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Pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections (PANDAS) – A review

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ABSTRACT

PANDAS are a rare disease in children which shows the relationship between group A beta hemolytic streptococcal infection with rapid onset of obsessive compulsive disorder and tic compulsive disorder. It has been proposed that children with PANDAS experience tics, obsessive-compulsive behavior, and perhaps other neuropsychiatric symptoms as an autoimmune response to streptococcal infection. This includes information on symptoms, pathophysiology, diagnosis and treatment about PANDAS. Molecular mimicry hypothesis proposed mechanism for the PANDAS. Five main diagnostic criteria are proposed for identifying PANDAS. Treatment includes medicinal treatment along with experimental therapy which involves environmental modifications, stress management, infection control etc. On the basis of current information available PANDAS remains yet unproven hypothesis.

Keywords: Autoimmune, Neuropsychiatric symptoms, Tics and obsession, GABHS infection.

INTRODUCTION

Pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections (PANDAS)

Describes a hypothesis that there exists a subset of children with rapid onset of obsessive-compulsive disorder (OCD) or tic disorders and these symptoms are caused by group A beta-hemolytic streptococcal infection.[1]The relationship between infection and these disorders is that, there is an initial autoimmune reaction to a GAβHS infection which produces antibodies that interfere with basal ganglia function, causing symptom exacerbations. This autoimmune response can result in a broad range of neuropsychiatric symptoms.[2][3] Obsessive-compulsive disorder (OCD) and related conditions including Tourette's disorder (TD) are prevalent disorders affecting as many as 0.3%–3% of the pediatric population.[4]They are chronic, recurrence disorders combine with marked impairment and disability. The causes of these disorders are unknown. Over the past several years, increasing evidence has pointed to immune-related problems are basis in some cases of childhood onset OCD, tic disorders and other anxiety disorder.[5]The most important immunologic convict involved in the onset of these symptoms is group A streptococcus (GAS).

About bacteria

GABHS in PANDAS is a spherical, Gram-positive, non-motile organism and the most common bacterial

cause of acute pharyngitis ("strep throat") in children. [6][7] Numerous serotypes of GABHS have varying degrees of disease activity with classification based on antigenic surface proteins M and T. They are the infectious agents of scarlet fever, acute rheumatic fever (ARF), glomerulonephritis, toxic shock syndrome, and necrotizing fasciitis, amongst others. Its defense of antigenic surface proteins and pyrogenic exotoxins, as well as its ability to lyse its way systemically and evade the immune system effectively, have been well characterized. For example, M.protein is the major virulence factor preventing phagocytosis, thus multiplying rapidly in human tissue and initiating the disease process. More than 80 types of *S. pyogenes* M proteins alone have been isolated [8] the serotype(s) in PANDAS is not yet known. . GAβHS is generally spread by direct personal contact, most likely through droplets of saliva or nasal secretions. Crowding increases transmission, and outbreaks are common through chronic asymptomatic carriers and in institutional settings, such as the military, daycare centers, and within households. Human contamination of food has also been reported.[9]

SIGNS AND SYMPTOMS

In addition to an OCD or tic disorder diagnosis, children may have other symptoms associated with exacerbations such as emotional lability, enuresis, anxiety, and deterioration in handwriting.[1] In the PANDAS model, this abrupt onset is thought to be preceded by a strep throat infection. As the clinical spectrum of PANDAS appears to resemble that of Tourette's syndrome, some researchers hypothesized that PANDAS and Tourette's may be associated; this idea is controversial and a focus for current research.[3][10][11][12][13]

Although there is no typical clinical course for children with PANDAS, families have identified the following behaviors. [14]

- Tics n Obsessions (e.g., preoccupation with a fixed idea or an unwanted feeling, often accompanied by anxiety)
- Compulsions (e.g., an irresistible impulse to act, regardless of the rationality of the motivation)
- Choreiform movements (e.g., milkmaid grip, fine finger playing movements in stressed stance)
- Emotional lability (e.g., irritability, sudden unexplained rages, fight/ flight)
- Personality changes n Age-inappropriate behaviors, particularly regressive bedtime fears/rituals
- Separation anxiety
- Oppositional behaviors
- Tactile/sensory defensiveness
- Hyperactivity, impulsivity, fidgetiness, or inability to focus
- Major depression n Marked deterioration in handwriting or math skills
- Urinary frequency/enuresis n Anorexia (particularly fear of choking, being poisoned, contamination fears, fear of throwing up)
- Joint pain, stiffness, and fatigue similar to other autoimmune disorders.[14]

PATHOPHYSIOLOGY

In patients with PANDAS, the symptoms caused by infection is controversial.[1][3][11][15][16][17] PANDAS and PITAND (pediatric infection-triggered autoimmune neuropsychiatric disorder) are thought to be similar to Sydenham's chorea, an autoimmune disorder in which antibodies meant to fight strep infections but attack the basal ganglia of the brain, which results in uncontrolled flailing of the extremities, trunk, and facial muscles, for a period of weeks or months. The cause of PANDAS and PITAND is thought to be the following sequence of events:

- A genetic pre-disposition to an abnormal immune response,
- Followed by the creation of an antibody that interferes with neuronal activity, and
- Finally a breach in the blood brain barrier, thought to be due to inflammation that allows the antibody to reach neuronal tissue and interfere with functioning.[18][19][20]

Typically developing children experiencing strep infections produce antibodies that assist the body in deactivating and removing the strep antigen. The immune system then remembers the surface of the strep antigen and antibodies are quickly produced in subsequent infections. [18] This process becomes problematic in children with PANDAS or PITAND. Basal ganglia cells have a surface that is similar to

the surface of the strep antigen. When antibodies from the blood of children with PANDAS or PITAND cross over the blood–brain barrier, they mistakenly recognize the basal ganglia cells as strep antigen, sending antibodies to deactivate the antigen. Rather than deactivating and destroying the basal ganglia cells, the antibodies appear to attach to neurons and interfere with neuronal signaling by increasing calcium–calmodulin dependent protein kinase II (CaM Kinase II) production in the basal ganglia, eventually affecting production of neurotransmitters, such as dopamine. When comparing antibodies in the blood serum of children who had strep infections and met the criteria for PANDAS to typically functioning children and children with obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), and tics, researchers have found significantly higher levels of the antibodies that trigger basal ganglia neuronal cell CaM kinase II production in children with PANDAS, indicating that PANDAS is different from traditional OCD, tics, or ADHD. This finding may one day lead to a blood test for diagnosing PANDAS.[20][21]

MOLECULAR MIMICARY HYPOTHESIS

The molecular mimicry hypothesis is a proposed mechanism for PANDAS[22] this hypothesis is that antigens on the cell wall of the streptococcal bacteria are similar in some way to the proteins of the heart valve, joints, or brain. Normally the antibodies set off an immune reaction which damages those tissues, the child with rheumatic fever can get heart disease (especially mitral valve regurgitation), arthritis, or abnormal movements known as Sydenham's chorea.[23] In a typical bacterial infection, the body produces antibodies against the invading bacteria, and the antibodies help eliminate the bacteria from the body. In some rheumatic fever patients, autoantibodies may attack heart tissue, leading to carditis, or cross-react with joints, leading to arthritis.[22]In PANDAS, it is believed that tics and OCD are produced in a similar manner. One part of the brain that may be affected in PANDAS is the basal ganglia, which is believed to be responsible for movement and behavior. It is thought that similar to Sydenham's chorea, the antibodies cross-react with neuronal brain tissue in the basal ganglia to cause the tics and OCD that characterize PANDAS.[1][24]

DIAGNOSIS

According to Lombroso and Scahill, 2008, five diagnostic criteria were proposed for PANDAS:

- The presence of a tic disorder and/or OCD consistent with DSM-IV;
- Prepubertal onset of neuropsychiatric symptoms;
- A history of a sudden onset of symptoms and/or an episodic course with abrupt symptom exacerbation interspersed with periods of partial or complete remission;
- Evidence of a temporal association between onset or exacerbation of symptoms and a prior streptococcal infection; and
- Adventitious movements (e.g., Motoric hyperactivity and choreiform movements) during symptom exacerbation" [22]

If the symptoms have been present for more than a week, blood tests (antistreptococcal titers) may be done to document a preceding streptococcal infection.[24][25]

COURSE OF ILLNESS

The main drawback of the proposed criteria for PANDAS is the principle source of debate around the definition and the difficulty in demonstrating an association between new GABHS infections and exacerbation of tics/ OCS throughout the course of illness. Recent work has underscored that unequivocal bona fide new GABHS infections with expected immune response require a precisely documented acquisition of GABHS followed by significant increase in both ASO [anti steptolysin o antibody] and anti-deoxyribonuclease B (anti-DNAseB) antibody titers. Rise in only one antibody may neither be sensitive nor specific enough for diagnosing a new GABHS infection accurately; additionally, it is crucial to demonstrate the rise in antibody titer, which requires continuous monitoring, since antibody titer may remain elevated for more than 1 year after the initial infection.[26]

A specific clinical phenotype that distinguishes PANDAS

In order to reduce unnecessary costly and potentially unrewarding follow ups Bernstein and colleagues discriminated PANDAS from non- PANDAS acute OCS/tics. They compared 21 children from the centre who fulfilled Swedo et al., PANDAS criteria to 19 children with non-PANDAS OCD. This analysis showed that separation anxiety, urinary urgency, oppositional defiant behavior, mood swings, inattention, hyperactivity, impulsivity, deterioration in handwriting, and decline in school performance were more likely to occur in PANDAS.[27]

TREATMENT

Treatment for children suspected of PANDAS is generally the same as the standard treatments for TS and OCD. [2][28][29]These include cognitive behavioral therapy and medications to treat OCD such as selective serotonin reuptake inhibitors (SSRIs); [28] [29] and "conventional therapy for tics. [2]

EXPERIMENTAL TREATMENTS

Prophylactic antibiotic treatments for tics and OCD are experimental [30] and controversial; over diagnosis of PANDAS may have led to overuse of antibiotics to treat tics or OCD in the absence of active infection. A single study of PANDAS patients showed efficacy of immunomodulatory therapy (intravenous immunoglobulin (IVIG) or plasma exchange) to symptoms, but these results are unreplicated by independent studies[15][31] The immune modulatory therapy [IVIG or plasma exchange [1] both carry a severe risk of adverse effects, thus use of these therapy should be reserved for children with particularly severe symptoms and a clear-cut PANDAS presentation.[29] The American Heart Association's 2009 guidelines state that, as PANDAS is an unproven hypothesis and well-controlled studies are not yet available, they do "not recommend routine laboratory testing for GAS to diagnose, long-term antistreptococcal prophylaxis to prevent, or immunoregulatory therapy (e.g., intravenous immunoglobulin, plasma exchange) to treat exacerbations of this disorder"[32]

EXPERIMENTAL THERAPY

Exacerbation of PANDAS and PITAND impacts virtually every area of daily living, including self-care, school-related skills, physical function, and social– emotional well-being. Occupational therapy can assists in negotiating exacerbation, but doing so requires a paradigm (pattern) shift. Children often lose skills during exacerbation, and traditional remedial intervention may be ineffective. Greater benefit may be found with adaptation and compensation for problems during exacerbation, followed by remediation of ongoing problems during remission.[33]

OCCUPATIONAL THERAPY

Occupational therapy is as essential as drug therapy; practitioners interview and observe the child, family, caregivers, and teachers to find out the underlying difficulties, such as obsessions, compulsions, or sensory needs. When needed, occupational therapy intervention should address the following areas.

Daily routines

Proactive, healthy routines can help families recognize and manage exacerbation periods. Regular homework schedules help families recognize when children are having difficulty with homework, as the completion time or degree of assistance required may increase when a child is entering exacerbation. Regular bedtime routines increase the likelihood of restful sleep and alert the family to a sudden change in routine, such as needing the light on longer or requiring the parent to be present at bedtime for longer periods of time. These changes often signal the separation anxiety seen in exacerbation. A structured routine can also help families by reducing chaos during the stressful periods of exacerbation.

Environmental modification

Environmental modification may include changing the location of activities while a child is in exacerbation. For example, completing homework in the kitchen with other family members nearby for a child with separation anxiety or, conversely, completing homework in a quiet area for a child with auditory defensiveness, may be enough of a change to help the child succeed. Task modification might include reducing homework or changing an art

project from finger painting to brush painting, depending on the child's individual needs.

Sensory tools

Sensory tools such as various aromas, deep pressure, and neutral warmth may help to calm a child. Fidget toys and the use of a therapy ball instead of a chair may help a child who is seeking sensation to focus better in the classroom. Gross motor breaks to move about and vestibular activities like jumping on a mini trampoline may help children experiencing lethargy to return to activities with more functional arousal**.**

Stress management

Stress-reduction techniques such as yoga, calming music, and progressive muscle relaxation can be added to healthy routines to help even out the stress and frustration of exacerbation. These techniques may be used by children with PANDAS or PITAND and may also be useful to other family members during each exacerbation.

Infection control

Because any type of infection may trigger exacerbation, it is compulsory that occupational therapy practitioners should be aware about infection control and consider the risk of a child contracting an infection from ordinary play items more often used by child.

Family support

Families are affected by PANDAS because parenting skills are questioned and socialization becomes restricted, it is necessary to improve the coping skills of all members of the family. This can be implemented by educating school, personnel and parents about the symptoms of PANDAS and PITAND, and by offering tools to manage exacerbation, occupational therapy practitioners can support families to reduce social isolation. Similarly, siblings are affected as parental time and resources are depleted while managing PANDAS and PITAND exacerbations. [34]

CONCLUSION

PANDAS are an autoimmune response to streptococcal infection. It is diagnosed clinically after a patient develops a number of physical and behavioral symptoms followed by strep throat infection. Diagnosis of PANDAS by community pharmacist without convulsive evidence is not suggestive. Medication and cognitive behavioral therapy are the primary treatments for PANDAS. PANDAS yet remain an unproven hypothesis. The optimum diagnostic and therapeutic approach awaits the results of additional research studies.

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