Autoimmune encephalitis

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DOPAMINE (post-streptococcal) related autoimmune encephalitis

Distinguishing features: movement disorders, tics, multifocal myoclonic jerks; OCD

Onset: reported from 3-4 years and above, and rarely after teenage
Course: frequently a relapsing disorder

Usually, this disorder sets in suddenly (“overnight”), rather than gradually

Typically, the clinical picture is limited to only a few of the associated symptoms
- Movement disorders: tics (motor, vocal), chorea (usually affecting limbs; maybe unilateral), facial grimacing, parkinsonism, dystonia
- Motor hyperactivity
- Obsessive compulsive disorder (OCD)
- Anxiety, episodes of unmotivated fear, emotional lability, attention deficit, psychosis
- Behavioral (developmental) regression
- Epilepsy: multifocal myoclonus (maybe elicited from thalamus), maybe series of hiccups (myoclonic jerks of the diaphragm) – thalamic origin?
- Multifocal myokymia
- Slowed cognition, memory dysfunction
- Sleep disorders, including sleep inversion enuresis or altered urinary frequency

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**Streptococcal post-infectious autoimmune encephalitis**

MRI of the brain in a somnolent patient with bradykinesia and rigidity, showing inflammatory lesions (arrows) in the
(a) midbrain and periaqueductal grey matter,
(b) Right putamen and
c) Bilaterally in thalami and midbrain.
(d) Convalescent imaging showing resolution of the inflammatory changes in the thalami and midbrain

A finding of anti-Streptococcal antibodies is quite common in children – with a frequency of about 90 % being typical. Moreover, variation of such titers in an individual patient is associated with an ongoing infection and detectable long time thereafter. This is an expected feature and serves to cure the infection – and is not a biomarker of autoimmunity including in the central nervous system.

Figure to the left: in particular, children with streptococcal infections and a subsequent neurological disorder may have elevated titres of these antibodies and/or an increased percentage of activated CamKII, which in the presence of associated symptoms suggests a post-streptococcal neurological disorder.

Most frequently, one or more titres of these autoantibodies are above the reference and more rarely, all titres are elevated along with an increased concentration of CaMKII. An isolated elevated percentage of CaMKII can also be found, although sometimes together with borderline values of one or more of these autoantibodies.

Animal models suggest that these autoantibodies play a role in the disease, but they can also be biomarkers. There are of course other types of tics and OCD which are associated with other infections and are not streptococcal related.

**Treatment of autoimmune post-streptococcal neurological disorders**

**Prophylaxis**
- **Primary** – V-penicillin as soon as possible on symptoms consistent with a streptococcal infection, e.g. a sore throat
- **Secondary** – long-term Azithromycin on risk of repeated infections with short intervals
Antibiotics have no effect on the neurological symptoms and are therefore given preventive or to shorten an on-going GAS-infection as much as possible. Moreover and due to variable compliance and other factors, a new GAS infection may set in anyway - and thereafter recurrence of neurological symptoms.

On neurological symptoms of a non-tolerable severity
- **Intravenous high-dose IgG** – alternatively, plasma exchange (IgG treatment is less traumatic for a child)
- In combination with steroid in cases with more severe features or prolonged symptoms
- **Rituximab**

Significant scientific advances suggesting explanations for some initial steps of the pathogenic mechanisms

**Functions of calcium/calmodulin-dependent protein kinase II (CamKII)**
Due to its ability for autophosphorylation, CaMK activity can outlast the intracellular calcium transient that is needed to activate it. In neurons, this property is important for the induction of synaptic plasticity. Pharmacological inhibition of CaMKII blocks the induction of long-term potentiation. Upon activation, CaMKII phosphorylates postsynaptic glutamate receptors and thus changes the electrical properties of the synapse.

The figure provides an overview of some effects of this multifunctional kinase. Within a context of post-streptococcal pathology, synthesis and release of neurotransmitters (dopamine and serotonin) and synaptic plasticity may be the most significant ones.

**Lyso-GM1**, a compound of neural cell membranes, stabilizes the level of intracellular Ca++. Antibody binding to lyso-GM1 may cause an increased level of intracellular Ca++ and thereby downstream activation of CamKII. However, other mechanisms of CamKII activation may also be operative as related to this type of autoimmune encephalitis.

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**Boosting synaptic sensitivity: CaMKII triggers nearby synapses to attract more receptors for the neurotransmitter glutamate: red arrows point to CamKII**

*Glutamate abnormalities contribute to the pathogenesis of OCD*

Activation of CamKII also causes an increased level of neurotransmitters, whereby **DOPAMINE abnormalities appear to contribute to the pathogenesis of movement disorders** associated with post-streptococcal neurology.

These features have been confirmed by a new animal model in Lewis rats as well as in a cell model using a culture of nerve cells, **please see below**.

### Animal model of autoimmune post-streptococcal neurological disorder

**Behavioral, pharmacological, and immunological abnormalities after streptococcal exposure: A novel rat model of Sydenham chorea and related neuropsychiatric disorders**


http://www.nature.com/npp/journal/v37/n9/abs/npp201256a.html

- In streptococcal immunized rats, there were antibody deposition in the striatum, thalamus, and frontal cortex, and concomitant alterations in dopamine and glutamate levels in cortex and basal ganglia.
- Autoantibodies (IgG) of GAS rats caused elevated calcium/calmodulin-dependent protein kinase II signaling in SK-N-SH neuronal cells.
- Discovery of autoantibodies targeted against dopamine D1 and D2 receptors.
- Such immunized rats exhibited motor symptoms (impaired food manipulation and beam walking) and compulsive behavior (increased induced-grooming).

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*“Treatment with Ketamine (a potent noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor) appears to be efficient in otherwise therapy-resistant OCD.”* Bri. *Psychiatry. 2012 Dec 1; 72(11): 964-70*

### Cellular model of autoimmune post-streptococcal neurological disorders

The Figure is a summary of reported findings after in vitro incubation of neuroblastoma cells with sera containing anti-lyso-GM1 (and maybe additional and currently unknown factors) or monoclonals with the same specificity. CamKII activates tyrosine & tryptophan hydroxylase and synapsin-1 controlling release of these two neurotransmitters. Binding of the autoantibodies causes a reduction of the inhibitory effect of lysoganglioside GM1 on CaMKII, whereby more neurotransmitters (dopamine & serotonin) are synthesised and released (synapsin 1). Please see flow chart below. **Note that both dopaminergic and serotonergic pathways are affected.**
Molecular mimicry

GlcNAc

N-acetylg glucosamine

Epitope on group A streptococci and also a part of lyso-GM1. Synapsin I and synapsin II do also contain terminal GlcNAc

In summary:

- Incubation with serum or monoclonal IgG against dominant GAS epitope
- The normal inhibition of CaMKII by lyso-GM1 of the CSF membrane is reduced
- Increased CaMKII activity
- More phosphorylation of tyrosine & tryptophan-hydroxylase
- Increased synthesis of serotonin
- Increased synthesis of L-dopa and thereby of dopamine
- More of these neurotransmitters are released into synaptic spaces
- CaMKII also regulates synapsin I located at preysytic terminals
- Increased synthesis of serotonin
- Increased synthesis of dopamine
- Increased CaMKII activity triggers nearby synapses to attract more receptors for the neurotransmitter glutamate
- Boosting synaptic sensitivity
- Glutamate abnormalities contribute to the pathogenesis of OCD
Table 1: PANDAS Diagnostic Criteria - All five diagnostic criteria must be met

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Presence of obsessive-compulsive disorder (OCD) or a tic disorder</td>
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<tr>
<td>2</td>
<td>Prepubertal symptom onset</td>
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<td>3</td>
<td>Acute symptom onset and episodic (relapsing-remitting) course</td>
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<td>4</td>
<td>Temporal association between Group A streptococcal infection and symptom onset/exacerbations</td>
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<td>5</td>
<td>Associated with neurological abnormalities, (particularly motoric hyperactivity and choreiform movements)</td>
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Table 2: Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), proposed diagnostic criteria

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<tr>
<td>I</td>
<td>Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake</td>
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| II        | Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories (see text for full description):
  1. Anxiety
  2. Emotional lability and/or depression
  3. Irritability, aggression and/or severely oppositional behaviors
  4. Behavioral (developmental) regression
  5. Deterioration in school performance
  6. Sensory or motor abnormalities
  7. Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency |
| III       | Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others |

Note: The diagnostic work-up of patients suspected of PANS must be comprehensive enough to rule out these and other relevant disorders. The nature of the co-occurring symptoms will dictate the necessary assessments, which may include MRI scan, lumbar puncture, electroencephalogram or other diagnostic tests

I. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake

“Abrupt, dramatic onset of OCD” is the first diagnostic criterion for PANS. The acuity of onset and initial severity of the OC symptoms are hallmarks of the diagnosis. The obsessive-compulsive symptoms must be sufficiently frequent and intense to meet DSM-IV criteria for OCD and must cause significant distress and interference in the child’s activities at home, at school and with peers. Although an acute and dramatic onset of OCD is required for a PANS diagnosis, a prior history of mild, non-impairing obsessions or compulsions does not rule out the syndrome, as children may have had subclinical symptoms present for an extended period prior to the sudden onset of the full disorder.

In addition to the obsessions and compulsions typically manifest in childhood, the first PANS criterion may also be fulfilled by restricted food intake and abnormal eating behaviors. NIMH investigators had noted eating restrictions in their sample of SC patients, but Sokol and Gray were the first to observe the acute onset of anorexia following untreated GAS infections. In some patients, body image distortions appeared to drive the weight-loss inducing behaviors; while in the majority, the body image distortions appeared only after the child had lost a significant amount of weight (10-15% of starting weight) as a result of food intake restrictions that were related to obsessional preoccupations with the texture of food and a fear of choking, vomiting or contamination from ingesting specific foods. Subsequent reports have confirmed the significant symptom overlap between eating restrictions and OCD. Thus, the working PANS criteria specify that the sudden onset of eating restrictions or anorexic behaviors can fulfill the first criterion, even in the absence of more typical symptoms of OCD.

II. Concurrent presence of at least two additional neuropsychiatric symptoms, with similarly severe and acute onset


The precipitous confluence of multiple neuropsychiatric symptoms is a second fundamental feature of PANS (see Criterion 2 in Table 2). The acuity and severity of symptom onset is such that parents will describe their children as “possessed” by the illness over the course of just a few days. Although there is uniformity in the acuity and severity of onset of the co-occurring symptoms, there is great variability in the type of symptoms that are manifest. For example, one child might have severe separation anxiety and developmental regression in association with his OCD, while another presents with new onset of motor tics, concentration difficulties and emotional lability.

Further, a child’s symptom profile may evolve over time, with one set of symptoms predominating at onset and others becoming problematic after a period of days or weeks. To allow for this variability, the draft criteria for PANS list seven different categories of symptoms and allow any combination of symptoms from two or more categories. The categories of co-occurring symptoms include:

1. **Anxiety**: The anxiety may be manifest as de novo or suddenly exacerbated separation anxiety, generalized anxiety, irrational fears or worries, or a specific phobia. Early in the course of illness, the child may appear “terror stricken”, hyper-alert and excessively vigilant, as if confronted by a constant threat of imminent danger. Over the course of a several days to a few weeks, the apparent panic may subside to a state of generalized anxiety, which might present with repeated requests for reassurance that the child didn’t do something wrong or that he’s safe. Children with separation anxiety may seek physical proximity, as well as reassurance about their safety. As the name implies, separation fears typically are focused on the health and safety of one or more loved ones, but in rare cases, they center on concerns about being parted from an inanimate object, such as a piece of furniture or a room in their home. The separation anxiety may become so severe that the child will insist on sleeping between his parents or staying within reach of his mother, even when she uses the restroom.

2. **Emotional lability and depression**: Emotionally labile children experience sudden and unexpected changes in mood states, often shifting from laughter to tears without obvious precipitant. The children may complain that they have an inner sense of restlessness and agitation, which is similarly unprecipitated and inexplicable. Some children may experience the abrupt onset of a clinical depression, which can become severe enough to be accompanied by suicidal ideation. Self-injurious behaviors and suicidal ideation are also common and are of particular concern among children with concomitant impulsivity and behavioral regression, as they may cause themselves serious injury.

3. **Aggression, irritability and oppositional behaviors**: These symptoms often top the list of parental concerns because they are so disruptive. The irritability and oppositional behaviors are present throughout the day and the aggression occurs without provocation or precipitant. Most notable is the striking contrast between these new behaviors and the child’s usual state of being “sweet-tempered and well-behaved” or “easy-going and well-liked”. Outbursts occurring in response to interruption of an obsessional thought or compulsive ritual should not be counted as a manifestation of this category, as they are an expected occurrence among pediatric patients with severe OCD.

4. **Behavioral (developmental) regression**: The symptoms of developmental regression include an abrupt increase in temper tantrums, loss of age-appropriate language (sometimes to the point of the child using “baby talk”), and other behaviors inappropriate to the child’s chronological age and previous stage of development. The developmental regression may be most apparent in the child’s school assignments or artwork, as shown in Figure 2.
5. **Sudden deterioration in school performance or learning abilities:** A number of factors may contribute to the child’s academic difficulties, including among others, a shortened attention span, difficulties with concentration or memorization, specific losses of math skills or visuospatial skills, and other disturbances of cognition or executive functioning. As with the other categories, the academic difficulties must represent a distinct change from previous levels of functioning that occurs at the time of the onset of OCD symptoms. Thus, chronic manifestations of attention deficit hyperactivity disorder (ADHD) or a learning disability are not counted here, nor are the visuospatial and fine motor skill deficits that are commonplace in chronic tic disorders and classical childhood-onset OCD.

6. **Sensory and motor abnormalities:** The sensory abnormalities may include a sudden increase in sensitivity to light, noises, smells, tastes or textures of foods or items of clothing; or conversely, sensory seeking behaviors, such as needing to touch or feel particular objects or textures. Visual hallucinations may also occur and might include frightening images and perceptions that objects are floating or that they’re larger or smaller than actual size. The visual hallucinations are usually brief and only mildly disturbing, but in severe cases, may be quite frightening and persistent, lasting for several hours or longer. Motor abnormalities occurring in PANS include a variety of signs and symptoms, such as an abrupt deterioration of the child’s handwriting (dysgraphia), clumsiness, motor hyperactivity, tics and choreiform movements. Dysgraphia is a particularly useful diagnostic feature, as handwriting samples obtained during the child’s acute illness can be compared against those produced during an asymptomatic period to document the motor changes, (see Figure 3) or even to identify precipitating infections by comparing longitudinally collected handwriting samples with infections documented in the child’s medical record. Choreiform movements must be distinguished from the choreatic movements of Sydenham chorea. While chorea is characterized by jerky or writhing, arrhythmic involuntary movements of the extremities, trunk and facial muscles, choreiform movements are described as “fine, piano-playing movements of the fingers” that are present only when the child maintains stressed postures such as a Romberg stance.

7. **Somatic signs and symptoms:** Sleep problems and disturbances of urination and micturation are among the most common physical manifestations of PANS. The sleep disturbances may include not only the new onset of terrifying nightmares and night terrors, but also difficulties falling asleep, staying asleep or waking up too early (early, middle or terminal insomnia). To avoid double-counting sleep disturbances, it is important to ensure that they’re not a manifestation of an anxiety disorder. Urinary symptoms are often the presenting complaint for children with PANDAS. A pediatric clinic-based case series reported that 7 of 12 PANDAS patients initially presented with urinary symptoms, including the new onset of night-time bedwetting (secondary enuresis), daytime urinary frequency, and an urgency to void, without evidence of urinary tract infection. Subsequent experience has confirmed that urinary symptoms occur frequently during recurrences, as well as at the onset of symptoms. The symptoms are occasionally related to obsessional concerns with toileting or contamination fears, but for most children, no cognitive or emotional explanation can be found.
III. Symptoms are not better explained by a known neurologic or medical disorder

The third major criterion for PANS requires that “Symptoms are not better explained by a known neurological or medical disorder, such as SC, systemic lupus erythematosus, Tourette disorder, or others.” Thus, to make a diagnosis of PANS, clinicians must perform a diagnostic evaluation that is comprehensive enough to rule out all other disorders, including toxic effects of drugs or medications, acute disseminated encephalomyelitis, and other neurologic disorders. A complete medical history and thorough physical and neurological examination is usually sufficient to exclude the possibility of SC and many other neurological disorders. The remainder of the diagnostic evaluation should be guided by the presenting signs and symptoms, and might include laboratory tests on blood and cerebrospinal fluid, an electroencephalogram, MRI scan, or other diagnostic tests, as indicated. In addition, it may be useful to obtain a throat culture for GAS or serial antibody titers, or to perform other laboratory tests that might identify a treatable precipitant for the neuropsychiatric symptoms.