CLINICAL SIGNIFICANCE OF IMMUNE IMBALANCE AND AUTOIMMUNITY IN NERVOUS SYSTEM DISORDERS (NSDs)

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Abstract

In recent years, the role of immune imbalance and autoimmunity has been experimentally demonstrated in nervous system disorders (NSDs) that include Alzheimer’s disease, autism, obsessive-compulsive disorder (OCD), tics and Tourette’s syndrome, schizophrenia, and some other NSDs. And yet, these NSDs are never counted as autoimmune diseases. Deriving from the rapidly expanding knowledge of neuro-immunology and autoimmune diseases, for example multiple sclerosis (MS), the author of this mini-review strongly recommends that these NSDs should be included while tallying the number of autoimmune diseases. This effort will help create an updated global database of all autoimmune diseases as well as it should help treat millions of patients who are suffering from debilitating NSDs for which there is no known cure or treatment currently.

Keywords: CNS disorders; autoimmune diseases; neuro-immune diseases

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**Вовед**

1. Нарушувањата на нервниот систем како автоимунни болести

Глобално, автоимунитетот е еден од најчестите проблеми при хроничните болести кај човекот. Според научните критериуми, околу осумдесет и пет медицински состојби се сметаат за автоимуни болести. Според Американската асоцијација за автоимуни болести (AAAIБ), повеќе од 50 милиони Американци и милиони низ целиот свет страдаат од автоимуни болести. Во овој број не се вклучени оните кои патат од нарушување на нервниот систем (ННС) и за кои има почеток за автоимунитет утврден со помош на лабораториско тес-титол (1–6). Примерите ги вклучуваат Алджајмеровата болест (АБ), аутизам, шизофренија, опсесивно-компulsивно нарушување (ОКН), тикови, Tourette синдром (ТС). Постои еден искусок од оваа категорија на ННС, а тоа мултиплекс склерозата (МС). МС се карактеризира со полу-претерана инфразација, ако покажуваат карактеристики на автоимуна болест. Значи, за почеток, авторот ќе предложи понатамошни студии кои треба да земат предвид дека постојат нови пациенти кои патат од нервни болести (болести на мозокот или ментални болести), а кои покажуваат карактеристики на автоимунна болест. Откако ќе се направи ова, бројот на лица кои имаќа автоимунна болест драматично ќе се зголеми низ светот. Дотога, не се искуваше да се имаат ННС. Околу 40 милиони Американци патат од Алджајмерова болест, а го-лем дел (65-85%) од повремени форми на АБ имаат автоимунни проблеми (2). Ова би претставувало голем број во категоријата на автоимуни болести. Аутизмот и поврзаните нарушувања се сречаваат кај 3 до 4 милиони деца и взрасни во САД, а 70-80% имаат карактеристични автоимуна проблеми (5, 6). Ова исто така ќе го зголеми бројот доколку и овие се вклучат во категоријата на автоимуни болести. Исто така, многу луѓе со тикови и Tourette синдром (ТС) и опсесивно-компulsивно нарушување (ОКН) имаат автоимуна болест на мозокот. Оваа популација исто така треба да се включи во истата категорија на

**Introduction**

1. Nervous System Disorders as Autoimmune Diseases

Globally speaking, autoimmunity is one of the most common problems in chronic diseases in man. Relying on scientific criteria, approximately eighty-five or so medical conditions are commonly regarded as autoimmune diseases. According to American Autoimmune Diseases Related Association (AADRA), more than 50 million Americans and millions more worldwide are known to suffer from autoimmune diseases. This number however never includes many more individuals who suffer from nervous system disorders (NSDs) and who have evidence of autoimmunity as demonstrated by laboratory testing (1–6). The examples are Alzheimer’s disease (AD), autism, schizophrenia, obsessive-compulsive disorder (OCD), tics and Tourette’s syndrome (TS). There is one exception to this category of NSDs which is multiple sclerosis (MS). MS is always accounted for in the epidemiological database of autoimmune diseases. Thus, to start with, the author would herby like to suggest that future epidemiological studies must take into the account that there is a new patient population that suffers from neurological problems (brain diseases and mental illnesses) and yet shows typical characteristics of an autoimmune disease. Once this is done, the number of people affected with autoimmune diseases will dramatically increase throughout the world. To that end, let us examine the number of people affected with NSD. Alzheimer’s disease affects an estimated 40 million Americans and a large proportion (65-85%) of the sporadic form of AD has autoimmune problems (2). This will represent a huge number to be considered in the category of autoimmune diseases. Autism and related spectrum disorders affects 3 to 4 million children and adults in the United States and 70-85% of them have well-characterized autoimmune problems (5, 6). This will also represent a large number to be included in the category of autoimmune diseases. Likewise, many more people with tics and Tourette’s syndrome (TS) and obsessive-compulsive disorder (OCD) have been shown to have autoimmunity to brain. This population should
автоимуне болести. Јасно е дека во овој случај бројот на автоимуне болести нагло ќе порасне ако оваа нова категорија бо- лести на нервниот систем кои вклучуваат автоимунитет се вклучат во епидемио- лошките студии. Ова не е направено досе- га, но нивниот број треба да се заведе во идните епидемиолошки студии.

Слика 1. Реципрочна врска меѓу имунолошкиот систем и нервниот систем

Ако имате автоимуна болест, вашиот иму- нолошки систем се расипува и започнува да ги напада здравите клетки, ткива и органи. Сепак, ова се случува на многу по- себен начин. Значи, во случај на мозочен автоимунитет, имунолошкиот систем ќе го отстрани автоимуниот одговор против мозокот или нервниот систем. Пред околу 30 години, призната е важноста на реци- прочната врска што постоела меѓу нашит имунолошки и нервниот систем. Ова се прикажано на слика 1. Како што е прикажано овде, имунолошкиот и нервниот систем се меѓусебно поврзани и оваа врска е со посредство на хемиски трансмитери, на пример цитокини кои се произведени од клетки во имунолошкиот систем како помошни Т-клетки (ПТ), супресорни Т-клетки (СТК) и антигено прет- ставувачки клетки каде што невротрансмитерите и невропептидите се произве-

also be included in the same category of autoimmune diseases. Quite clearly then the number of autoimmune diseases will rise sharply if this new category of nervous system diseases involving autoimmunity are included in the epidemiological studies. This has not been done so far but their numbers should be tallied in future epidemiological studies.

Figure 1. Reciprocal Relationship between Immune System and Nervous System

If you have an autoimmune disease, your immune system goes haywire and begins to attack healthy cells, tissues and organs. However this must happen in a highly select way. Thus, in the case of brain autoimmunity, the immune system will elicit autoimmune response against the brain or nerve tissue. Approximately 30 years ago, we recognized the importance of a reciprocal relationship that existed between our immune system and nervous system. This is illustrated in Figure 1. As illustrated here, the immune and nervous systems are interconnected with each other and this relationship is mediated by chemical messengers, for example cytokines produced by immune system cells like T helper cells (TH), T suppressor cells (TS) and antigen-presenting cells (APC) whereas neurotransmitters and neuropeptides produced by
dendrites and glial cells. As we know it now, this relationship occurs at both the cellular level as well as the molecular level. But nearly 30 years ago, we postulated that the disruption of this neuro-immune or immune-neural circuitry might actually be the reason underlying a wide-range of brain diseases and mental illnesses (7). Environmental factors such as a viral or bacterial infection, trauma or brain injury, and other dietary factors can easily break down this circuitry. In that regard, one of the most important findings in the field is the observation that autoimmune disease of the nervous system is the most common problem when the neuro-immune circuitry breaks down. This should prove to be clinically quite relevant because autoimmune diseases of the nervous system could be medically recognized and be treated with immune therapies that are currently being used for other autoimmune diseases. This is already beginning to happen as exemplified by immune therapy for individuals with autism, OCD and TS. Recently, we hypothesized that the disruption of neuro-immune circuitry could cause neuro-immune imbalance in the body, thereby it may also affect brain plasticity, brainwave pattern, and brain function (8).

2. Link between Infections and Nervous System Disorders

What causes autoimmune diseases is still unknown but it is commonly recognized that they are triggered by environmental factors, in particular viruses. As summarized in Table 1, the examples include Epstein-Barr virus (EBV) and human herpes virus-6 (HHV-6) in MS, measles virus in autism, herpes simplex virus (HSV) in AD, and streptococcal infection in OCD and TS. More recent studies have found a much closer involvement of EBV in MS (9). As recently described in a much greater detail elsewhere (6) and when properly evaluated by specialized immune tests, just about every second autistic child has elevated level of antibodies to herpes virus (HSV) in AD, and streptococcal infection in OCD and TS. More recent studies have found a much closer involvement of EBV in MS (9). As recently described in a much greater detail elsewhere (6) and when properly evaluated by specialized immune tests, just about every second autistic child has elevated level of antibodies to measles virus. This is not an exaggeration but a real scientific fact deriving from solid laboratory research
risk of having children with typical form of autism but not the children with autistic spectrum disorders (ASD) which includes a highly heterogeneous diagnosis of neurobehavioral disorders. Virus infections are now known to change the permeability of the blood-brain barrier, which permits the entry of immune cells and proteins into the brain. Inside the brain, the microglial cells can also produce pro-inflammatory cytokines that are involved in the autoimmune process known as neuroinflammation or inflammation of the brain (2–4).

### Table 1. Immune Imbalance in Patients with Nervous System Disorders (NSDs)

<table>
<thead>
<tr>
<th>Nervous System Disorders (NSDs)</th>
<th>Immune Imbalance in Patients</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autism / Autism</strong></td>
<td>Намалени / Down</td>
<td>Намалени / Up</td>
</tr>
<tr>
<td>Опсесивно-компulsive однесување (ОКО) / Obsessive-Compulsive Disorder (OCD)</td>
<td>Намалени / Down</td>
<td>Намалени / Up</td>
</tr>
<tr>
<td>Алхимерова болест (АБ) / Alzheimer’s Disease (AD)</td>
<td>Намалени / Down</td>
<td>Намалени / Down</td>
</tr>
<tr>
<td>Мултиплекс склероза (МС) / Multiple Sclerosis (MS)</td>
<td>Намалени / Down</td>
<td>Намалени / Down</td>
</tr>
<tr>
<td>Депресивно нарушување (ДН) / Major Depressive Disorder (MDD)</td>
<td>Намалени / Down</td>
<td>Намалени / Down</td>
</tr>
<tr>
<td>Алкохолизам / Alcoholism</td>
<td>Намалени / Down</td>
<td>Намалени / Down</td>
</tr>
<tr>
<td>Шизофренија / Schizophrenia</td>
<td>Намалени / Down</td>
<td>Намалени / Down</td>
</tr>
<tr>
<td>Tourette синдром (ТС) / Tourette’s Syndrome (TS)</td>
<td>Намалени / Down</td>
<td>Намалени / Down</td>
</tr>
<tr>
<td>Синдром на хроничен замор (СХУ) / Chronic Fatigue Syndrome (CFS)</td>
<td>Намалени / Down</td>
<td>Намалени / Down</td>
</tr>
</tbody>
</table>

*MBP=Myelin Basic Protein / Миелински основен протеин; CN=Caudate Nucleus / Јадро; AP40=Amyloid-beta-protein (1–40) / Амилоиден бета протеин; Serotonin receptors=Brain receptor proteins that binds to serotonin neurotransmitter / Серотонин рецептори = рецептори на протеини во мозокот кои се врзуваат со невротрансмитерот серотонин; Cholinergic cells=Acyethylcholine neurotransmitter containing cells/Холинергички клетки = Ацетилхолински невротрансмитери кои содржат клетки. Вidi реф. #1-7, 10 and 13.
3. Neuro-Immune Imbalance in Nervous System Disorders

Some 30 years ago, we also recognized that our immune system vastly impacts our nervous system (7). This prompted Dr. Singh to study the role of immune system in NSDs for two main reasons: First, this might help discover biomarkers for brain diseases and mental illnesses, and secondly, it might also help find novel approach to therapy with immune modulating agents for these neuro-disorders. The fruits of labor are now beginning to pay-off because many researchers are now finding positive results. Similar to all other typical autoimmune diseases, the experimental evidence for autoimmunity to brain or neuroautoimmunity has been found in NSDs (see Table 1). The positive test results include specialized proteins of the immune system (for example, antibodies and cytokines), autoimmunity testing, and immunotherapy. Immune activation, which is the first step in the onset of autoimmunity, has been shown in patients with autism, MS, AD, TS and OCD. Patients with these diseases also harbor elevated levels of autoantibodies that bind specifically to brain proteins, for example antibodies to caudate nucleus of the basal ganglia in autism, TS, and OCD, antibodies to amyloid protein-beta in AD, and antibodies to myelin basic protein in autism and MS. It’s interesting to point out that subsequent to the original finding of antibodies to caudate nucleus (located deep within the brain) in autistic children (10), some researchers have now found neuroimaging evidence of structural and functional abnormalities in the caudate nucleus of children with autism (11-12). Interferon-gamma and interleukin-12, the two proteins of the immune system that initiate autoimmunity, are also activated in patients with brain diseases (13). Furthermore, many patients also show improvement when administered with immunotherapy using intravenous immunoglobulin, plasmapheresis, transfer factor, and other
имунотерапија со интравенозен имуног-лобулин, плазма-терапија, трансфер-фактор и други имунолошки агенти (3, 5, 6).

Во однос на Tourette синдром (ТС), една скорашна студија ги поврза невротрансмитерот хистамин кај ТС и тиковите. Истражувачите идентификувале ретка мутација на ХДС-комплексот кој го кодира ензимот 1-хистидин декарбоксилаза кој е включен во хистаминергичните нервни патеки (14). Оваа студија предлага дека пациентите со ТС можеби не создаваат доволно хистамин и овој недостаток на хистамин може да доведе до нарушување на функцијата на рецепторите на хистамин во мозокот. Хистаминот има различни рецептори во мозокот, на пример Х2 тип на рецептори. Особено е важно Х2 рецепторите да бидат во зголемен број во корпус стриатум и во nucleus caudatus (15) – мозочна структура која е нападната кај пациенти со аутизам, ТС и ОКН (види реф. #10). Значи, може да се каже дека овие пациенти имаат автоантитела во мозочните рецептори за Х2, исто како и автоантитела во мозочните рецептори на серотонин кај деца со аутизам (16).

4. Нови откритија за автоимуноболести

Постојат некои нови откритија за автоимунолошките болести кои можат да бидат релевантни на автоимунна нарушувања на нервниот систем.

- Автоимуните болести се поврзани со оксидативниот стрес (ОС) – знак за намалена функција на производство на енергија во интрацелуларните организи на митохондрии. Користејќи ги белите крвни зрнца, особено лимфоцитите, ОС е открен кај пациенти со нервно дегенеративни нарушувања како Алцхајмерова болест, Паркинсонова болест, шизофренија и аутизам. Во однос на ова, една непосредна студија покажа дека ОС вклучува биохемиски дефект на клучни митохондрични ензими наредени НАДП оксидаза. Откако е откривено дека ОС ги користи лимфоцитите, ова откритие може да се интерпретира како намалено ниво на енергија за имунолошките клетки, што ав-

immune modulating agents (3, 5, 6).

With regards to Tourette’s syndrome (TS), a recent study has linked histamine neurotransmitter system in TS and tics. Researchers have identified a rare mutation in the HDC complex that encodes 1-histidine decarboxylase enzyme involved in histaminergic neural pathways (14). The study suggests that the patients with TS might not be making enough histamine and this reduction in histamine might impair the function of histamine receptors in brain. Histamine has different receptors in the brain, for example H2 type receptors. It is of considerable interest that H2 receptors are enriched predominantly in corpus striatum or caudate nucleus (15) – a brain structure which is also targeted by autoimmunity in patients with autism, TS, OCD (see cross-ref. #10). Thus it is tempting to speculate that these patients might actually have autoantibodies to brain histamine H2 receptors, much like autoantibodies to brain serotonin receptors in children with autism (16).

4. Novel Findings for Autoimmune Diseases

There are some interesting new findings for autoimmune diseases that may also be relevant to autoimmunity in nervous system disorders.

- Autoimmune diseases are associated with oxidative stress (OS) – a sign of reduced function of energy-producing intracellular organelles called mitochondria. Using white blood cells, mainly lymphocytes, the OS has been found in patients with neurodegenerative disorders including Alzheimer’s disease, Parkinson’s disease, schizophrenia and autism. In this regard, a very recent study has shown that OS involves a biochemical defect of a key mitochondrial enzyme called NADP oxidase. Since the OS was found using lymphocytes, this finding may be interpreted as reduced energy level for immune cells, which could ultimately
treatment may lead to imbalance of immunoregulatory T
cells causing autoimmunity and
inflammation.

• Interferon-gamma (IFN-gamma), a pro-
imflammatory cytokine produced mainly
by T cells, has been shown to increase the
expression of immune protein called
major histocompatibility complex (MHC)
in the brain. IFN-gamma is well known to
increase the expression of MHC on
neural cells and thereby increase the per-
meability across the blood-brain barrier.
Recently it was found that the enhanced
expression of MHC is related to abnormal
brain development, which would suggest
a role for this protein in disorders like
autism and schizophrenia. Since IFN-
gamma is a key cytokine inducer of
autoimmune response and it is elevated in
patients with autism and Alzheimer’s
disease, the expression of MHC might
also be related to autoimmune pathology
of nervous system disorders.

• Vitamin D has recently been found to
play a crucial role in activating immune
response defenses. It controls human T-
cell function to elicit an effective immune
response against invading viruses and
bacteria. It was found that without
sufficient intake of the vitamin, the killer
cells of the immune system -- T cells --
will not be able to react to and fight off
serious infections in the body (17). Thus
the insufficient amount of vitamin D can
cause imbalance of immunoregulatory T
cells. Since these cells are abnormal in
autoimmune diseases, vitamin D will play
a vital role in nervous system disorders.
Indeed, many patients with nervous
system disorders are deficient in vitamin
D and therefore a daily intake of this
vitamin is highly recommended. In that
regard, vitamin D deficiency has recently
been found in children with autism and
the oral intake of this vitamin was shown
to improve core characteristics in autistic
children (18). It is quite possible that
rakteristite na auustichnite deca (18). Mno no ovo vitamin da ja pop-
rali funkcijata na T-kljetkite; broj-
ot na T-kljetkite, kako i namalenata
funkcija na ovie kljetki kaaj auusti-
tichni deca.

- Slaboto spisene ili nedostatokot na
son go zgleumva vospalenieto kako
sho se pokazuvja pri zgleumen CRP.
Ovoj serumski protein e protein na
akutna fazha i e povrzan so avtomumu-
nite bolyesti. Ova otkritite e vajno
za narushuvanta na neryvnot sistem.
Na primjer, na deca sa autizam
obichno im nedostasua son ili ne
spijat dbrdo i imaat zgolemeno nivo
na CRP (19).

- Postoi prica da se veruva deka te-
rapija na matichnite kljetki moze
da im pomogne na pacientite sa avto-
muuni bolyesti, inklujuvaki gi i na-
rushuvanta na neryvnot sistem
(NHC). Matichnite kljetki, osobeno
nie vo koskenata srrh, imaat uloga da
bidat imunoizhki kljetki kako lim-
fovitite. INF-gama e privoj chuvam
od infekcijii so mikroorganizmi. Toj
istotaka go regulira normalnoot
ravoj na imunoizhki kljetki od
coskenata srrh - dobini matichni
kljetki - proces piznat kako xemato-
pozea. Edna skorashna studija pokaze-
juva deka INF-gama go potkiknuva
proizvodstvoto na imunoizhki
kljetki od coskenata srrh - predci
na matichnite kljetki za vreme na
bakteritska infekcija (20). Zatoa shto
INF-gama e proiflamatoren citot-
kine, ova otkritite ima golem poten-
cijal za imunoizhka terapija so
matichni kljetki za narushuvana
na neryvnot sistem. Ova bi biil nov
mekhanizam za matichnite kljetki da
proizveduvat imunoizhki kljetki
koj funkcioniraat normalno, sho vo
terija treba da pomognat da se
nadmine imunoizhkiot disbalans, a
so toa i avtoimuinitetot. Alternativni-
ven pristap bi bil da se iskoristat
faktorite za razvoj i drugi hranliv
produkti za da se obezbedi standard
koja bi bila korisna za sity
imunoizhki kljetki, neryvni kljetki i drug-
gite vidovi kljetki. Mege
razlichite

vitamin D supplementation might
improve the function of T cells; the T-cell
number as well as the function is well-
known to be decreased in children with
autism.

- Poor sleep or sleep deprivation increases
inflammation as shown by elevated level
of CRP. This serum protein is an acute-
phase protein and is associated with
autoimmune disease. This finding is
relevant to nervous system disorders. For
example, children with autism generally
are sleep deprived and do not have good
sleep patterns and elevated levels of CRP
have been found in children with autism
(19).

- There is reason to believe that stem cell
therapy can be used to help patients with
autoimmune diseases, including nervous
system disorders (NSDs). Stem cells, in
particular those of the bone marrow, are
committed to become immune cells like
lymphocytes. IFN-gamma is a front-line
immune defender against microbial
infections. It also regulates normal de-
velopment of immune cells from bone
marrow-derived stem cells – the process
is known as hematopoiesis. A recent
study has now found that IFN-gamma
prompts and promotes the production of
immune cells from bone marrow pro-
genitor stem cells during bacterial infec-
tions (20). Because IFN-gamma is a pro-
flammatory cytokine, this finding has
tremendous potential for immune therapy
with stem cells for nervous system disor-
ders. This would be a novel mechanism
for stem cells to produce normally-
functioning immune cells that in theory
should help overcome immune imbalance
and therefore autoimmunity. Alternative
approach would be to use growth factors
and other nutraceuticals to provide an
environment that will be conducive to
yielding immune cells, neural cells or
other type of cells. Among various factors,
vitamin C is being used to culti-
фактори, витаминот Ц се користи за култивирање на нервните клетки во ткивните системи на матични клетки. Кога луѓето помислуваат на терапија со матични клетки за невролошки болести, тие мислат само на поправање на нервните клетки во мозокот. Но, треба да се нагласат и имунолошките клетки, бидејќи тие имаат големо влијание на функцијата на нервниот систем. Идеално кажано, треба да се направи обид да се обноват и нервните клетки и имунолошките клетки од матичните клетки.

Concluding remarks

In summary, several lines of scientific evidence suggest a pathogenic role of immune imbalance and brain autoimmunity in nervous system disorders (NSDs). Concerning the future directions of NSDs, the first step is to account for the NSDs patient population in all future epidemiological studies if we are going to realize the actual impact and financial burden of autoimmune diseases in our society. Immunotherapy with immune modulating agents offers a novel promising approach to helping people affected with these medical conditions. Autoimmunity in the brain (for example, binding of antibodies to brain antigens) may also cause a shift in brain waves thereby resulting into a functionally “imbalanced brain.” This type of autoimmune injury to brain would in fact be very similar to traumatic brain injury (TBI) and the outcome may be a life-long event. Thus, the author of this article strongly suggests that the immune therapy should be administered first to bring about “Immune Balance” before administering medical or alternative treatment for nervous system disorders – an idea he originally proposed about 6 years ago in 2009 (21). It is furthermore implied that the immune balance means establishing a normal balance of immunoregulatory function of T cells (balance between T helper and T suppressor cells). It should also be noted that this approach is totally different from the approach of simply boosting or suppressing the immune function which is
currently done by professionals all over the world. This approach might be particularly suitable and effective in patients who receive neuro-therapies and neurofeedback technology to balance the brain function. Naturally, therefore, the immune balance would be a prerequisite for treating NSDs. According to the World Health Organization (WHO), the financial burden of all brain diseases and mental illnesses surpasses that of cancer and heart disease. Since up to 85% of patients with nervous system disorders have scientific evidence of autoimmunity, a huge number of this patient population could potentially be helped by immune balancing modalities to target autoimmunity in the brain. The first step is to recognize that a vast majority of NSDs involving autoimmunity are autoimmune diseases similar to all other medically-recognized autoimmune diseases. Then, the immune balance first before the neurotherapy might very well prove to be a novel approach to helping patients suffering from NSDs. Who knows someday in not too distant future the healing power of neuro-immune balancing act might very well turn out to be one of the most important endeavors for helping people with nervous system disorders (NSDs). This naturally calls for extensive experimental research and unbiased careful attention of researchers and medical professionals throughout the world.

Conflict of interests
Author declares no conflict of interests.

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