% of the cases and is usually associated with a late age of developing the disease (Selmaj, 2005).

There are several forms of the disease which differ from the typical course. These include mild form of MS, which is characterized by the absence of significant neurological dysfunction in the 15 years since its beginning.

The malignant form of MS or rapidly progressive (Schilder disease) is characterized by a rapid onset and rapid progression of severe neurological symptoms.

Another variant of MS is inflammation of the optic nerves and spinal cord, known as Devic's disease. It is characterized by the occurrence of spastic paraparesis and blurred vision. It is characterised by quickly recurring throws but there are also cases of a mild (Selma, 2005).

The initial symptoms of MS can include two types of symptoms:

- CIS (Clinically isolated syndrome), which is defined as the occurrence of a single symptom of CNS involvement (75% of cases) or more symptoms simultaneously. Clinically CIS may be manifested as an optic neuritis and Benedikt syndrome or set of single-core symptoms or multi-focal supratentorial structures involvement. Regardless of the type of CIS symptoms risk of developing full symptomatic SM is 45 - 85%. In the patients with CIS with changes in MRI suggesting MS, the risk of MS was 85% and in the presence of protein in the cerebrospinal fluid - until 96% of cases.
- originally a progressive set of symptoms (IP, insidious progression) is a beginning in approximately 15% of patients who then develop a primary progressive form or relapsing-progressive MS. Neurological symptoms in these cases appear and grow unnoticed (primary progressive form) or occur as throws of variable intensity of signs against a clear progression of the disease (progressive – relapsing form) (Zakrzewska-Pniewska, 2010).

The MS consist of many symptoms, some of the symptoms are common and characteristic of the disease, others are rare and unusual.

The most common symptoms are: pyramidal paresis, sensory disturbances, impaired coordination, bowel control, visual acuity (inflammation of the retrobulbar optic neuritis), dizziness, nystagmus, diplopia, dysarthria known also as a fatigue syndrome and cognitive deficit.

Due to very different dynamics of the symptoms and course of MS, there is no single laboratory test or a clinical test that would be sufficient to bring a certain diagnosis. To diagnose MS it is necessary to obtain objective evidence of sclerosis in time and space typical demyelinating lesions of the disease and to exclude other possible causes of the condition. The current diagnostic criteria according to McDonald's modifyfied by POL-MA include the role of research in studio in the diagnosis of MS, particularly magnetic resonance imaging (MRI), cerebrospinal fluid examination, assessment of the presence of oligoclonal bands and IgG index, and visual evoked potentials, VEP (visual evoked potentials) (Ziółkiewicz et al, 2011).

Epidemiology

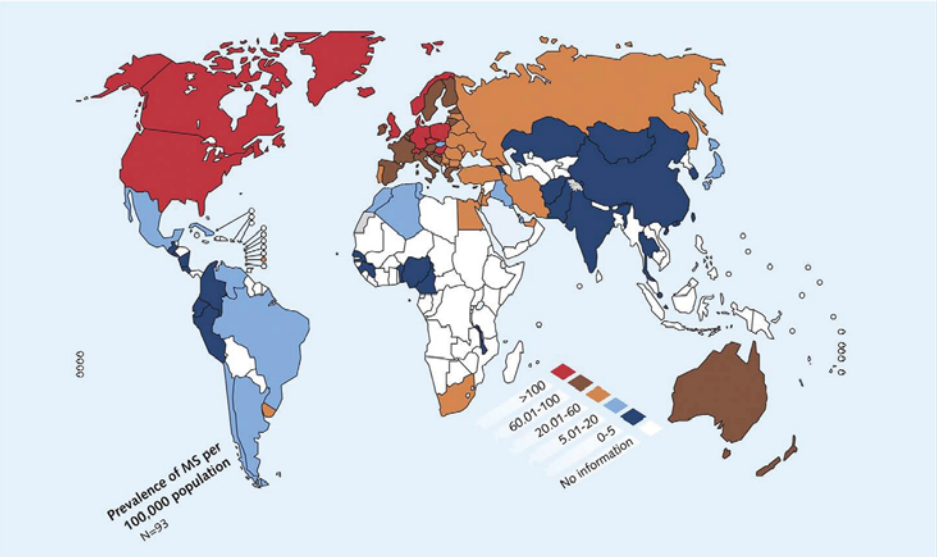
The total number of people living with MS across the world is estimated at 2 - 2.5 million (Milo et al, 2010).

The disease usually starts between 20 and 40 years of age. Rare disease starts before the age of 16 (2.4 - 4.4% of the total) and the 50 (10% of all cases) (Pierzchała et al, 2009). If the disease occurs before the age of 16 is defined as children's form of MS.

Women suffer more often than men, a ratio of 2:1. MS is very common among the Caucasoid race and much less common among the Negroid and mongoloid race (Selmaj, 2006).

Multiple sclerosis is characterized by uneven geographical distribution. There is a high correlation between disease incidence and latitude. Incidence of MS increases with increasing of latitude. In the northern hemisphere areas of high prevalence rate are those occurring between 44° and 64° latitude, and moderate risk areas are located between 32° and 44° (Selma, 2006). A similar situation occurs in the southern hemisphere. The highest incidence occur in cool and temperate climates.

Prevalence rate in the world ranges from 15 to 180 per 100 000 people (Uchman, et al), the highest is in the middle of the North America, the northern and central parts of Europe, New Zealand and South - Eastern Australia.



Differentiation of MS prevalence in the world
Source: Atlas Multiple Sclerosis Resources In The World, 2008

In northern European countries such as the United Kingdom, the number of cases is 100 - 112 people per 100 000 inhabitants (Rosiak et al, 2012). The lack of reference to the geographical area was observed in Italy, where the prevalence is as high as in Germany. Despite the geographical conditions similar to areas at high risk such a correlation does not exist in Japan, which has a low incidence - 1.4 / 100 000 inhabitants (Rosiak et al, 2012). Various factors of prevalence were observed in areas which are located in short distances - Sicily (54/100, 000) and Malta (8/100, 000) (Pierzchała et al 2009).

Due to uneven incidence of MS on the Earth it is quite difficult to estimate the average incidence of MS in the world.

Based on epidemiological data available from 1966 trouhg 2007 incidence rate of MS per 100 000 inhabitants can be estimated at 3.6 (95% confidence interval (95% CI) 3.0 - 4.2) among women and 2.0 (95 % CI 1.5 - 2.4) among men (Alonso, et al, 2008).

In this study it was found that the highest incidence rates - standardized to the age of the population - were observed in Seinajoki (Finland) in the years from 1977 to 1993 and they amounted to 10.3 (women) and 6.2 (men) / 100 000 inhabitants. Large increase in incidence was also found in Sicily e.g. Caltanissetta from 1999 to 2002, it was 12.4 (women) and 7.0 (men) / 100 000 population (Alonso, et al, 2008).

In Europe and the United States, the incidence is 3 - 5 cases per 100 000 inhabitants (Zakrzewska-Pniewska, 2010).

Epidemic outbreaks (called clusters) are geographically limited areas in which the incidence of MS high. On the basis of epidemiological studies it was found that these areas are Scandinavia, Iceland, the Shetland Islands and the Faroe Islands (Zakrzewska-Pniewska, 2010).

The Orkney and Shetland prevalence rate reached the highest value in the world, reaching 258/100000 inhabitants (Potemkowski, 2001).

Poland is among the countries with high prevalence. The number of people suffering in our country is unknown which is caused by the lack of the statistics.

In Poland, there was no epidemiological research covering the whole country, given the prevalence rate is different and ranges from 45 to 92 per 100 000 inhabitants (Uchman et al, 2012).

The estimated data indicates 1300 to 2100 new cases per year in Poland, the majority of women to men 2:1 (Potemkowski, 2009).

On the basis of analyzing the epidemiology of MS conducted in Lublin (prevalention day is scheduled for 31.12.1997) prevalence rate was calculated for the entire population of patients in the city in 57.3 / 100, 000, for the ill women 74.3 / 100 000, for ill men 37.9 / 100 000. The ratio of women patients and male patients was 2,24:1. The incidence rate in 1990-1995 was 1.7/100 000, for the population of ill patients / 100, 000 for women 2.05 / 100, 000, for men 1.31 / 100 000. The average age of onset of MS in the general population was calculated at 30.1 years (30.4 years for women, men 29.9 years). Early disease occurred at 5-year-old girl and 52-year-old woman (Łabińska et al 2004).

Prevalence rate for Leszno in 1981 was 117.12 / 100 000, in 1991 for Gniezno 89.3 / 100 000, in 1992 for Szczecin 81.26 /100 000 inhabitants (Łabińska et al, 2004).

Studies conducted in selected areas of Poland (1995), on the border of the former voivodships of szczecinskie and gorzowskie, show a seat of SM, where prevalence rate was 110.54 and it was twice as high than in eight control regions. Prevalence rate of women 141,24 / 100 000 was almost twice as high as men 79.74 / 100 000. For other areas, this ratio stood at 61.14 / 100 000 women and 44.29 / 100 000 men (Potemkowski, 2001).

The first nationwide study on a large scale was a multicenter pilot study (according to the estimates were included in the 18% of patients with MS) which the demographic profile of patients was analyzed, medical history of MS, disability, comorbidities, diagnostic methods and treatments used. The data obtained about 3581 patients, 2494 women (69.6%) and 1030 men (28.8%) - sex ratio: 2.4 : 1. The mean age was 40.7 ± 11.9 years. The monofocal beginning was noted in 80.8% of cases, frequently indicated was the location of supratentorial faults (36.1%), then were taken optic nerves (26.5%) and spinal cord (29.1%). The disease took an average of 10.2 ± 8.8 years (range 0,04-53 years), and from the first symptoms to diagnosis was passing an average of 2.6 years. Familial SM was observed in 6.4% of cases. Relapsing – remitting form of MS patients was 70.5%, secondary progressive - 16.8%, primary progressive 8.45, 2.55 au diagnosed with “mild” SM (Kułakowska et al, 2010).

Data on the prevalence and incidence of MS among children is mixed. This data is largely retrospective or based on an analysis of the adult population, and it is difficult to accurately assess the risk of both disease and its incidence to children. According to the latest estimated prevalence of MS among children for about 2 to 10/100, 000 annually. Analysis of a large

population of patients with MS showed that in 2 - 10% of all patients, the disease began before age 18. About 3 to 10% of cases begins in childhood and adolescence, less than 2% below 10 years of age and in 3% of the average of between 8 - 14 years of age. Examining 49 children with onset before age 6 was found that more than 10% of them onset occurred between 10 and 23 months of age. MS in children is three times more common in females, the male advantage is only seen in children under 10 years of age (Wilczek, 2010).

Immunopathogenesis of MS

Currently, there is widespread belief that the development of MS occurs as a result of a pathological activation of the immune system. An important role in the development of MS is attributed to specific for myelin proteins autoreactive CD4 + T cells. The activity of these subpopulations of CD4 + T cells in the central nervous system can affect the pathology and clinical course of MS (Zawada, 2012). CD4 + subpopulation of patients with MS is characterized by inflammation after the process Th1 cytokine profile, over-expression of encoding genes proteins and anti-apoptotic molecules deficient synthesis of interferon beta. It is believed that the CD4 + T-cell activation may occur in parallel by two mechanisms: non-specific activation of the inflammatory process associated infections and the specific activation by an infectious agent by the similarity of the antigen (molecular mimicry) (Zakrzewska-Pniewska, 2010). Activated T cells have the ability to move through the blood-brain barrier, infiltration of the CNS, proliferate in response to antigen specific stimulation repeated then activated microglia and other immune cells through the release of pro-inflammatory cytokines, which leads to demilizational-axonal damage (Yong et al, 2010). Potential triggers of MS and affect the course of the disease.

The etiology of MS is not fully understood. Research on the detection of the cause of the SM showed no specific causative agent of disease.

Many studies have shown that genetic factors play a role in the development of MS. Demonstrated a higher incidence of cases of MS in relatives of patients with MS than in the general population. In first-degree relatives the risk is 10-20 times higher in relation to the population risk, and for second-degree relatives about 3 times larger. The present study identified a number of genes associated with susceptibility to MS. The most important relationship between the presence of SM and genes of the HLA class II and above all by the presence of HLA allele DRB1 * 1501 (Sospedra, et al, 2005).

It is believed that an important role in the development of MS remain infection, probably viral nature. They may be involved in the initiation of disease with genetic factors and lead to the development of an autoimmune reaction resulting in the formation of demyelination, and clinical symptoms. Observations indicate a strong relationship between viral infections and deterioration of the SM (Losy, 2009).

For viruses suspected of compounds with the development of human SM exchanged herpes virus 6 (HHV-6), Epstein-Barr virus (EBV), varicella zoster (VZV) and human endogenous retroviruses (HERV).

HHV-6 is a human herpes virus type 6. It is responsible for two entities: a sudden rash in children (also called a three-day illness) and mononucleosis-type syndrome in adults. The virus is widespread - over 95% of people (usually in childhood) is infection of HHV-6. MS patients found to have high titer antibodies against HHV-6.

Epstein-Barr virus (EBV) causes infectious mononucleosis. EBV virus is very common in our population. People with SM probably suffered previously mononucleosis, and higher antibody titers against EBV is associated with an increased risk of developing MS. Elevated levels of these antibodies are detected many years before the onset of MS.

Chickenpox is caused by VZV (herpes virus varicellae). After an illness varicella virus takes hidden the form. When it comes to lowering the immune system it can lead to reactivation of the virus and the development of shingles. Epidemiological studies of the areas where the occurrence of MS has increased in recent decades have shown a high incidence of zoster in patients who later developed MS. It is also suggested that the human endogenous retroviruses may be the causative agents of diseases characterized by inflammation, and activation of macrophages, as it happens in MS (Zawada, 2012).

Vitamin D is an important compound of regulating the immune system. Vitamin D deficiency caused by insufficient exposure to sunlight increases the risk of developing MS. The need for vitamin D is about 5 g per day. About four fifths of the dose is synthesized in the body when exposed to sunlight, and the fifth the dose should come from a diet.

Studies of vitamin D concentrations in serum of patients with MS show that the level is decreased in most patients. It has been shown while young healthy person observing, that in those patients who had a concentration of 25-OH D3 than or equal to 99.2 nmol/l risk was about 62% lower compared to those in whom the level of 25-OH D3 was less than 63,3 nmol/l (Ascherio, 2010). Studies conducted in Canada involving children from the first group of MS symptoms (clinical isolated syndrome - CIS), shown at 100% of children decreased levels of 25-OH D3 in serum. Through years of observation vitamin D3 was used in children. In 16% of the patients to the development of MS in them had lower levels of serum vitamin than other people (Pierzchała et al, 2009). The assumption linking vitamin D deficiency and the risk of MS is consistent with the observed geographical distribution of the disease. People living above the 40 parallel of northern and southern hemispheres, are at risk of deficiency of solar radiation and thus reduce the level of vitamin D. It is in these areas have the highest incidence.

Epidemiological studies have shown that an important role in SM is taken by place of birth and time of migration. Migrants at the age of 15 remain prone to the disease characteristic of the place of their birth. Conversely, migrants from the age of 15, which have a tendency to disease characterised by migration. It is suggested that those born in spring more likely to be ill that those born in the autumn.

Important environmental factors that may influence the occurrence of MS are geological conditions. The presence in soil and drinking water of heavy metals: cobalt, molybdenum, barium, copper oxide, chromium may predispose to collapse MS. The risk of MS is increased in people living in areas rich in peat. It was hypothesized by which heavy-metal compounds or mixtures of aromatic compounds can form haptens body proteins that cause autoimmune reactions. Similarly, can act aromatics, nitrophenols contained in the resin of coniferous trees (Rosiak et al, 2012).

During pregnancy, the incidence of relapses decreased 3 times, respectively, compared with the period before pregnancy. The deterioration was observed during the first three months after birth.

The results suggest that unsaturated fatty acids have a positive effect on the course of MS, while receiving large amounts of saturated fatty acids, may increase the risk of developing MS. A role in the diet is attributed to vitamin D, its adoption is associated with a lower incidence of MS, as well as a less activity of disease.

The role of macro- and micronutrients, antioxidants, various vitamins is not confirmed unequivocally. The only malnutrition may exacerbate the disease. The use of special diets (avoidance of polyunsaturated fatty acids) is a procedure that supports and supplements the treatment.

Other factors which can provoke or affect on MS can be pollution, hormones, smoking cigarettes.

Results

Multiple sclerosis is a complex disease of unknown etiology. Number of patients worldwide is estimated at 2 - 2.5 million. Women have a higher prevalence of MS than men. In Poland, there was no epidemiological research covering the whole country. The prevalence rate is mentioned in different ways and ranges from 45 to 92 per 100 000 inhabitants. SM development involves overlapping immune factors, genetic and environmental factors. Information shown above illustrates how complicated medical problem MS is. The research on these factors that provide new information, bring us closer to understanding the mechanisms of the growth of MS.

Bibliography

1. Alonso A., Hernán MA. (2008) Temporal trends in the incidence of multiple sclerosis: a systematic review. "Neurology" 71: 129-135.
2. Ascherio A. (2010) Witamin D deficiency as a risk factor. Multiple Sclerosis 16: S7-S39.
3. Kułakowska A., Drozdowski W., Bartosik-Psujek H., Stelmasiak Z., Mitosek-Szewczyk K., Hożejowski R. (2010) Wybrane aspekty epidemiologiczne stwardnienia rozsianego w Polsce – wieloośrodkowe badanie pilotażowe. „Neurologia i Neurochirurgia Polska" 44(5): 443-452.
4. Losy J. (2009) Rola czynników immunologicznych i zapalnych w patogenezie stwardnienia rozsianego. "Polski Przegląd Neurologiczny" 5(4): 159-165.
5. Łabińska A., Stelmasiak Z. (2004) Wybrane epidemiologiczne aspekty stwardnienia rozsianego w populacji miasta Lublin. "Neurologia i Neurochirurgia Polska" 38(5): 361-366.
6. Milo R., Kahana E. (2010) Multiple sclerosis: Geoepidemiology, genetics and the environment. "Autoimmunity Reviews" 9: A387-A394.
7. Peterson LK, Fujinami RS. (2007) Inflammation, Demyelination, Neurodegeneration and Neuroprotection in the Pathogenesis of Multiple Sclerosis. "Journal of Neuroimmunology" 184: 37 - 44.
8. Pierzchała K, Kubicka K. (2009) Rola czynników środowiskowych w patogenezie stwardnienia rozsianego. "Wiadomości lekarskie" LXII,1: 37- 41.

9. Potemkowski A.(2001) Analiza epidemiologiczna ogniska stwardnienia rozsianego na terenie byłego województwa szczecińskiego. ” Przegląd Epidemiologiczny” 55(3): 331- 341.
10. Potemkowski A.(2009) Stwardnienie rozsiane w Polsce i w świecie. ”Aktualności Neurologiczne” 9: 91-97.
11. Rosiak K., Zagożdżon P. (2012) Czynniki środowiskowe w epidemiologii stwardnienia rozsianego. ”Problemy Higieny i Epidemiologii” 93(4): 627-631.
12. Selmaj K. (2005) Stwardnienie rozsiane – kryteria diagnostyczne i naturalny przebieg choroby. ”Polski Przegląd Neurologiczny” 1(3): 99 –105.
13. Selmaj K. (2006) Stwardnienie rozsiane. Wyd. Med. Termedia, Poznań: 10 -105.
14. Sospedra M, Martin R. (2005) Immunology of multiple sclerosis. ”Annu. Rev. Immunol.” 23: 683-747.
15. Uchman D., Kochanowski J., Baranowska B. (2012) Stwardnienie rozsiane – teraźniejszość i przyszłość – sukcesy i porażki. ”Postępy Nauk Medycznych” supl. 3: 22-26.
16. 16.Wilczek A. (2010) Stwardnienie rozsiane u dzieci: objawy kliniczne, diagnostyka, różnicowanie i leczenie. ” Neurologia Dziecięca” 37(19): 75-82.
17. Yong VW, Marks S. (2010) The interplay between the immune and central nervous systems in neuronal injury. ” Neurology” 74 (suppl 1): S9-S16.
18. 18.Zakrzewska-Pniewska B. (2010) Podstawy diagnostyki i leczenia stwardnienia rozsianego. Via Medica Gdańsk: 3-26.
19. Zawada M. (2012) Potencjalne czynniki patogenne w stwardnieniu rozsianym (SM). “Postępy Hig Med Dosw” 66: 758-770.
20. Ziółkiewicz J, Kaźmierski R. (2011) Ewolucja kryteriów diagnostycznych stwardnienia rozsianego. „Neuroskop” 13: 112-119.

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