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Multiple sclerosis and pregnancy

Stwardnienie rozsiane a ciąża

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Summary

Multiple sclerosis (MS) is the most common demyelinating condition of the central nervous system. According to the Polish Association for Multiple Sclerosis, MS is the most common cause (excluding injuries) of disability in young adults. Its etiopathogenesis is complex and can be associated with multiple factors acting together or in a cascading manner, leading to the development of the disease. Genetic, environmental and infectious factors are taken into account. Despite intensive worldwide research attempts to develop treatment that would completely halt the progression of MS and prevent disability have not succeeded. Multiple unknowns about the MS and its course were probably the main reason behind healthcare professionals' negative attitude towards female MS patients planning to become parents. The PRIMS (Pregnancy In Multiple Sclerosis) multicenter prospective clinical study has completely changed the views on pregnancy in female MS patients. The research clearly demonstrated that pregnancy decreases the risk of relapse and progression during its course, while the increased risk of relapse during the first three months after delivery has no negative impact on the degree of disability compared to women who have never been pregnant. The analysis of this phenomenon is the subject of extensive research and new concepts in the field of MS treatment.

Streszczenie

Stwardnienie rozsiane (łac. *sclerosis multiplex* – SM), jest najczęstszą chorobą demielinizacyjną ośrodkowego układu nerwowego. Według Towarzystwa Stwardnienia Rozsianego jest to najczęstsza przyczyna (z wyjątkiem urazów) niepełnosprawności młodych dorosłych. Etiopatogeneza choroby jest złożona i może się wiązać z wieloma różnymi czynnikami działającymi jednocześnie lub kaskadowo, prowadząc do rozwoju choroby. Pod uwagę brane są czynniki genetyczne, środowiskowe oraz infekcyjne. Pomimo intensywnych badań prowadzonych na całym świecie dotychczas nie udało się opracować terapii pozwalającej całkowicie zatrzymać postęp choroby i uchronić pacjentów przed wynikającą z niej niepełnosprawnością. Wiele nieznanych jeszcze przyczyn związanych z SM i jego przebiegiem było przyczyną negatywnego nastawienia lekarzy do planów prokreacyjnych chorych pacjentek. Doniesienia z wielośrodkowego prospektywnego badania PRIMS (ang. *pregnancy in multiple sclerosis*) całkowicie zmieniły zapatrywanie na ciążę u kobiet z SM. Ponad wszelką wątpliwość wykazano, że ciąża zmniejsza ryzyko rzutów i postępu choroby w trakcie jej trwania, zaś zwiększone ryzyko rzutu w pierwszych trzech miesiącach po porodzie nie wpływa negatywnie na stopień niepełnosprawności w porównaniu do kobiet, które nigdy nie były w ciąży. Analiza przyczyn takiego stanu jest przedmiotem wielu badań i nowych koncepcji na sposób leczenia SM.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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INTRODUCTION

Multiple sclerosis is a multifactorial disease characterised by inflammatory, neurodegenerative lesions as well as impaired repair mechanisms in the central nervous system. The aetiology of MS is complex and probably involves a number of different factors acting together or in a cascading manner, leading to the development of the disease (1).

The disease usually manifests in individuals between 20 and 40 years of age, however, MS symptoms can develop in people of all ages. MS is more common in women. It seems that there has been a continuous rise in the female-to-male MS ratio (2, 3), which is estimated to be approximately 2.67:1 (3). The neuromodulatory role of sex hormones is probably the reason

for this disproportion. Also, a relationship is observed between gender and age of onset. The onset of symptoms usually occurs between 18 and 30 years of age in women and between 30 and 40 years of age in men.

The prevalence of MS varies in different latitudes. MS is more common in regions with lower sunlight exposure, and thus higher vitamin D deficiency (1, 4). The role of sunlight exposure has been confirmed in studies in monozygotic twins, comparing the incidence of MS in siblings (5). It was found that low vitamin D levels (hypovitaminosis D) are related to increased MS incidence (6). Studies on serum vitamin D levels in MS patients demonstrated that vitamin D deficiency occurs in most patients, even in the earliest stages of the disease (7). Furthermore, it seems that appropriate vitamin D supplementation can alleviate the disease (8).

Genetic factors also play a role in MS aetiology. The causes of the disease are also sought among HLA factors, genes for T cell receptors and endogenous viruses contained in the human genome (1).

The impact of Chronic Cerebrospinal Venous Insufficiency (CCSVI) is also contemplated (9). This theory seems to be most controversial due to different views on MS pathogenesis, and thus a different approach to MS treatment. As a result of this controversy, the FDA published an official statement warning patients against the risks involved in the invasive treatment of unconfirmed efficacy (10).

SYMPTOMS

MS symptomatology can vary considerably. Periodic neurologic symptom recurrence or increase (i.e. relapses) is a constant characteristic of the disease. Periods of complete or partial remission are observed between relapses. The most common symptoms include visual disorders (including optic neuritis, diplopia, nystagmus), autonomic disorders (bladder dysfunction affects 80% of patients) (11), impaired sensation (paraesthesia, heat intolerance) as well as motor, cerebellar, cognitive and mental disorders.

DIAGNOSIS

The initial diagnosis is usually based on the characteristic clinical picture, i.e. manifestation of symptoms in the form of relapses and remissions. First MS signs are often ignored by patients. A thorough medical history allows to identify relapses long before the diagnosis.

Additional tests help confirm the initial diagnosis. MRI of the central nervous system reveals typical multifocal demyelination of the white matter. Oligoclonal proteins are found in the cerebrospinal fluid in approximately 80% of MS patients (12, 13). Prolonged latencies in the evoked potential (EP) tests can indicate demyelination even in asymptomatic patients (14).

TREATMENT

There is no effective treatment for MS. Intravenous corticosteroids are usually administered during exacerbations. If their efficacy is insufficient, plasmapheresis and intravenous immunoglobulins can be considered. Although there are a number of disease modifying treatments available, none of these is able to completely halt the progression of the disease. It should also be noted that none of these preparations is approved for safe use in pregnant or breastfeeding patients.

Symptomatic treatment aimed at alleviating current symptoms (bladder dysfunction, spasticity, tremor, pain and many more) is also important. MS patients should receive continuous, individualised rehabilitation care aimed at improving the quality and length of life.

THE EFFECTS OF PREGNANCY ON MS

For years, attempts were made to confirm the negative effects of pregnancy on MS and vice versa, which resulted in the discouragement of family planning among patients of childbearing potential (15). This view started to evolve in the 90's and was completely abolished in 1998, when first PRIMS reports were released (16).

PRIMS was the first large prospective, multicenter study which aimed to assess the possible influence of pregnancy, delivery and postpartum period on the clinical course of multiple sclerosis. The clinical status of women in different trimesters of pregnancy as well as two years after delivery was compared to their clinical state in the year before pregnancy. A total of 227 females meeting the Poser's diagnostic criteria for multiple sclerosis were included in the study (17). The degree of disability was assessed by the Disability Status Scale (DSS), which involves an assessment of 8 functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, mental, and others. DSS uses a symptom severity rating scale ranging from 0 to 10, where 0 stands for absence of any symptoms, while 10 stands for death due to MS (18). The occurrence, recurrence or exacerbation of symptoms persisting for more than 24 hours was considered a relapse.

The study clearly demonstrated a reduction in MS relapse rate compared to the year before pregnancy (19). Interestingly, MS symptom reduction was so high that it could not be achieved using any treatments outside pregnancy (20) and was most pronounced in the third trimester.

Although the risk of recurrence is significantly increased during the first three months postpartum, MS relapse did not occur during this time in 72% of women. Between months 4 and 24 postpartum, the severity of symptoms did not differ from that in the year before pregnancy (19).

Three potential prognostic factors for relapse in the first three months postpartum were identified. The risk was increased:

- 1.7-fold with each relapse experienced during the pre-pregnancy year,
- 1.8- fold with each relapse during pregnancy,
- in women with higher DSS score at pregnancy onset (19).

The following factors had no effect on relapse in the early postpartum period: breastfeeding, epidural analgesia for labour, the age at which first symptoms occurred, number of pregnancies, total number of relapses in the period between diagnosis and pregnancy as well al child's sex (19).

The immunomodulatory effects of estrogens and other pregnancy hormones on Th1/Th2 balance seems to be the most probable theory accounting for the protective effects of pregnancy on MS (20, 21). Therefore, researchers are seeking new therapeutic strategies by combining disease-modifying therapies (DMT) with combined oral contraceptive pill (22) or estriol (8 mg/day) (23). These findings are very promising, but yet insufficient to introduce a new standard of therapy.

Furthermore, some studies indicate that pregnancy has beneficial long-term effects on the clinical course of MS. A long-term observational study in 200 patients showed that the degree of disability requiring the use of a wheelchair was reached significantly later by women with at least one pregnancy. Women with children began to use a wheelchair after an average of 18.6 years, whereas females who had never been pregnant – after 12.5 years from the diagnosis (24).

There is an ongoing research to find treatment that could prevent MS exacerbation during the early postpartum period. There are promising reports on reduced relapse rate in females receiving intravenous immunoglobulins (IVIG) both during pregnancy and after delivery (25, 26). There is also an ongoing clinical trial (Prevention of Post-Partum Relapses with Progestin and Estradiol in Multiple Sclerosis – POPART'MUS) aimed at assessing the efficacy of oral nomegestrol and transdermal estradiol vs. placebo in decreasing MS relapse rate in the early postpartum period (27).

THE EFFECTS OF MS ON PREGNANCY

Many MS women resign from having children for fear of potential adverse effects on the course of pregnancy. The disease itself does not increase the risk of maternal or foetal complications (20). No increase in the incidence of miscarriages, birth defects, stillbirths or infant mortality was found in MS patients (28). The potential occurrence of complications depends on the level of disability at the time of becoming pregnant. Urinary tract disorders, which can increase during pregnancy, are more common in females with higher degree of disability. The risk of thromboembolic complications is additionally increased during pregnancy in patients with impaired mobility. However, it should be noted that adequate perinatal care allows to predict the risk of potential complications and implement measures to reduce the risk of their actual occurrence.

The data on the impact of MS on delivery are contradictory. Finnish studies reported an increase in instrument-assisted deliveries in MS patients compared to healthy population (16.4 vs. 6.5%, respectively) (29). However these findings are contradicted by a report from Canada (30). The study showed no increased risk of instrument-assisted labour, but an increased risk of perinatal complications was shown in females with significant disability.

In light of these data, there is no reason to discourage MS patients from becoming parents. It should be noted, however, that pregnancy should be carefully planned, and the patient should receive a comprehensive multidisciplinary care.

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