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From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)

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Abstract

Despite continued debates about the role of Group A streptococcal infections in the etiopathogenesis of PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections), experts on both sides of the controversy agree that a subgroup of children with obsessive-compulsive disorder (OCD) have an unusually abrupt onset of symptoms, accompanied by a variety of comparably severe and acute neuropsychiatric symptoms. The acuity of symptom onset is the hallmark feature of their clinical presentation and the basis for the name proposed for an expanded clinical entity: Pediatric Acute-onset Neuropsychiatric Syndrome (PANS). Modifying the PANDAS criteria to eliminate etiologic factors and to clarify the initial clinical presentation produced three potential diagnostic criteria for PANS. These three criteria are discussed in detail. The article also proposes strategies for applying the PANS criteria in clinical settings and evaluating their validity and reliability through prospective research investigations.

Introduction

When the initial description of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) was published in 1998, it was a compilation of more than a decade of research by clinical investigators in the intramural research program of the National Institute of Mental Health (NIMH) [1]. Establishing a connection between childhood-onset obsessive compulsive disorder (OCD) and preceding infections with Group A streptococcal (GAS) infections was the result of two parallel lines of research - longitudinal studies of OCD and a series of investigations of Sydenham chorea (SC) [2-4]. Prospective evaluations of children with OCD revealed that a subgroup had an atypical symptom course, characterized by an unusually abrupt onset (from no symptoms to maximum intensity within 24-48 hours), a relapsing-remitting symptom course, and significant neuropsychiatric comorbidity, including separation anxiety, ADHD-like symptoms and motor tics [1,2]. Often, the OCD symptoms were preceded by a bacterial or viral infection, such as influenza, varicella and Group A streptococcal (GAS) pharyngitis. The first case series suggested the name, "Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders (PITANDS) "to reflect the variety of infectious organisms that had been observed [5]. Cases with onset of OCD symptoms following a GAS infection were of greatest interest to the NIMH investigators because of their concomitant research findings in SC which demonstrated that obsessions and compulsions were present in 60 – 75% of the affected children [3,6,7]. The children with SC reported that the obsessive-compulsive symptoms began 2 – 4 weeks prior to onset of the adventitious movements, leading the investigators to hypothesize that the neuropsychiatric symptoms might represent a *forme fruste* of SC and be manifest by children with a history of (untreated) GAS infections, even in the absence of chorea [6,7]. Dozens of post-GAS cases were subsequently identified and their unique clinical characteristics served as the basis for the diagnostic criteria for the PANDAS subgroup [1] (See Table 1).

Subsequent research at a number of institutions revealed that not only are there clinical similarities between SC and PANDAS [8-11] but the two disorders also have similar profiles of cross-reactive antineuronal antibodies [12-15], responses to immunomodulatory therapies [16-17] and vulnerability to non-GAS recurrences [18-20]. Despite these commonalities, it is important to note that PANDAS is not equivalent to a "mild case of SC", as the presence of chorea, rheumatic carditis or any of the other major manifestations of rheumatic fever (RF) is an exclusionary criterion for PANDAS [1,21]. By ruling out RF and SC before considering a diagnosis of PANDAS, decisions about antibiotic prophylaxis can be made appropriately. Clinical practice guidelines from the American Heart Association require antibiotics prophylaxis for all cases of RF, including those presenting only with chorea [22]. In contrast, antibiotics prophylaxis is not generally recommended for children in the PANDAS subgroup. Although two separate clinical trials in PANDAS demonstrated that

All five diagnostic criteria must be met:

1) Presence of obsessive-compulsive disorder (OCD) or a tic disorder

2) Prepubertal symptom onset

3) Acute symptom onset and episodic (relapsing-remitting) course

4) Temporal association between Group A streptococcal infection and symptom onset/exacerbations

5) Associated with neurological abnormalities, (particularly motoric hyperactivity and choreiform movements)

Table 1: PANDAS Diagnostic Criteria.

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prevention of GAS infections was associated with decreased numbers of neuropsychiatric symptom exacerbations and overall improvements in symptom severity, the results were not considered generalizable to the larger population of PANDAS patients because both studies were limited by methodological constraints, including small sample sizes [23-24].

The NIMH investigators' decision to limit their investigations to the PANDAS subgroup, rather than the broader category of PITANDS, was a research strategy designed to take advantage of knowledge gained from studies of SC and rheumatic fever [7-8]. As other groups also directed their research efforts towards the role of GAS infections in the etiology of OCD and other neuropsychiatric symptoms, attention was diverted from the larger class of post-infectious neuropsychiatric disorders. A few cases of OCD and tic disorders occurring after mycoplasma infections or in association with chronic Lyme disease were reported [25-27], but these anecdotal reports have not been replicated and extended through systematic investigations, so it remains unknown whether those microorganisms play an etiologic role in acute-onset OCD and tic disorders. Further research is warranted to determine which microorganisms produce sequelae that include acute-onset neuropsychiatric symptoms and to investigate the variety of etiologies and pathogenic mechanisms.

The requirement that PANDAS patients demonstrate "temporal association of neuropsychiatric symptom onset with preceding GAS infection" created difficulties for clinicians, who often were confronted with patients who met all criteria for the PANDAS subgroup, except for evidence of a preceding GAS infection [28]. Unfortunately, establishing an etiologic role for GAS in the onset of PANDAS is often as difficult as it is for SC, where the chorea may lag behind the inciting GAS infection by six months or longer [6,29]. By then, the GAS infection has been cleared from the throat (so cultures are negative) and the rise in antibody titers has already occurred, so it is no longer possible to establish a causal relationship between GAS and the neuropsychiatric symptoms. Spuriously positive associations are similarly problematic, as positive cultures and elevated antibody titers may be completely unrelated to the neuropsychiatric symptoms, since GAS infections are such a common occurrence among school-age children [30]. Additional impediments to establishing GAS as the etiologic agent in PANDAS include the need for an appropriately performed throat culture to differentiate GAS pharyngitis from other pathogens; the lack of sensitivity of rapid strep tests and throat cultures (5-15% false negatives), the presence of a carrier state among 1 in 20 children, and the need for serial measurements of anti-streptococcal titers at specified intervals in order to document an immune response to an acute infection [31-32]. Prospective, longitudinal investigations would appear to be the solution to this problem, as they are designed to detect GAS infections which precede exacerbations of neuropsychiatric symptoms, but those studies also may fail to establish an etiologic relationship, since the cross-reactive antibodies may be nonspecifically released during the early, innate immune response [33]. A generalization of the immune response might provide a partial explanation for the results of two recent prospective studies of children with tic disorders, which found increased numbers of neuropsychiatric exacerbations following a variety of immune stimulants, including viral infections and psychosocial stressors, as well as after GAS infections [19-20,34].

An additional problem encountered in the prospective longitudinal studies was the lack of clear separation between PANDAS cases and non-PANDAS cases [19-20]. Difficulties distinguishing the "acute, dramatic onset" of tics in the PANDAS subgroup from the typically "acute" onset of tics in non-PANDAS tic disorders were predicted by the fact that both are described as having an "off-on" onset [35]. Indeed, studies that did not clearly establish acuity of onset for their PANDAS cases found few differences between the cases and non-PANDAS controls [19-20,34]. The overlap not only limited the results of the clinical studies, but also impacted laboratory studies dependent upon clear separation of cases and controls [36]. Not surprisingly, such studies produced negative data, which was interpreted as refuting the PANDAS hypothesis. In contrast, studies that adhered closely to the PANDAS diagnostic criteria produced positive data and were seen as supporting a role for GAS in the etiology of neuropsychiatric symptoms (reviewed by Murphy et al. [37]). Adding to the confusion of the conflicting data reports were editorial debates about the validity of the PANDAS subgroup and the utility of its hypothesized etiology [38-41]. The resulting "PANDAS controversy" adversely affected researchers, clinicians and acutely ill children and their parents, who were all left confused about the appropriate course of action to be taken in the face of such diametrically opposing views.

To address these issues, a group of clinicians and scientists were assembled in July 2010 for a workshop on "PANDAS". The quotation marks indicate that the discussions were not limited to cases meeting the five published criteria for the PANDAS cohort. In fact, the planning committee had elected to broaden the scope of the workshop to include all possible cases of acute-onset OCD, regardless of potential etiology. Primary tic disorders were not a topic of discussion, because of the reported difficulties in accurately identifying PANDAS among patients presenting with primary tic disorders (described above). In making these changes, the workshop organizers hoped not only to facilitate discussion of the broader spectrum of acute-onset OCD and related neuropsychiatric disorders, but also to aid in the development of descriptive criteria that could concisely summarize the clinical features distinguishing these patients.

From PANDAS to PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)

Six clinicians (Drs. Elana Ben-Joseph, Boston MA; Josephine Elia, Philadelphia PA; Miroslav Kovacevic, Hinsdale IL; Elizabeth Latimer, Rockville MD; Tanya K. Murphy, Tampa FL; and Margo Thienemann, Palo Alto CA) presented clinical data extracted from their evaluations of more than 400 (total) children and adolescents who had been diagnosed with PANDAS. Each of the physicians summarized their patients' demographic information; clinical presentation at initial onset of symptoms and during subsequent exacerbations; and laboratory results. Specific details of the case reports are not presented here, but are comparable to those recently reported by Murphy and colleagues [42]. Several trends that had been observed in the first 50 cases in the PANDAS subgroup [1] were again apparent: boys outnumbered girls 2:1; symptom onset occurred most frequently before age 8 years; obsessive-compulsive symptoms were universally present; and comorbid neuropsychiatric symptoms were observed in more than 90% of patients.

On the basis of the clinical summaries, the conference participants were asked to identify the symptom or symptoms which best

characterized the collective group of patients. There was unanimous agreement that an "acute and dramatic symptom onset" was the key clinical feature. Particularly noteworthy were cases where parents had been able to identify the exact date and time that their children's symptoms had begun, and their descriptions of the onset as "ferocious", "overwhelming" or "severe enough that we took him to the ER". Acute onset was considered integral to the clinical presentation and was incorporated into one of the names proposed for this new clinical entity -- Pediatric Acute-onset Neuropsychiatric Syndrome (PANS). Childhood Acute-onset Neuropsychiatric Syndrome (CANS) was also proposed [41], but was not favored because "childhood" would exclude adolescents, while "pediatric" extends to at least age 18 years (and in some definitions, 21 years). Because adolescent cases were not uncommon in the clinicians' experience, the conference participants decided that the new syndrome should not exclude cases with post-pubertal onset, as the PANDAS criteria had done [1,43].

As shown in Figure 1, PANS is postulated to be much broader than PANDAS and PITANDS, including not only disorders potentially associated with a preceding infection, but also acute-onset neuropsychiatric disorders without an apparent environmental precipitant or immune dysfunction. Because cases of PANS are defined clinically, the syndrome is expected to include a number of related disorders which have different etiologies but share a common clinical presentation – the foudroyant (lightning-like) onset or recurrence of OCD which is accompanied by two or more co-occurring neuropsychiatric symptoms. The diagnostic criteria proposed for PANS are shown in Table 2.

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 [44]. Although an acute

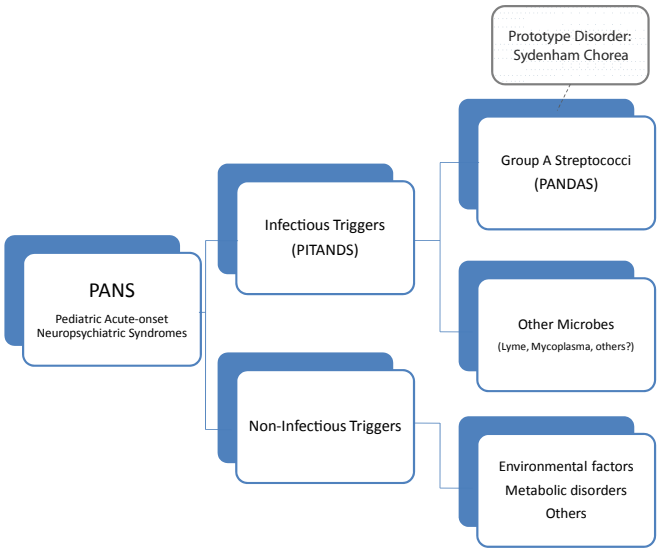


Figure 1: Hierarchy of the Pediatric Acute onset Neuropsychiatric Syndrome.

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

Table 2: Diagnostic Criteria Proposed for Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).

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 [6-7], but Sokol and Gray [45-46] 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 [6,7,45-46]. Subsequent reports have confirmed the significant symptom overlap between eating restrictions and OCD [47,48]. 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.

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:

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.

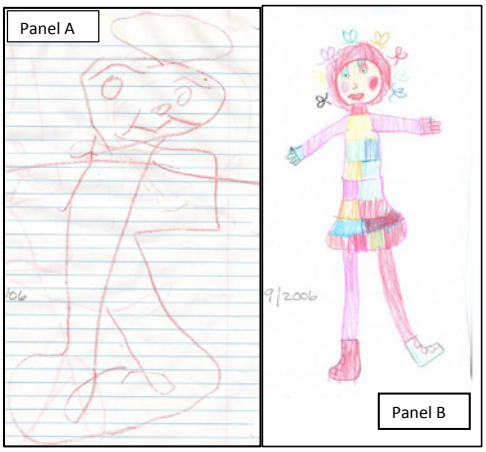
Emotional lability and depression : Emotionally labile children experience sudden and unexpected changes in mood states, often shifting from laughter to tears without obvious precipitant. The children may complain that they have an inner sense of restlessness and agitation, which is similarly unprecipitated 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.

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.

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.

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



Panel A– Drawing produced during an acute exacerbation of OCD and other symptoms of PANDAS which appears quite messy and immature.

Panel B – Age-appropriate picture drawn after treatment with IVIG and symptomatic improvement.

Figure 2:

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 [49,50].

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 [51]. 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 [52].

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

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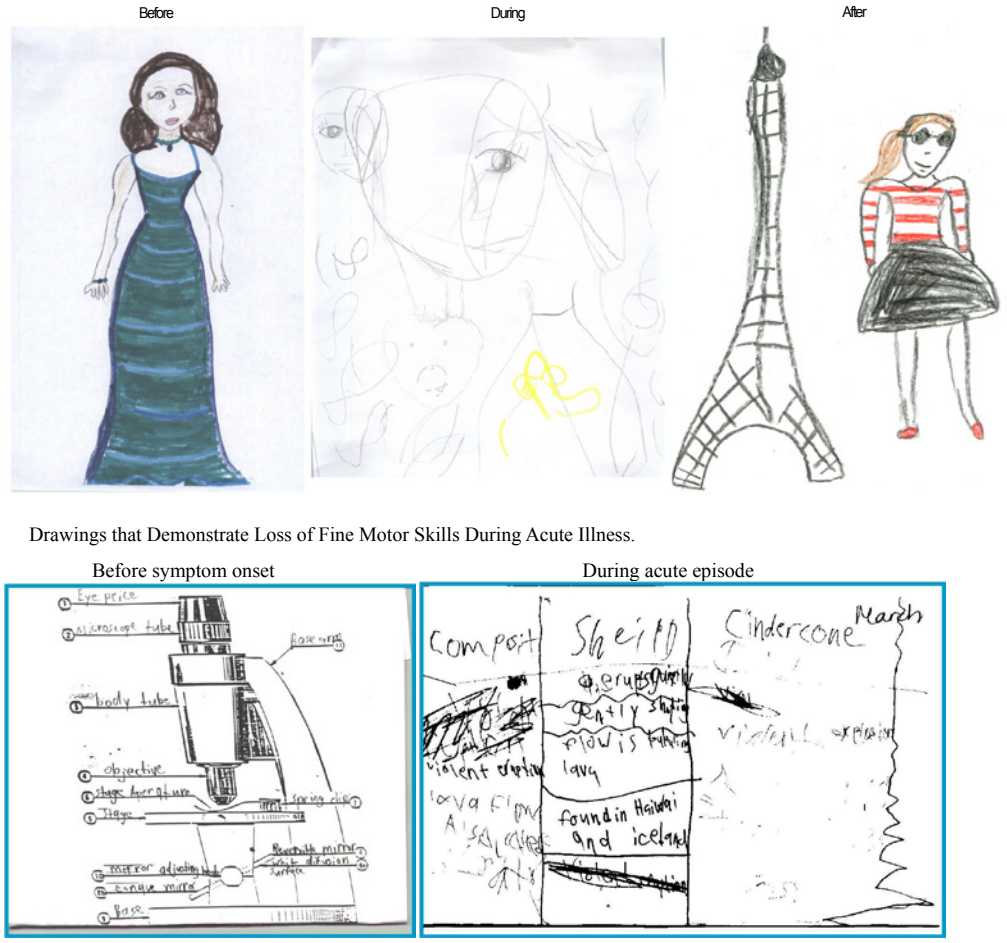

Figure 3: Handwritng samples documenting dysgraphia during acute illness.

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 [53]. 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.

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.

Use of the PANS Criteria

The goal of the new PANS criteria is to attempt to define the clinical presentation of a relatively narrow group of patients in order to improve the comparability of research samples. Given the breadth of potential etiologies for PANS, it will be essential for its clinical presentation to be as uniform and homogeneous as possible. The current criteria were based on the presentations commonly seen in moderately to severely affected patients with acute-onset OCD and admittedly may exclude children with only mild symptom severity or those with an atypical presentation. Excluding such cases was considered preferable to broadening the criteria to include all borderline cases, as that was likely

to introduce extraneous patient groups and further complicate the search for common disease mechanisms for PANS. During the process of refining the diagnostic criteria for PANS, it will be helpful to learn about cases in which a child "almost met" the PANS criteria but could not be included because of variances from the published description. Atypical presentations also will be of interest and may be helpful in determining the clinical boundaries of the syndrome.

The proposed criteria should be considered as "working criteria", which will undergo modifications and refinement as additional clinical and research experience is accrued. To aid in this effort, it is essential that the clinical features of PANS are described in such a way that between-site comparisons can be made. A PANS diagnostic and assessment tool is currently under development at Yale University to provide a reliable and valid means of standardizing the diagnostic evaluation of children suspected of having PANS.

Summary and Future Directions

A set of criteria for Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) has been proposed in order to identify a unique and homogenous group of patients who share key clinical characteristics, including the fulminant onset of obsessive-compulsive symptoms and a multiplicity of co-occurring signs and symptoms. The draft criteria must now be validated through careful, systematic application in clinical practice and research investigations. Systematic clinical observations are needed in order to learn more about the clinical characteristics, natural and treated history, and prognosis of PANS, as well as to identify potential precipitants of symptom onset and exacerbations. Research investigations are required to evaluate the validity, reliability and utility of the draft criteria, as well as to evaluate potential etiologic factors and mechanisms of disease that might be common to the disorders subsumed under the PANS clinical description.

To achieve those objectives, a number of immediate and longer term research studies are required. Large-scale epidemiologic studies and a centralized registry are needed to evaluate the sensitivity and specificity of the draft criteria for PANS and to characterize the incidence, prevalence and demographics of the syndrome. These community-based studies may also serve to identify environmental risk factors and precipitants, just as epidemiologic efforts were critical to the discovery that cigarette smoking causes lung cancer and heart disease. Unfortunately, such large scale epidemiologic investigations are likely to be prohibitively expensive, as the accurate diagnosis of PANS currently requires the investment of sufficient amounts of time to allow interviewers to obtain a detailed description of the onset and course of the neuropsychiatric symptoms, comprehensive medical and family histories, and information about a wide variety of environmental factors that might put a child at risk for PANS or trigger the onset or worsening of the neuropsychiatric symptoms. While chart reviews and other retrospective methodologies may be useful in narrowing the scope of the prospective investigations, they cannot provide the data needed to definitively establish an etiological role for a proposed trigger or set of environmental precipitants. Ideally, biomarkers identifying at-risk and affected individuals will be developed that can be utilized in the epidemiologic studies to accurately separate cases from controls.

In addition to the community-based studies, research on PANS should include a wide variety of clinical, translational and basic science investigations. The studies should build on the past two decades of research on PANDAS by applying those findings to the larger cohort of patients with PANS. For example, animal models recently demonstrated that GAS infections can trigger the production of cross-reactive antibodies that not only induce neurologic and behavioral symptoms in the originally infected mice, but also evoke symptoms when passively transferred to donor mice [54-55]. Expanding these investigations to evaluate the effects of a variety of infectious agents and other immune stimulants would be useful, particularly if the animal models can be used to evaluate potential therapeutic interventions. Investigations of other neuroimmune disorders, such as systemic lupus erythematosus, may also provide insights into the disease mechanisms underlying the OC symptomatology in PANS [56]. As research on PANS progresses, close collaborations between basic and clinical scientists will ensure that laboratory findings are translated rapidly into clinical practice through the development of new and more effective therapeutic and preventive interventions.

While waiting for the results of those research investigations, clinicians are encouraged to consider PANS when children present with acute-onset of obsessive-compulsive symptoms, separation anxiety or emotional lability. Because OCD is a disorder of "rational irrationality", affected children often recognize the absurdity of their obsessional thoughts and compulsive rituals and will not volunteer information about the content of their OCD symptoms; they may also downplay the severity of their distress. In such cases, standardized instruments, such as the Children's Yale-Brown Obsessive-Compulsive Scale [57], can be useful in documenting the nature and extent of the child's symptoms.

PANS should also be included in the differential diagnosis of secondary enuresis or daytime urinary frequency (after ruling out a urinary tract infection), and when an older child abruptly develops motoric hyperactivity, handwriting deterioration, or academic difficulties. If the child fulfills the clinical criteria for PANS, the possibility of PANDAS should also be considered and appropriate laboratory studies obtained to determine if GAS played a role in the etiology of the child's symptoms. Depending on the child's history and physical examination, other infectious triggers might also be considered and appropriate laboratory studies obtained. In children for whom no etiologic trigger can be identified, therapeutic interventions for PANS are limited to symptomatic treatments, including medications and behavioral therapies. Standard therapeutic approaches are often helpful, including use of an SSRI for obsessive-compulsive symptoms or an anti-dopaminergic medication for tics. However, treating clinicians must "Start Low and Go Slow!" as children with acute-onset neuropsychiatric disorders are exquisitely sensitive to psychotropic medications [42]. Supportive therapies also may be indicated, as the symptoms of PANS can be distressing not only to the affected child, but also to his parents or caregivers.

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