The neuropsychiatric features of corticosteroid treatment in child with myasthenia gravis

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ABSTRACT:

Myasthenia Gravis in children comprises different characteristics and raises difficult enough clinical approach and adjustment of corticotherapy. In this respect, the neuropsychiatric effects of steroid therapy and its impact on the immune system of child are described briefly, via immunopharmacologically and biosynthesis mechanisms. Very few studies have been focused on steroid usage and their effects in children. Even in children the steroids can be responsible from the very mild transient symptoms leading to persistent psychiatric illness. It will be desirable and really necessary that the child with myasthenia be monitored by a pediatric neurologist, pediatric neuroimmunologist and a pediatric psychiatrist.

Key words: neuropsychiatry, corticosteroid, child, Myasthenia Gravis.

REZUMAT:

Miastenia Gravis la copil, comportã caracteristici diferite și ridicã un abord clinic și o ajustare a corticoterapiei suficient de anevoioasã. În acest sens, sunt descrise pe scurt efectele neuropsihiatrice ale terapiei cortizonice și impactul asupra sistemului imunitar la copil prin mecanisme imunofarmacologice și de biosintezã. Foarte puþine studii sunt concentrate pe folosirea steroizilor și efectele lor asupra copiilor. Chiar și la copii, steroizii pot fi responsabili de simptome tranziție foarte ușoare pânã la boalã psihicã persistentã. Ar fi de dorit și chiar necesar ca monitorizarea copiilor cu miastenie să fie fãcutã de către neurologul pediatru, neuroimunologul pediatru și psihiatrul pediatru.

Cuvinte cheie: neuropsihiatrie, corticosteroizi, copil, Miastenia Gravis.

Several autoimmune diseases in children such as asthma, juvenile rheumatoid arthritis, myasthenia gravis, are characterised from the molecular point of view by an increased expression of some types of cytokines, chemokines, kinins and corresponding receptors, adhesion molecules and enzymes with an inflammatory potential, such as nitric oxide synthetase (NOS) and /or cyclo oxygenase (COX-2).

According to Newton (2000), at cellular level, the inflamed regions show an important area of various inflammatory cells, plasma protein leakage. Taking as example myasthenia, when a chronic inflammatory myophaty coexists, these molecular and cellular effectors of the inflammatory process are effectively activated.

With regards to the immunopharmacologically effects of corticoids, in the treatment of myasthenia gravis, these reduce T-cell proliferation, at the same time increasing T-cell apoptosis via mechanisms that are at least the result of T-cell growth factor inhibition, and IL-2. Again, in the inflammatory/cortisonic myophaty or in classical muscle inflammatory infiltrate (lymphoragia), the monocyte apoptosis could be stimulated by a meaningfully influx of other infiltrating inflammatory cells as well as the migration of the inflammatory cytokines and chemokines to the inflammation site.

PSYCHOPHARMACOLOGY OF STEROID ANALOGS IN BRIEF

Therapeutically speaking the ability to retrench the number of inflammatory effectors, ensure corticosteroids the quality of being most potent anti-inflammatory agents, currently available for the treatment of several autoimmune diseases.

Table 1: Clinical Classification of Psychological Response to Steroids

<table>
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<tr>
<th>Grade</th>
<th>Definition</th>
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<tr>
<td>1</td>
<td>Mild euphoria, lessened fatigue, improved sensation, increased sense of intellectual capacity.</td>
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<tr>
<td>2</td>
<td>Heightened euphoria. Patients are effusive, expansive, volatile, hypomanic, exhibit flight of ideas, impaired judgment, refractory insomnia.</td>
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<tr>
<td>3</td>
<td>Difference responses to reflecting the ego characteristics of the patient, such as anxiety, phobia, rumination, obsessional preoccupation, hypomania, or depression.</td>
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<tr>
<td>4</td>
<td>Grossly psychotic reaction with hallucinations, delusions, extreme variations in mood.</td>
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Data from Rome and Braceland, 1952.

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For example, Methylprednisolone is frequently used in myasthenia gravis treatment.

The chemical name for the methylprednisolone is: pregn-a-1,4-diene-3,20-dione,11-17,21-trihydroxi-6-methyl-(6a,11b).

Molecular weight is 374.48.
The molecular formula is C_{22}H_{30}O_{5}.

According to European and American guidelines the recommended dosage is 0.5 to 1mg/kg/day, continuing until the patient is out of flare. After that the dosage will be slowly and progressively decreased.

The chronic treatment with corticosteroids in children refers to the fact that it will take a long time but in a minimum dose. Ideally the corticotherapy duration should be in an alternative dosage. The medical opinions differ but what is also important is the clinical course of the disease.

In addition, more knowledge on the management of steroid-related neuropsychiatric effects in children with myasthenia is needed to guide the clinicians in their treatment decisions, and more so, they must be able to identify the patients with a possible risk.

ALTERNATION/DISCONTINUATION OF CORTICOSTEROIDS

It is now accepted that the primary intervention is to decrease a discontinued steroid medication. We must reflect upon this issue, by thinking about the cause daily - dose/psychiatric syndromes. On the other hand, we must bear in mind, a risk-benefit judgment concerning the risk conditions of the neuropsychiatric complications.

HIGH VERSUS LOW DOSES

It can appear as a direct effect of a dose-response relationship for psychiatric symptoms during steroid treatment.

The etiology and pathogenesis of the corticoids effects on the brain, is still not completely understood. The adverse reactions of cortisone may be: complex, severe, irreversible, often severe, extremely varied: labile mood? psychotic manifestations.

As a treatment algorithm for children with corticosteroid medication and psychiatric disturbances, pedopsychiatry advice is needed for evaluation of suicidal ideation, agitation level.

NEUROBIOLOGY

The neuropsychiatric sequelae of steroid treatment are still under clinical and biomedical research. Generally, there is a link between neuronal activation of dopaminergic and cholinergic systems. The corticosteroid levels in the brain tissue are also an important factor. Neuropsychiatric literature has stated that the high levels of corticosteroids cause an increase in the dopamine levels.
Contrary to this, central and peripheral decreases in serotonin secretion are in connection with steroid administration (Ingram et al; 2003). It is not clear evidence that selective serotonin reuptake inhibitors (trycyclics) in treated corticosteroid-induced depression.

**NEUROIMMUNOLOGY**

The role of the immune system in psychiatric symptoms is still under discussion. Medication of some illnesses associated with immune system alterations and their relationships to psychiatric disturbances including HIV infection-A.I.D.S., Systemic Lupus Erythematosus (S.L.E.), Cortisone miophaty, Polyradiculoneuritis (Guillain-Barré syndrome) are all associated with a psychiatric symptomatology. Due to the bidirectional communication between the brain and the immune system, as an impact of corticoids treatment versus treating the psychiatric disease, the stress-inflammatory pathways are also involved in the antidepressant treatment. While analyzing the effects of steroids on neuroimmune function, we must reflect on IL-1α as a key component of the neuroimmune-endocrine axis.

**NEUROPSYCHIATRIC FINDINGS**

The variety of neuropsychiatric characteristics comprises of a spectrum of symptoms from anxiety, irritability, impaired cognition to depression, mania, psychosis and suicidality. It is a notable problem that the usage of steroids also exists in the therapeutic approach/management of non-psychiatric diseases, for example Non-Hodgkin lymphoma, musculoskeletal disorders such as acute and chronic back pain (Curatolo et al, 2001; Deyo, 2006).

Wolkowitz and colleagues (1990), report the reversible cognition deficits and mood symptoms on healthy control subjects after administration of prednisone and dexamethasone. More than this, Newcomer and collaborators (1994), also report a significant reversible cognitive deficit in healthy controls after dexamethasone and hydrocortisone administration. Steroid-induced cognitive deficits seem to be specific for declarative verbal memory. The range of the specific cognitive deficits can also include impairment in memory, retention, attention, concentration and scholar/occupational performance (Squire, 1992). The state of confusion and delirium could constitute a rare psychiatric syndrome in this context.

Affective symptoms are the most predominant clinical feature in children with myasthenia, together with position disturbances, both being expressed by disthymia or anxiety reaction. Affective ambivalence and affective lability can be observed too.

Depression is another important psychiatric symptom in adolescents with myasthenia. The spectra of these psychiatric features are probably dependent on the reduction or withdrawal of corticosteroids and on the duration of the treatment. Another influence could be exerted by rapid or inadequate changes in steroid dose (Koh et al, 2002).

Premorbid personality is also a depending factor of psychiatric symptomatology in myasthenia gravis.

Anxiety disorders leading to panic attacks are most frequent in boys with myasthenia due to the dependence on the environment.

Depression is most common in girls with myasthenia (adolescent), due to self-image changes and modifications in the body scheme, as well as to the uncertain social status.

Neuropsychiatric disturbances could be the direct or the indirect consequence of the autoimmune processes at the central nervous system level, secondary to therapy, caused by the psychological impact of the autoimmune component of the disease, as a result in restrictions and life quality.

As for the psychiatric symptoms in Myasthenia Gravis, the following aspects could be outlined:

**THE MOMENT OF THE DISEASE DIAGNOSIS**

*Early diagnosis* - emotional-reactive disturbances determined by changes in family life, social interactions, school performances, imposed by disease (changes in family roles, reduced professional activity and diminished social contacts).

*Tardily diagnosis* - far from the onset - panic attacks or depression may appear because of chronically muscular weakness, or the misperception of the entourage, or because they were not noticed by a physician who had with no qualifications regarding this affection.

*After diagnosis* - anxiety or depression. Psychic excitement triggered by:

- information about the disease
- chronic medication with its complications
- the need of lifestyle changes

**CONCLUSIONS**

Children with steroids-induced neuropsychiatric symptoms could have a good recovery, with 80% success rate, by the sixth/seventh week. However, those with
affective disorders can need a longer period of time to recover. Research studies are required to find the most adequate and most effective treatment scheme.

In order to avoid neuropsychiatric manifestations, it would be prudent to adjust the dose according to the clinical course of the disease and age. The parents of children with myasthenia, must be informed about the neuropsychiatric impact of cortisone medication.

Children are more vulnerable to the psychiatric effects of steroids and their management of treatment may be difficult to establish, taking into account the co-existence of psychical conditions such as drug-drug interactions and acceptance of the disease.

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REFERENCES


