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The influence of sex hormones on clinical and radiological activity in multiple sclerosis.

INTRODUCTION:

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS). Inflammatory (including autoimmune) and neurodegenerative processes are involved in the pathogenesis of MS. The first symptoms most often occur between of 20 and 40 years of age. The disease is considered to be the most common non-traumatic cause of disability among young adults with incidence in Europe estimated at 108/100,000. There is a significant predominance of women suffering from MS with incidence three times higher than in men. Additionally, differences in clinical course and severity of MS between women and men are linked with hormonal changes during puberty, pregnancy, menopause as well as endocrine disorders such as hypogonadism. It suggests the involvement of sex hormones (SH) in the regulation of the pathological mechanisms of the disease. However, male gender is considered as a risk factor for faster progression of neurological disability in MS, which is associated with greater severity of gray matter atrophy. These data also suggest that SH may serve as predicting factors of the severity of progression of MS and biomarkers useful for monitoring treatment efficacy.

Sex hormones have immunomodulatory and neuroprotective effects.

TESTOSTERONE:

Male sex hormones play an important role in the process of neuroregeneration, including remyelination. The action of testosterone in the CNS takes place through two main mechanisms: (1) binding to the intracellularly located androgen receptor (AR), and (2) through conversion with the participation of aromatase to estradiol. The effect of testosterone is the propagation of the influx of astrocytes, which influence the proliferation and differentiation of oligodendrocyte progenitor cells necessary for the repair of myelin sheaths in the CNS.

ESTROGENS:

Activation of estrogen receptors (ER) has anti-inflammatory and preventive effects on neurodegeneration. In an animal model of MS (Experimental autoimmune encephalomyelitis, EAE) in the third trimester of pregnancy, a decrease in disease activity and its sudden deterioration in the postpartum period were demonstrated, which may be related to the increase in estriol concentration in the last weeks of pregnancy and its decrease following delivery.

LUTEINIZING HORMONE (LH):

Estradiol and luteinizing hormone are linked by negative feedback. Also, an experimental study showed that low LH levels are associated with increased spatial memory. There is data suggesting that memory disorders observed in postmenopausal women may result from high LH levels and that reducing them will improve memory.

FOLLICLE-STIMULATING HORMONE (FSH):

FSH hormone activates its receptor expressed in the hippocampal and cortical neurons. In animal model of Alzheimer's disease blockade of FSH signalling resulted in signifficant improvement of cognitive functions.

PROGESTERONE:

Progesterone in the CNS has anti-inflammatory and neuroprotective effects. Moreover, the ratio of estrogen to progesterone concentrations seems to be important. A high value of the concentration ratio of these hormones is positively correlated with radiological activity in MS patients.

The aim of the study is to assess the relationship between the level of the most important sex hormones (testosterone, estradiol, progesterone) in the serum and the clinical and radiological progression of the disease in patients with multiple sclerosis, taking into account the response to therapy with disease modifying therapy (DMT).

HYPOTHESES:

Sex hormones are involved in the regulation of the pathological process in MS in a gender-specific manner.

The level of individual sex hormones in MS patients in the early phase of the disease correlates with the relapsing activity of the disease.

The level of individual sex hormones in MS patients correlates with the radiological activity of the disease.

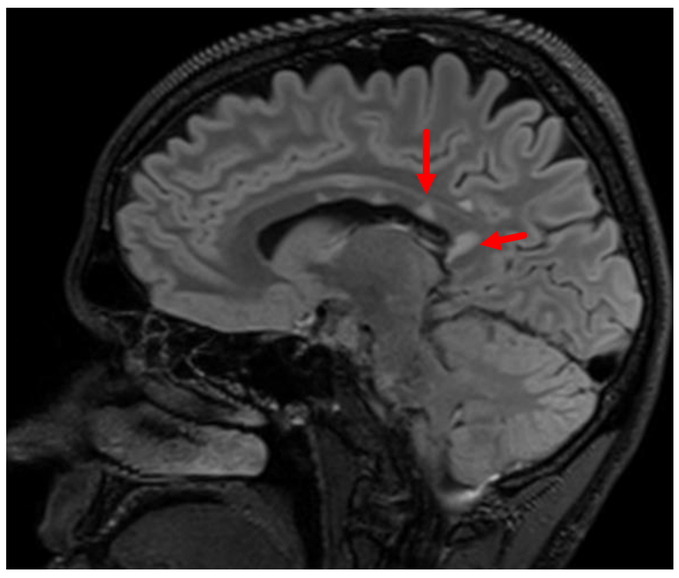
Correlation of sex hormone levels, clinical and radiological data will allow the creation of prognostic algorithms for disease activity and progression in MS patients.

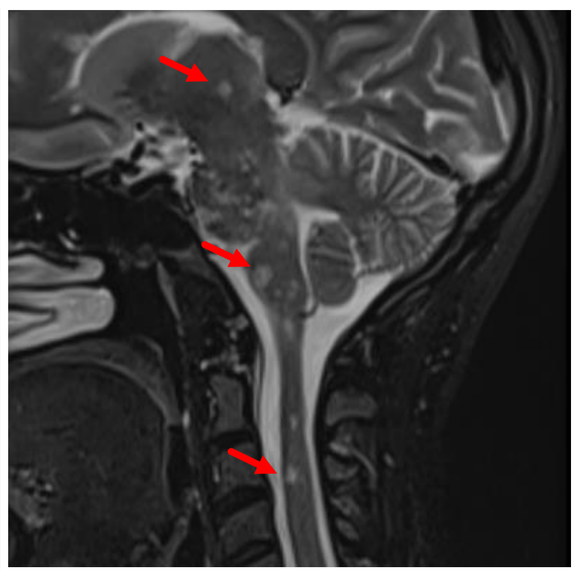
METHODOLOGY:

Presented work is part of the project entitled: "The role of selected clinical, neuropsychological, radiological and molecular parameters as prognostic markers of disease activity and response to therapy in multiple sclerosis." The study protocol and all procedures covered by the study received a positive opinion from the Bioethics Committee of the Medical University of Lodz (consent no.: RNN/31/24/KE of January 9, 2024 - attached). The study is conducted at the Department of Neurology of the Medical University of Łódź. Participants are recruited among patients treated in the Department of Neurology and the Neurology Outpatient Clinic of USK No. 1 in Łódź. The study includes patients > 18 years of age, with relapsing-remitting MS diagnosed according to the currently applicable McDonald criteria, with disease duration ≤ 10 years, without DMT or patients DMT initiated ≤ 3 years before inclusion in the study. Peripheral blood is collected from each study participant to assess the serum concentration of sex hormones (testosterone, estradiol, progesterone). The place for determining laboratory parameters will be the Medical Laboratory of Immunological Diagnostics, Central Clinical Hospital of the Medical University and the Neuroimmunology Laboratory of the Department of Neurology. The determination of hormone concentrations will be performed using an immunological chemiluminescence test, used for the quantitative determination of hormones in blood serum. All determinations will be performed on each participant at 3 time points: 1. Starting point of the study; 2. 12 months after baseline; 3. 24 months after baseline. Patients will be divided into groups according to the DMT used. The results of hormonal tests will be correlated with clinical data, including: relapse activity (ARR) and degree of neurological disability (EDSS), as well as the results of extended radiological assessment in magnetic resonance imaging (MRI) of the head (new / newly enlarging T2/FLAIR focal lesions, contrast-enhancing lesions, atrophic parameters).

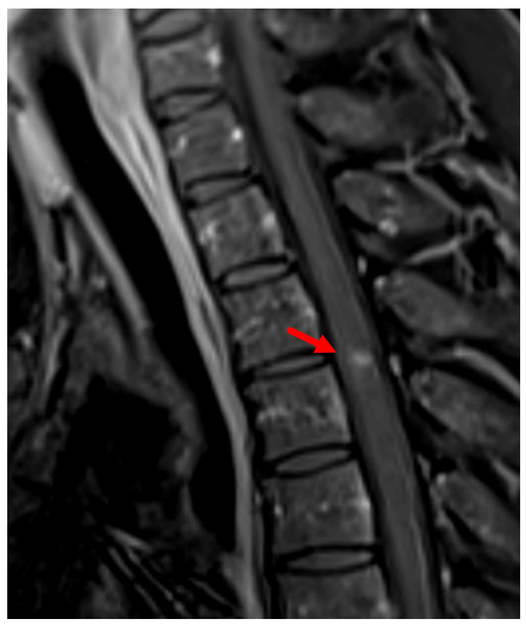
At the time of report submission, 47 patients with RRMS meeting the inclusion criteria were included in the study. 10 ml of peripheral blood was collected from each study participant. Blood samples were subjected to a standard serum isolation procedure. Serum samples were frozen at temperatures below -20 Celsius degrees for further analysis. All study participants were also subjected to an assessment of their neurological condition, including: EDSS (Expanded Disability Status Scale) assessment and the occurrence of disease relapses, as well as radiological assessment using head MRI, in accordance with the protocol of the Polish Neurological Society and the Polish Medical Radiological Society. The MRI images will then be subjected to an extended analysis of the results, taking into account parameters of brain atrophy, as well as the presence of focal cortical lesions.

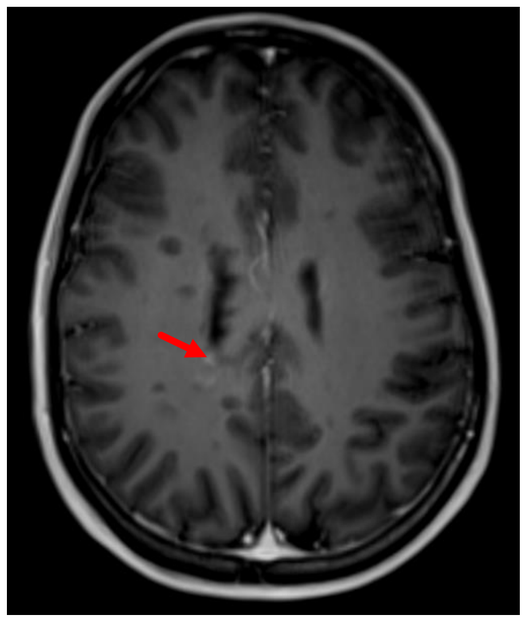
T2/FLAIR LESIONS:





CONTREST-ENHANCING LESIONS:





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