ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 11, Issue, 01, pp. 43952-43955, January, 2021
https://doi.org/10.37118/ijdr.20933.01.2021

RESEARCH ARTICLE OPEN ACCESS

PANDA SYNDROME: DIAGNOSIS AND TREATMENT

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ARTICLE INFO

Article History:
Received 20th October, 2020
Received in revised form
06th November, 2020
Accepted 11th December, 2020
Published online 30th January, 2021

Key Words:

PANDA syndrome; Streptococcal Infections; Neuropsychiatric; Autoimmune; Pediatric.

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ABSTRACT

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (or PANDAS), is a neuropediatric disorder with abrupt evolution. This study is a narrative review, carried out between the months of October and December 2020. It was found in 20 articles, symptoms must, It was indexed in international databases and dated from 2016 to 2020. Anxiety, depression or emotional lability, behavioral regression, poor school performance, motor or sensory changes, as well as somatic symptoms are the characteristics reported by the parent's child. The initial medical treatments are empirical medication and educational intervention, while specific symptomsmust be treated according to the child's specific presentation as described below.

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Citation: Gabrielle Grisolia Assad, Bruna Eduarda Slongo, Mariana Gomes de Oliveira Santos, Natália Ferrari, Mayara Lucia Webber and Juliana Yacubian, 2021."Panda syndrome: diagnosis and treatment", *International Journal of Development Research*, 11, (01), 43952-43955

INTRODUCTION

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (or PANDAS), is a neuropediatric disorder that is characterized by an abrupt evolution following a Group A beta-hemolytic streptococcal infection (GABHS), it is manifested with exacerbation or of onset obsessive compulsive disorder (OCD), tics and neurological abnormalities (Swedo and Grant, 2005; Singer, 2004). It is a rare syndrome, of unknown prevalence and incidence. It is estimated to be a base disease in more than 10% of tic disorders and obsessive-compulsive disorders in children (Ferreira, 2019). It is often more common in males, in a ratio of 2.6 men to 1 woman, and it is more prevalent for those with a family history of Rheumatic Fever (Ferreira, 2019). According to Laza (2006) and Souza (2018), to be diagnosed with PANDAS, it must meet five cardinal criteria: obsessive compulsive disorder (OCD) and/or a tic disorder; prepubertal onset; relapsing and remitting course of symptoms that are temporally associated with GABHS infection and altered neurological test results, as well as an abrupt onset or pathological course marked by periods of quiescence and sudden exacerbation episodes (Laza, 2006; Souza, 2018). The most common obsessive-compulsive symptoms are related to cleaning behaviral and fear of contamination, while tics can be motor or vocal, and it is common for several tics to appear simultaneously (Ronchetti, Böhme and Ferrão, 2004). Emotional lability, motor hyperactivity and choreiform movements are also particularly frequent among neurological changes (Swedo and Grant, 2005; Singer, 2004; Laza, 2006; Marcerollo and Martino, 2013). The latter are typically abrupt and irregular, they involve the distal muscles and are easily assessed on a child placed in an orthostatic position, with arms outstretched in pronation and eyes closed, deviation of pronation and fine *piano playing* movements on the child's fingers and toes can be observed (Swedo and Grant, 2005; Singer, 2004; Laza, 2006; Marcerollo and Martino, 2013). Other common findings of the PANDAS syndrome are: Separation anxiety, anxiety, irritability, impulsivity, oppositional defiant behavior, inability to focus, moodinstability, behavioral regressions, somatosensory amplification, tactile and motor defensiveness, urinary urgency, decline in school performance, deterioration of small motor skills or poor handwriting, sleep disorders with a higher occurrence of nightmares and bedtime rituals (Swedo and Grant, 2005; Souza, 2018; Baytunca and Donuk, 2016). According to Ferreira (2019) and Singer (2004), the temporal relationship between streptococcal infection and the onset of PANDAS symptoms is variable, resulting in acute exacerbations coexisting with GABHS-positive oropharyngeal secretion cultures, within two weeks after infection. Such episodic exacerbations are alternated with periods of remission based on negativity in oropharyngeal culture tests and titration of anti-streptococcal antibodies (Swedo and Grant, 2005; Ferreira, 2019). Although the PANDAS pathogenesis is not yet elucidated, it is believed that, in a genetically susceptible host, the infection by group A beta-hemolytic streptococci results in the IgG antibodies production which cross-reacts with the neuronal proteins of the basal ganglia. Such anomalous immune reaction compromises the neurobiological

functioning of the caudate, putamen, and pale globe nucleus, as well as the cortico-striated-thalamus-cortical circuit (Laza, 2006; Ronchetti, Böhme and Ferrão, 2004; Chiarello, 2017). In addition, the serum marker D8 / 17, an alloantigen associated to autoimmune B lymphocytes after streptococcal infection, which is present in 90% of cases of rheumatic fever, is overexpressed in patients with PANDAS, corroborating the pathogenic hypothesis of autoimmunity (Swedo and Grant, 2005). The M Protein, a GABH virulence factor that gives phagocytosis by polymorphonuclear leukocytes resistance, presents antigenic sites similar to the cytoskeletal epitopes, nucleus and plasma membrane of the basal ganglia neurons, is pointed out by several authors as the triggering element of the cross reaction (Ronchetti, Böhme and Ferrão, 2004). The genetic susceptibility to PANDAS also needs clarification. However, family studies of children with the syndrome have shown higher rates of tic disorders and obsessive compulsive disorders in first-degree relatives than in the general population, showing a genetic predisposition in affected individuals (Swedo and Grant, 2005, Ronchetti, Böhme and Ferrão , 2004, Lougee et al., 2000). Despite the complexity of clinical manifestations that permeate the diagnosis and treatment of PANDAS, both the diagnosis and the management of the syndrome remain unclear to the medical literature, it lacks studies capable of providing broad and updated information on these topics. The main goal of this review is to contribute to the syndrome recognition through the heterogeneity of its presentation, as well as to briefly expose the interventions and therapeutic conduction available for PANDAS treatment according to the effectiveness of each approach and its suitability to the individual aspects of each patient.

METHODOLOGY

This is a narrative review, carried out between the months of October and December 2020. Articles indexed in the databases SciELO, MEDLINE, LILACS and ELSEVIER, published in English since 2015, which database research was included using the terms "autoimmune", "peadiatric", "psychiatric", "tics", "treatment" combined through the Boolean operator "AND". Repeated studies, of systematic reviews of which themes did not meet the present study objectives were left out.

RESULTS

The selected articles were indexed in international databases and dated from 2016 to 2020. They are shown in the table below, separated according to the title, year of publication, journal and authors.

DISCUSSION

The first diagnostic criteria for PANDAS were introduced in 1998, and included a diagnosis of obsessive-compulsive disorder (OCD) or TICdisorder by DSM-III, IV or IV-TR; onset of symptoms within the age of 3 and the beginning of the pubertal period; episodic course guided by onset or abrupt exacerbation of symptoms; presence of

Table 1.

Title	Year of Publication	Journal	Authors
PANDA/PANS in childhood: Controversies and evidences	2019	Paediatrics and Child Halth	Wilbur et al.
Establishing a Pediatric Acute-Onset Neuropsychiatric Syndrome Clinic: Baseline Clinical Features of the Pediatric Acute-Onset Neuropsychiatric Syndrome Cohort at Karolinska Institutet	2019	Journal of Child and Adolescent	Gromark et al.
Paediatric acute-onset neuropsychiatric syndrome in children and adolescents: an observational cohort study	2019	The Lancet	Johnson et al.
PANDAS	2017	Elselvier	Dean et al.
Psychotic symptoms in youth with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) may reflect syndrome severity and heterogeneity	2019	Journal of Psychiatric Research	Silverman et al.
Antibodies From Children With PANDAS Bind Specifically to Striatal Cholinergic Interneurons and Alter Their Activity	2020	American Journal of Psychiatry	Xu et al.
Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part I–Psychiatric and Behavioral Interventions	2016	Journal of Child and Adolescent	Thienemann et al.
Psychiatric manifestations and psychopharmacology of autoimmune encephalitis: A multidisciplinary approach	2019	Psychopharmacology of Neurologic Disease	Schieveld et al.
Cognitive behavioral therapy and acceptance and commitment therapy as augmentation treatment for paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): A case report	2017	European Psychiatry	Pozza et al.
Obsessive-compulsive disorder	2020	Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease (Sixth Edition)	Bloch et al.
Childhood Tic Disorders: diagnosis and management	2018	Paediatrics and Child Health	Malik et al.
Tourette syndrome or PANDAS – a case report	2020	Wien Med Wpchenschr	Singh et al.
Psychiatric Treatment and Management of Psychiatric Comorbidities of Movement Disorders	2018	Seminars in Pediatric Neurology	Walsh et al.
Alternative Frameworks for Advancing the Study of Eating Disorders	2020	Trends in Neurosciences	Stern et al.
Gilles de la Tourette syndrome	2019	Chormatin Sgnaling and Neurological Disorders	Selvini et al.
Antibodies against Group A Streptococcus, dopamine receptors, and ganglioside GM1 cross-react with a variety of food antigens, potentially interfering with biomarkers for PANS and PANDAS	2020	Biomarkers in Neuropsychiatry	Vojdani et al.
Increased vulnerability to impulsive behavior after streptococcal antigen exposure and antibiotic treatment in rats	2020	Brain, Behavior, and Immunity	Mora et al
Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections	2016	Journal of the American Academy of Child and Adolescent Psychiatry	Williams et al.
Tonsillectomy remains a questionable option for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)	2016	Head and Neck Surgery	Windfhur
PANDAS/PANS Syndromes: What are They and How are They Diagnosed and Treated	2019	ADHD Complex	Gephart

neurological abnormalities; and association with infection by group A beta-hemolytic streptococci (Wilbur et al .; 2019). In 2012, the abrupt emergence of OCD symptoms or preventive-restrictive food intake disorder was defined as new criteria; and presence of neuropsychiatric symptoms unexplained by other neurological diseases, which included at least two of the categories, appointed: anxiety; depression or emotional lability; behavioral regression; poor school performance; motor or sensory changes; as well as somatic symptoms. Among the broad spectrum of somatic symptoms, sleep disorders are included; Nocturnal Enuresis; urinary frequency change; signs of ear, nose and throat infection; palatine petechiae; cardiac and / or joint abnormalities; skin rash and eczema (Wilbur et al .; 2019; Johnson et al., 2019; Dean et al .; 2016). Gromack et al (2019); in a study with a cohort of 45 patients with PANDAS, he identified laboratory findings of low serum ferritin and vitamin D serum, elevated blood cells count, activation of complement system and positive culture for beta-hemolytic streptococci. However, serologies and cultures were only performed for clinical needs, and blood samples were collected at different stages of the disease's evolution, limiting the results validation (Johnson et al., 2019). The authors, corroborating with other studies (Johnson et al., 2019; Silverman et al, 2019; Xu et al, 2020), highlighted the absence of specific serological biomarkers for PANDAS and the sovereignty of the clinic in diagnosing the disease, so that the titration of anti-streptococcal antibodies and additional laboratory tests may not be required.

The treatment for PANDAS should be multidisciplinary, involving the pharmacological, psychological and educational spheres (Silverman et al, 2019; Schieveld et al., 2019). The pharmacological approach must be initially empirical, aiming at the patient's recovery and considering family risks in case of patients prone to physical violence, impulsivity and suicide (Silverman et al, 2019; Thienemann, 2017). In turn, educational intervention must cover family and school, providing guidance on the disease and building strategies to minimize symptoms impact on children's socialization and learning (Dean et al. (2018); Pozza, 2017). Antibiotics such as penicillin and azithromycin are the first-line treatment against beta-hemolytic streptococcal infection, which can be associated with corticoids, immunoglobulin and plasma exchange, thatare alternatives to manage the autoimmune inflammatory response (Johnson et al., 2019; Silverman et al. ., 2019; Xu et al. 2020; Mora et al., 2020; Williams, 2016). Tonsillectomy is quoted in the literature as a radical approach to PANDAS treatment, but its efficacy and therapeutic benefits still lack scientific evidence (Dean et al. 2016; Windfuhr, 2016). In a study of 58 patients with PANDAS conducted by Shimasaki et al. (2020), antibiotic therapy provided symptomatic improvement in 70% of the patients and, as previously documented, the association of antibiotics with other classes of therapeutic interventions resulted in a minimal increased improvement (Gephart, 2019). Cognitive Behavioral Therapy (CBT) is proven to be effective and intrinsic to the treatment of obsessive-compulsive and depressive symptoms for PANDAS, and it must be started early and concomitantly with the use of selective serotonin inhibitors (IRSS) such as fluoxetine, sertraline and fluvoxamine, which beneficial effects can occur in weeks (Schieveld et al. 2019; Pozza, 2017; Blochet al., 2020; Singh et al., 2020; Walsh, 2018).

As for the rest of the pharmacological arsenal, it must be composed according to the child's symptomatic presentation. Tics are treatable with alpha-adrenergics, clonidine and guanfacine (Pozza, 2017; Selvini, 2019). Episodes of irritability, which can last from 40 to 60 minutes, are treated with antihistamines (diphenhydramine), benzodiazepines (lorazepam) (Schieveld et al, 2019). Psychosis, severe tics and episodes of severe irritation are treated with antipsychotics (risperidone, aripiprazole or haloperidol), although these should be used carefully, considering the side effect of prolonged QT interval (Johnson et al., 2019; Xu et al. , 2020; Schieveld et al, 2019; Pozza, 2017; Mora et al., 2020; Selvini, 2019). For anxiety treatment, the temporary use of benzodiazepines, antihistamines, gabapentin, clonidine and selective serotonin inhibitors is considered. The latter being carried out according to current guidelines for the treatment of OCD (Thienemann et al, 2017; Schieveld et al. , 2019). Parental hypervigilance, common in families with PANDAS patients, can block children from developing their own stress management mechanisms and corroborate with anxiety, cognitive-behavioral therapy associated with pharmacological intervention must be worked on (Thienemann et al, 2017 ; Malik et al, 2018). Avoidant-restrictive eating disorders with sudden food intake reduction are diagnostic criteria for PANDAS, requiring careful evaluation to exclude structural, inflammatory or neurological causes of dysphagia and nausea. Poor nutrition associated with restricted food intake needs to be promptly treated in view of its consequences on physiology and pharmacodynamics, and must be investigated on an outpatient basis, through orthostatic and vital signs verification, as well as blood sample collection for electrolyte analysis, including magnesium and phosphorus (Thienemann et al., 2017; Stern SA, Bulik CM, 2020). Cognitive therapy with diet expanding incentives and raising the amount of intake, as well as gradual exposure to food or situations that trigger stress or fear, is crucial for controlling anxiety linked to eating disorders. Its association with postural, respiratory, and relaxing techniques from occupational therapy can be useful, particularly in patients who fear choking or vomiting. In order to maintain nutrition and hydration, feeding tubes can be used during periods of acute illness and, in patients with anorexia nervosa linked to infection, antibiotic therapy shows high therapeutic efficacy. When obsessions or compulsions are at the heart of the eating disorder, the psychopharmacological approach characteristic of OCD treatment is suggested (Thienemann et al., 2017). Sleep disorders are another symptom with an important impact on the child's organism, which must be managed with the establishment of a sleeping routine, healthy habits and restriction on the use of electronic devices and caffeine (Dean et al., 2016).

CONCLUSION

PANDAS, despite its low prevalence and the controversies that permeate its diagnosis, constitutes an extremely impacting disease on life quality of the carrier child and family. In this work, the prominent role of Cognitive Behavioral Therapy in the non-pharmacological management of PANDAS was highlighted. In the context of drug interventions, it is possible to medicate according to the patient's symptoms and, given the broad spectrum of drugs available and their drug interactions, there is still a need to develop guidelines for medical professionals in their clinical practice.

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