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MEDICAL HYPOTHESES

SOME NEUROCHEMICAL DISTURBANCES IN MULTIPLE SCLEROSIS

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ABSTRACT
The data presented in this manuscript suggest a pivotal role of the central nervous system (CNS) in the regulation of immune status. We describe here that some neurochemical disturbances may provoke development of various diseases including multiple sclerosis. Some theoretic and practical backgrounds, how to improve the multiple sclerosis sufferers and patients with other autoimmune disorders, are also given.

Keywords: Multiple sclerosis, neurotransmitters, tryptophan, immunomodulation.

RESUMEN
Los datos que presentamos en este manuscrito, sugieren un papel guia del sistema nervioso central (SNC) en la regulación del estado inmune. Describimos aquí que varias alteraciones neuroquímicas pueden provocar el desarrollo de varias enfermedades, incluyendo esclerosis múltiple. También se comenta acerca del trasfondo teórico y práctico, y cómo mejorar a víctimas y pacientes con

esclerosis múltiple y otras alteraciones autoinmunes.

Palabras clave: Esclerosis múltiple, neurotransmisores, triptofano, inmunomodulación.

INTRODUCTION

A bulk of studies devoted to multiple sclerosis (MS) is concentrated on therapy of the disease while works on the MS pathogenesis are not so numerous. But even herewith, number of the risk factors amounts to dozens: presence of various microorganisms (human herpesvirus 1 and 6 (HHV-1 and 6) and Epstein-Barr virus (EBV), papovavirus, Semliki Forest virus, Visna virus, varicella zoster virus, *Chlamydia pneumoniae*, some mycoplasmas) is associated with development of MS and its animal analogues[1-12]. In this situation, it is clear that Koch's paradigm "one organism, one disease" cannot be applied to such inscrutable disease like MS. It is very speculative to connect any disease with any microorganism until the whole population will not be tested on the carriage of the same microbe. Any epidemiologist understands that it is a very difficult task. Unfortunately, the similar situation is observed in the MS genetics: at least 32 alleles of the major histocompatibility complex (MHC) are associated with development of MS[13-14].

By our mind, the most logic are concepts that connect the MS pathogenesis with the dialogue disturbance between the nervous and immune systems, particularly due to imbalance of neurotransmitters. We try here to point out some issues connected to this problem.

The role of the neurotransmitter imbalance in MS and some other diseases

It is known by the moment that imbalance of neurotransmitters is an obligate condition in the MS patients as well as in people with other somatic and psychiatric disorders. For example, alterations in the serotonin content were described in details for MS patients both with relapsing-remitting, primary and secondary progressive forms[15-18]. Also, neurochemical disturbances were detected in patients with schizophrenia[15, 19], cystic fibrosis[20], pulmonary hipertension[21], pancreatitis[22], gallbladder muscle dysfunction[23] and in many other cases. Moreover, some research groups showed evidently that reversibility of normal signalization within the CNS might result in normalization of functioning of various organs and systems[15] and leading to improvement in people with neuroendocrine carcinoid syndrome[24], bronchial asthma[25], acute pancreatitis[26] and during many other conditions.

Currently, neurological manifestations of MS are generally associated with the axon demyeliniation, which is considered also as an examination criterion[27]. However, clinical data suggest that a strong correlation between brain lesions and clinical presentation is absent. For example, as far back as last sixties researchers showed that the vision recovery after the optic neuritis episode cannot be explained by remyelination[28]. Moreover, it is known that sometimes people with intensive demyeliniation events may have no neurological deficit[29]. Also, brain lesions and spinal cord lesions may be observed accidentally in people long before development of the first clinical signs of MS[30-33]. The accumulated data suggest that the MS challenges cannot be considered as the direct manifestation of demyeliniation and that other possible factors, particularly imbalance of neurotransmitters, should be taken into account.

Over thirty years ago, the level of 5-hydroxyindoleacetic acid (5-HIAA) was shown to be decreased in the cerebral spinal fluid of patients with MS[16, 17]. Additionally, the level of the above-mentioned metabolite of serotonin was more decreased in the most severely disabled MS patients[18]. So, the presented data confirm a correlation between the level of cerebral serotonin and the disease course.

Since the beginning of sixties of the last century, intensive investigations of neurotransmitters and their metabolites are carried out in the Institute of Experimental Medicine (Caracas, Venezuela). Over 30000 healthy and diseased individuals were analyzed and some general conclusions were made. In particular, the investigators showed that patients with Th-1 immune profile (increased cellular immunity) display neurochemical features similar to those observed in major depression[15]. Namely, in patients with MS, Grave's ophthalmopathy, Crohn's disease, rheumatic arthritis, psoriasis and many others, a similar neurochemical disturbances are observed: increased norepinephrine to epinephrine ratio plus decreased level of tryptophan in the blood plasma. Alternatively, in Th-2

diseases (increased humoral immunity) - myasthenia, thrombocytopenic purpura, hemolytic anemia and others - the opposite neurochemical defects are detected (profile of maladaptation to stress)[15]. Numerous works by these authors have demonstrated that redressement of the observed neurotransmitter imbalance may result in improvement of patients. Moreover, one therapeutical scheme may work efficiently in patients with different disorders but incoming into one group (Th-1 or Th-2 diseases)[15, 34-36].

It should be noted here that many studies have confirmed an entwinement between activity of immune and nervous systems[37-38]. Immunological changes observed in the MS patients are similar to those detected in the major depressed patients[39]. It is also known that depletion of the serotonin neurotransmission may be mediated by activation of indoleamine-2,3-dioxygenase (IDO) by inflammatory cytokines[39]. Some reseachers showed that the tryptophan derivates (3-hydroxy-kynurenine (3OH-KYN) and quinolinic acid (QUIN) arisen in the kynurenine cycle have neurotoxic effect[40-41]. Increased level of the above-mentioned metabolites is detected in neurodegenerative diseases and major depression[40, 42]. In turn, 3OH-KYN is able to induce the reactive oxygen species formation whose cytopathogenic effect is well documented[43]. Thus, the accumulated scientific data suggest neurochemical disturbances are obligate in any neurological disease and, as some investigators stated[15], psychosomatic disorder. Therefore, prescription of some appropriate neurotrophic drugs able to restore neurotransmitter balance may be useful in many autoimmune diseases including MS.

Some steps in the MS neuroimmunomodulation

According to opinion of some authors[15], enhancement of the central serotonin neurotransmission is an important step. The simplest way to increase serotonin neurotransmission is administration of the serotonin precursors like L-tryptophan and 5- hydroxytryptophan (5-HTP); the second might be synthesized in the human organism from the former. However, 5-HTP (a commercial product produced from the seeds of the African plant *Griffonia simplicifolia*) became the most popular and is used in clinical practice since the last seventies[44]. Efficiency of 5-HTP was confirmed in fibromyaligia, insomnia, chronic headaches and some other pathology[45]. This substance crosses the blood-brain barrier without difficulties, and increases significantly the serotonin synthesis in CNS[46]. Some vitamines and minerals may enhance serotonin synthesis in CNS. We have to note here that glucocorticoids frequently used for treatment of MS are able to induce IDO (an enzyme participating in the tryptophan catabolism) this fact is known since 1980s[47].

In 1987, the selective serotonin reuptake inhibitors (SSRI) were introduced into clinical practice. Initially, this type of antidepressants was used entirely in psychiatric practice. However, during the last decade, some immunological activities of these drugs were described. At present, it is know that SSRI can cause significant decrease in synthesis of inflammatory cytokines and increase in the production of anti-inflammatory ones[48-51] as well as mediate reduction of the interferon-γ to interleukin 10 (INF-γ/IL-10) ratio whose importance for T-cell activation was shown previously[52].

The presence of the increased levels of inflammatory cytokines in the MS patients was confirmed by many studies[53-55]. Therefore, we consider that application of SSRI and other serotonin promoting substances with the immune downregulation properties should be studied. Moreover, there were some positive results: administration of L-tryptophan to the MS patients resulted in improvement of autonomic, motor and sensory functions[56]. Expediency of the SSRI administration in the MS patients is under discussion now[57]. This type of antidepressant was shown to cause anti-inflammatory and anti-asthenia effects[58-59] as well as have analgesic action[60-61] that is very important for the MS sufferers.

CONCLUSION

Although close contact do exist between the CNS and immune system[15, 62-63], it is impossible to conclude at present whether neurochemical disturbances are entirely related to MS pathogenesis or they are only consequences of autoimmune disease. Anyway, one thing is definitely clear that some neuropharmacological therapies aimed at correction of the neurotransmitter level and, as a result,

modification of CNS and other nervous activities, may lead to improvements in patients with MS. Prescription of drugs with sympathomimetic actions (precursors of some neurotransmitters, some antidepressants, antagonist and agonists of α2- and ß2-adrenergic receptors, use of *Bacillus* Calmet-Guerin) may significantly reduce challenges of MS and cause other beneficial effects[56, 59, 64-66]. A vast experience obtained in the Institute of Experimental Medicine (Caracas, Venezuela) confirms the possibility to manage some autoimmune diseases without development of relapse during a long time[15, 34-35]. In addition, application of some physiotherapeutic procedures with the prior proserotonergic therapy may contribute to general improvement and long-term remission in the MS patients[67-69]. Taking into account low efficiency of currently used immunomodulators and their low safety profile[70-71], prescription of unexpensive remedies with good tolerance and comparable efficiency seems rational decision. We hope that neurologists engaged in the MS study find the presented material valuable.

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Markelov and Trushin correctly state that the etiology and pathogenesis is not yet well established in multiple sclerosis and make some suggestions about them. Although some are too general and based in isolated data in diseases that have not much in common, they should be considered for further investigation, as unconventional points of view have often solved mysteries as is multiple sclerosis today.

Comment of the reviewer Carlos Musso, MD.Hospital Italiano. Buenos Aires. Argentina
As Dr Markelov and Dr Trushin pointed out in their article scarce works are devoted to multiple sclerosis (MS) pathogenesis. This situation is even reflected in the MS diagnosis criteria which are based on morphological aspects (demyeliniation areas without axonal damage and perivascular infiltration by inflammatory cells) instead of a physiopathological mechanism.

The neurological and immunological systems share important characteristics such as their capability to learn from their experiences and to influence any organ of the economy. The neurotransmitters represent a sort of language that links both systems.

The authors proposed a very interesting hypothesis regarding the etiology of the multiple sclerosis which is attributed to a neurotransmitter imbalance: a reduction in the serotonin neurotransmission, and consequently the possibility to restore it pharmacologically.

This line of research could also explain the roots of many other entities as is the case of the autoimmune diseases as well as the psychosomatic disorders.

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