Neuroimmunology of involuntary movements in child

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ABSTRACT
The significance of neuroimmune mechanisms in triggering of some neuro psychiatric disorders in child, comprises an important aspect, although little discussed, that should be brought to the attention of the clinician. The impact of the interactions between the nervous and immune system is not standing alone being neurochemical and neuroendocrine mediated. Participation of various biological components of the nervous and immune system, sometimes can cause both disorders and disabilities in the neurological or psychiatric area. Actually, the reaction mechanisms and their adverse consequences, explain the origin of the disease as a result in starting point of cellular and molecular alterations, leading to characteristic symptomatology and clinical course of the disease. In this article we tried to explain as much as possible the involving of the neural-immune axis in the neuropsychiatric child pathology, with brief characteristic examples.

Key words: neuroimmunology, involuntary movement, child, neuropsychopathology

REZUMAT
Importanța mecanismelor neuroimunitare în declanșarea unor afecțiuni neuro psihiatric la copil, comportă un aspect important, care deși puțin discutat trebuie adus în atenția clinicianului. Impactul interacțiilor dintre sistemul nervos și cel imunitar nu este de sine stătător, fiind mediat neurochimic și neuroendocrin. Participarea diferitelor componente biologice ale sistemului nervos și celui imunitar, uneori poate cauza disfuncții și dizabilități în sfera neurologică sau psihiatrică. De fapt, mecanismele de reacție și consecințele lor nefavorabile, explică originea bolii, ca rezultat cu puct de plecare al disfuncțiilor celulară și moleculară, ducând spre simptomatologie și evoluția clinică caracteristică bolii. În acest articol am încercat să expunem pe cât posibil participarea axei neuro-imune în patologia neuropsychiatrică a copilului, cu scurte exemple caracteristice.

Cuvinte cheie: neuroimunologie, mișcare involuntary, copil, neuropsihopatologie

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections for example, is susceptible to be a post streptococcal autoimmune disorder (Chung at al., 2007). Sometimes, from immunologically point of view the interactions between the nervous and immune system occur in different areas of the brain.

In other words, the failure of the immune system correlated with clinical exacerbations in children with pediatric autoimmune neuropsychiatric disorders associated with viro-microbial infection (i.e. streptococcal infections) raises an important and more specific pathophysiological mechanism in the function of brain immunity.

Tics – are rapid, brief involuntary movements. They can be primarily motor, such as facial grimacing, or the vocal tics such as throat clearing or sniffing. Tics are common in children. Up to 8% of all children do a single transient tic. Often, these involuntary movements are manifested in one muscle group and acquired transiently (Tibbles et al., 1986). For example a clinical entity in this sense could be the Tourette syndrome.

Myoclonic movements- occur commonly in sleeping infants and are frequently misinterpreted as seizures. Myoclonic movements are sudden, shock-like and involuntary too. They can be a result of muscle contractions (positive myoclonus) a inhibition (negative myoclonus). Myoclonus can be seen in a different neurological instances or conditions. As example, myoclonus may be present in a child after a severe hypoxic-ischemic injury. In the neurodegenerative diseases, myoclonus can be observed too in a context of a neuronal ceroid lipofuscinosis. It is also possible that most children will exhibit sleep myoclonus, as a totally normal movement, for example when a child is falling asleep or just prior to awakening.

Stereotypies- may be present in normal children too
as well as in children who are delayed in their development or autistic. These kind of movements are repetitive, no purposeful, rhythmic, and the child can exert some degree of volitional control over the movements. Stereotypies can be transient too, and could persist for years.

Intricate movements (Choreo-Athetotic movements) – for example this kind of movements cannot be integrated in chorea or hemiballismus, being a combination of involuntary movements.

Athetosis- consists in the inability to sustain a contraction of a muscle group, most commonly of the tongue, arms, or hands, having result in constant writhing movements.

Hemiballismus- is characterized by wild flinging of the arm contralateral to the subthalamic nucleus lesion that produce it, being the most violent involuntary movement.

Paroxysmal movement disorders- Some movement disorders occur paroxysmally or intermittently. Paroxysmal movement disorders are characterized by sudden attacks of involuntary movements of the body without loss of consciousness (Sleigh et al.,1981).The movements can be: choreic, athetotic, tonic, dystonic or ataxic. In this respect we can think at the following situations: paroxysmal kinesigenic dyskinesia, paroxysmalnonkinesigenic dyskinesia, paroxysmal exertional dystonia, nocturnal paroxysmal dystonia, episodic ataxia, ataxia-teleangiecistasia, i.e.

The neuro-immune interaction

The role of basal ganglia in brain autoimmunity

Location of the neurological injury occur at the level of basal ganglia. In order to demonstrate the impact of a neuropsychiatric disorder being autoimmune, we must have in our view ,five features, needed to be highlighted: presence of autoantibody, immunoglobulin at target structure, response to plasma exchange and certain laboratory blood tests and cerebrospinal fluid tests. In the current practice research another criteria involves inductions of disease in an animal model, for example serum of children with psychiatric autoimmune neuropsychiatric diseases infused into rats induced tics in the animal, further evidence for a direct role of the antibody in pathogenicity. For example Sydenham’s Chorea occurs weeks or months after Group A Streptococcal infections. This is a body of evidence which suggests that Sydenham’s chorea is an immune-mediated brain disorder with regional localization to the basal ganglia. The anatomical aperture of basal ganglia refers to a collection of putamen(also called the stiatum), globus pallidus, subthalamus and substantia nigra. Dysfunction in the basal ganglia results in extrapyramidal movements, even parkinsonism in adult. The basal ganglia is responsible for control of movements too and have an important role in control of the behaviour and emotion. An example could be the inflammatory burst at the level of bilateral caudate nuclei, bilateral putamen and thalamus, in Post streptococcal Encephalitis, that can clinically give dystonias and behavioral disturbances (Banks et al.,1997).

In this neuroanatomical area an interaction between cytokines, interleukins, lymphokines and pro-inflammatory factors is possible via to tissue-molecular adhesion interchanges.

According to Dunn at al (1992), the ultimate molecular aspect would be to characterize the basal ganglia proteins involved in antibody binding, which could provide central clues to the neurotransmission or second messenger systems neurochemically activated and even point towards new drug targets. Anti-neuronal antibodies in post streptococcal central nervous system syndromes, can be generated too and induce an immune response which cross-reacts with the brain. Now we can think beyond the molecular and cellular mediators of the disease as an immune components(or bacterial toxins) that are capable to entering in the central nervous system. We conclude here that, recent experiments have shown that activated lymphocytes or antibodies are capable to interact with cellular and molecular architecture of the central nervous system, but with disruption or without disruption of blood barrier. At the level of the basal ganglia, for example the circulating lymphocytes recognize the antigens and immune activation may occur with consequent neural dysfunction or damage. A functional antibody-mediated disease, as example Sydenham’s chorea experimental support pleads for cytotoxic T-cell-mediate disease, defined also by the presence of anti-neuronal antibodies. In the picture bellow (Fig.1), the neuro-immune axis( and its involved components that implies a neuroimmune, neuroendocrine and neurochemical cross reactivity) is well outlined and easy to understand.

Streptococcus and brain epitope cross-reactivity- Even the streptococcal organisms can play a role as a immune –mediator in specific pediatric autoimmune neuropsychiatric disease that can lead to tics manifestations. Today, little attention is centered on beta-hemolytic streptococcus. This streptococcus is able to produce an immunoviral-mediated brain disease with neuropsychiatric components. The major hypothesis seems to be that antibodies cross-react between streptococcal and brain epitopes through an immune mediated mechanism (molecular mimicry). In the light of anterior mentioned would be to just focus solely on the fact that M protein of Group A streptococci is considered to be as a major factor of virulence.
Blood–brain barrier and its interaction with the immune system via cytokines, in a nutshell.

The blood-brain barrier is believed to mediate interactions between the immune and central nervous systems in several ways and mechanisms, also we can focus our attention only on the fact that the blood-brain barrier is a secretory system for cytokines, prostaglandins, nitric oxide, as a immune-active factors (Abbas et al., 2000). Circulating immune cells that can cross the blood-brain barrier are simultaneously both inside the central nervous system and outside it, being capable to activate and reactivate the chemical exchanges even at the neuronal level. Anyway more subtle aspects of blood-brain barrier func-

**Fig. 1** interactions between the brain and components of the endocrine and immune systems. The ability of the brain to alter immune system function via a variety of endocrine pathways and the autonomic nervous system, and conversely the routes by which peptides and cytokines produced by cells of the immune system act on the brain are indicated. Abbreviations: E, epinephrine; ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; CS, corticosteroids; Enk, enkephalins; GH, growth hormone; NE, norepinephrine; NPY, neuropeptide Y; SP, substance P; TNF, tumor necrosis factor (Adapted from Dunn and Wang 1999)
tion are involved in a variety of ways, with the neuroimmune system, and cytokines which mediate and regulate most of neuroimmunological interactions. As example the function of the endothelial cells of the blood-brain barrier has been shown after application of lipopolysaccharides to the abluminal membrane of the endothelial cells.

Interleukin-6 (IL-6) secretion increased from its luminal membrane by about 10-fold. Also, when brain endothelial cells are exposed to luminal gp-120 (HIV-1 viral coat protein), they secrete cytokine endothelin-1 (ET1) into abluminal compartment (Chen et al., 2001). Also, other cytokines (as TNF-α, IL-1), cocaine, HIV-1 releated proteins can be considered as immune active substances as inducers of proinflammatory cytokine production. This is why children with HIV and acute bacterial meningitis, or HIV-associated dementia may include involuntary movements in the disease evolution.

**Neurotropic viruses and psychiatric disorders**

Over the last two decades it becomes clear that some of neuropsychiatric disorders have heterogeneous and multifactorial causes. Neurotropic viruses can induce brain damage with result in several mental alterations. We know that the immune response to a pathogen is a classic example of genetic and environmental factors activation, in this way determining specific and a variety of symptoms types. For example the ability of a virus to produce encephalitis with distinct neurological signs does not exclude that the same virus could be involved subtler neurobehavioral syndromes. We can only imagine, as we also know that the cytomegalovirus infection is a cause of severe neuropsychiatric abnormalities in infants. The immune system could be responsible to the virus-host interaction in mental illnesses and capable to clear viruses from both peripheral and central nervous compartments.

Psychiatric disorders that have been connected with viral infection:

Alzheimer’s disease:
- herpes simplex virus (HSV-1)
- Intracellular bacterium
- Chlamydia pneumoniae

Also, alteration and disfunctions in: growth factor beta-TGF-β-, IL13, vascular endothelial growth factor (VEGF), brain derived neurotrophic factor (BDNF), Neurotrophin3 (NT3) are involved.

**Attention Deficit Hyperactivity Disorders (ADHD)**

Various congenital in childhood infections have been incriminated and susceptible to contribute as causes of ADHD, but definitive and complete evidence is lacking. Associations between viruses and immune phenomena could have an influence but not neurobiologically proved yet.

**CONCLUSIONS**

A neuroimmunological aspect of some cases in which interaction between a viral infection and nervous system could trigger a neuropsychiatric disorder is the situation in which specific antibodies are synthesized against an epitope on the infectious agent cross-reacting with an epitope in the central or the peripheral nervous system.

When this immune-viral reactivity and neuroimmune response take place in the basal ganglia or their associate neuro-immune circuits, the result will be an alteration of their modulatory function and as clinical features the involuntary movements could be as a component of the primary disease and even neurobehavioral disorders.

**REFERENCES**


