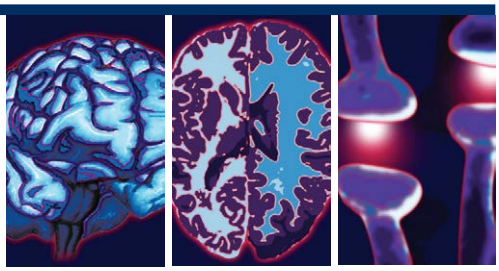
Research



Otorhinolaryngologic Findings in Pediatric Patients with Pandas

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ABSTRACT

With PANDAS (Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) are defined a spectrum of pathologies with different neuropsychiatric phenotypes related to a current or previous trigger infection favored by group A beta-hemolytic streptococcus (SBEGA). Their main pictures are characterized by acute-onset infantile movement and behavioural diseases in which it can occur the presence of END or other otorhinolaryngologic symptoms.

Built retrospective descriptive study over a multicenter court of 73 patients, the current work is proposed as one of the first attempts to analyze links and relationships with END manifestation and sequent findings in patients with PANDAS. From our analysis comes out that even if respiratory diseases could be present in a subgroup of patients, they are mainly related to hypertrophic or malformation conditions, reason why surgical therapy is still considered a first-line therapy.

Keywords

Pediatric autoimmune neuropsychiatric disorders, otorhinolaryngologic symptoms, malformation conditions

Introduction

The PANDAS syndrome is a set of acute-onset neuropsychiatric disorders characterized by movement disorders and obsessive-compulsive disorder (OCD) associated with a previous or current group a beta-hemolytic streptococcus infection (SBEGA), described for the first time by a group of researchers at the National Institute of Mental Health in 1998 [1]. The onset is typically in the pediatric age, on average between 5 and 15 years, with rare cases in youth (over 18 years). It is characterized by a relapsing/intermittent clinical course, it presents a neuropsychiatric symptomatological tract formed by OCD, by TIC (mainly disorders of movement and vocal trait) and sometimes also by eating disorders. Recent studies [2-4], have provided a new vision of the clinical phenotype of PANDAS, making a subgroup of childhood neuropsychiatric syndromes in acute onset of more broad-minded, leading to the definition of PANS (Pediatric Acute Onset Neuropsychiatric Syndrome) as a distinct syndrome from PANDAS without specify the causative agent, in view of the fact that can both be triggered by streptococcus from other infectious or environmental factors

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or, finally, by metabolic causes [5]. The PANS recognizing as triggers multiple etiologic agents factors (including genetic and immunological causes), with presentation or less than a previous or contextual streptococcal infection [6], it is described as a set of acute symptomatic OCD onset or exacerbation which, if present with a high antistreptococcal antibody rate, tends to present itself with a higher severity of OCD, along with various and possible comorbidities such as anxiety, behavior regression, depression and sometimes even tendency to suicide. Widely described are in the literature the clinical aspects of PANDAS syndromes and PANS related to the presence of pharyngeal infections, but still no clinical study has been carried out in order to significantly encode the presence of a potential framework symptom borne upper aerodigestive tract related to streptococcal infection. Recently Mahony et al. [7] has focused attention on the presence of rhinosinusitis as a possible non-specific trigger in triggering the neuropsychiatric disorder. This figure was also substantiated by recent animal studies suggest that the presence of a specific cellular antigen Th17 generated inside the nasal lymphoid tissue can migrate through the olfactory tract, cribroid cross the membrane and break the blood brain membrane; in such circumstances would create an activation of microglia with potential subsequent modification of sinaptic mechanisms [8]. The evidence detected have recently focused attention on how many patients had a correlation between rhinosinusitis and PANS, and how adequate treatment for rhinosinusitis in these patients may lead, in some cases analyzed, the regression of the symptoms.

In this study we evaluated otorhinolaryngologic problems, such as upper airway obstruction, respiratory sleep disorders (SDB), middle ear pathology, hearing and other breathing problems in PANDAS patients, through a study aimed at the detection of the significant role and potential evolution of signs associated and/or secondary oropharyngeal streptococcal infection.

Materials and Methods

It was conducted a retrospective descriptive, non-randomized and multicenter study, between 2012 and 2017 that enrolled 73 patients with a clinical diagnosis of PANDAS. The cohort of patients was selected from a larger group of 112 PANDAS patients. Inclusion criteria were as follows: signs and/or symptoms and/or history of ENT disease in patients of aged between 5 and 15 years with a recognized diagnosis of PANDAS.

Various data were collected including: general demographic characteristics (gender and age), assessment of sleep respiratory disorders, adenotonsillar objectivity, etiological factors, middle ear pathology, rhinosinusal involvement and auditory functionality.

■ Presence of SDB [9,10]

Evaluated according to the guidelines prepared by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), by PSG with evaluation of the AHI index (Apnoea-Hypopnoea Index). The diagnosis of Obstructive Sleep Apnea Syndrome (OSA) was defined with an AHI value ≥ 1/h. The degree of severity was determined by evaluating the number of episodes of obstructive apnea and hypopnea per hour of sleep. According to AHI severity, we divided patients into three groups (1–5, 5–15 and >15/h).

■ Adenoid and tonsil size [11]

The first measured by nasofibroscopy examination in four degree. Tonsils were graded as follows:

1) small tonsils confined to the tonsillar pillars;

2) tonsils that extend just outside the pillars;

3) tonsils that extended outside the pillars but did not meet in the midline;

4) large tonsils that met in the midline.

■ Etiologic agent

The microbiological diagnosis was made on the basis of the result by culture (performed according to standard procedures) of the throat swab performed on all the patients of the study object.

■ Middle ear pathology [12]

In relation to a condition of effusive otitis media (OME) or acute otitis media (AOM). In order to this was necessary to detect the simultaneous presence of the following elements:

OME: Presence of an effusion, glue-like fluid behind an intact tympanic membrane in the absence of signs and symptoms of acute inflammation. Abnormal color (eg, yellow/amber/blue), retracted/concave tympanic membrane, and air–fluid levels. Hearing testing: mild conductive hearing loss and tympanogram: immobile ear drum or negative middle ear pressure.

AOM: Mild bulging of the tympanic membrane with otalgia and intense tympanic membrane erythema; presence of subjective symptoms arose sharply in the last 48-72 h; middle ear exudate detection.

■ Rhinosinusal involvement

The diagnosis of rhinosinusitis was performed on the EPOS 2012 criteria and that is, on the presence of at least 2 major symptoms or greater + 1 ≥ 1 minor symptoms.

■ Sensorineural/transmission hearing loss presence

The premise that the choice of the techniques for audiological evaluation was age-dependent actual pediatric patient and his motor skills, patients underwent conventional tonal audiometry, for survey the threshold by air (at the frequencies 125, 250, 500, 1000, 2000, 3000, 4000 and 8000 Hz), and with the mastoid vibrator for the relief of the via bone conduction threshold (to 250-4000 Hz) frequencies, specifying the degree of hearing loss both from a quantitative and a qualitative point of view. The degree of hearing loss both from a qualitative point of quantity has been defined, after the guidance of the World Health Organization (WHO) on average 500-1000-2000-4000 frequency in Hz: Normal: 0-25 dB - mild hearing loss: 25-40 dB - moderate hearing loss: 41-55 dB–moderately severe hearing loss: 56-70 dB -severe hearing loss: 71-90 dB-profound hearing loss:>91 dB. In non-collaborating subjects for the assessment of the auditory threshold, objective methods and examinations were used: acoustic otoemissions and impedance test.

Exclusion criteria were (1) patients in/or previous orthondontic or orthognathic treatment, (2) cranio-facial anomalies, (3) genetic disorders, neuromuscular diseases, cognitive deficits and or mental retardation, (4) children younger than 36 months of age, (5) obesity, (6) lingual tonsil hypertrophy and (7) previous history of any tonsilloadenoid surgery. The approval of institution's Ethics Committee (no: 15-20/2012) and informed consent of the caregivers and children were obtained accordingly.

■ Data analysis

The data were analyzed using the SPSS 16.0 statistical software (SPSS inc. Chicago, IL, USA); for the continuous numerical variables the differences between groups were evaluated by t-test or non-parametric tests (Mann-Whitney test), with regard to the categorical variables, were evaluated with the exact Fisher test. Values of P<0.05 were considered indicative of statistical significance.

Genetic factors, alimentary diet, environmental factors such as xenobiotics or bacterial lipopolysaccharides induction factors that may be involved in the pathogenesis of this disease where not study in this manuscript.

Results

The presence of ENT symptoms associated with pharyngo-tonsillitis was significantly detected in 73 patients of 112 (relative frequency (%) 65.1–*P*=0.046). In relation to demographic factors, significant differences have emerged regarding the sex with a significant prevalence of the male sex (53 male *vs.* 20 female) (relative frequency (%) 72.6 *vs.* 27.4-*P*= 0.043), by contrast no significant differences were found with respect to age (*P*=0.081) **(Table 1).**

In relation to SDB, 54 of children have presented nocturnal respiratory obstructive symptoms (relative frequency (%) 73.9-*P*=0.033) **(Table 2)** with obstructive severity average type correlated to the consensual development of adenotonsillar obstruction observed abnormal in 48 subjects (65.7%) **(Table 3)**.

In etiological agent causal relationship, significant findings were noted in order to only presence of GABHS (relative frequency (%) 79.9-*P*=0.041). Not to be underestimated, although not significant in this study, the presence of still other etiologic agents in PANDAS group, probably related to a temporary super infection EBV (relative frequency (%) 16.4-*P*=0.073) and Mycoplasma Pneumoniae (relative frequency (%) 3.7-*P*=0.084).

The presence of rhinosinusitis showed no significance in terms of observational (relative frequency (%) 28.6-*P*=0.065) **(Table 4).**

The audiological deficits found was mostly transmissive type (relative frequency (%) 79.4-

Table 1: Demographic data of subject.

	Total (*N*=73)	*n* (%)	*p* value
Gender			
Male	53	72.6	
Female	20	27.4	0.043*
Age (years)			
5-8	25	34.2	
8-10	28	38.5	0.068
>10	20	27.3	

Table 2: Respiratory Sleep Disorders (RSD).			
	Total (*N*=73)	***n* (%)**	***p* value**
AHI (*Severity of OSA*)			
< 1 (*Absence*)	19	26.2	0.061
1-5 (*Mild*)	24	32.8	0.047*
5-15 (*Moderate*)	28	38.3	0.043*
>15 (*Severe*)	2	2.7	0.085
AHI (*apnea/hypopnea index*)			

Table 3: Relationship between RSD and abnormal adenotonsillar size.			
	Size 1-2 (%)	***Size 3-4 (%)***	***P value***
AHI (*Severity of OSA*) (*n*)			
< 1 (*Absence*) (19)	16 (21.9)	3 (4.1)	0.071
1-5 (*Mild*) (24)	6 (8.2)	18 (24.6)	0.047
5-15 (*Moderate*) (28)	3 (4.1)	25 (34.2)	0.034
>15 (*Severe*) (2)	0 (-)	2 (2.7)	0.001
Total	25 (25.3)	48 (65.7)	0.033
AHI (*apnea/hypopnea index*); OSA (*Obstructive Sleep Apnea*); Adenotonsillar Size 1-2 (*Normal*); Adenotonsillar Size 3-4 (*Abnormal*).			

Table 4: ENT pathology associated with pharyngo-tonsillitis.			
Pathology	**Absence**	**Presence (%)**	***p* value**
Respiratory Sleep Disorder	23	54 (73.9)	0.033
Adenotonsillar hypertrophy	25	48 (65.7)	0.035
Effusive otitis media	15	58 (79.4)	0.029
Rhinosinusal pathology	56	17 (28.6)	0.065
Hearing problems (SNHL)	69	4 (5.4)	0.082
SNHL: Sensorineural Hearing loss			

P= 0.029) OME correlable and linked to the presence of occasional episodes of AOM (relative frequency (%) 23.7-*P*=0.079). The four cases, insufficient albeit, of subjects with sensorineural hearing loss reported have nevertheless been related to causal phenomena prenatal or perinatal rather than the illness itself (relative frequency (%) 5.5-*P*=0.082) (Table 4).

Discussion

ENT manifestations in PANDAS disease represent a diagnostic challenge for the pediatricians, otolaryngologist and child neuropsychiatrists. There are diseases of systemic action that present themselves with localized manifestations, and the region of the head and neck is an important site in this nosological entity. Often, otolaryngologists are consulted only because of recurrent streptococcal infections in these children and, hence, should be aware of the possibility of concurrent ENT disorders.

This study represents one of the first works that aims to examine a complete ENT profile of children with PANDAS. Numerous studies have focused on the tonsillar role both as the main clinical evidence (tonsillopharyngitis) and as a therapeutic target (tonsillectomy) [13]. Equally numerous they are also studies that put the attention on the various therapeutic approaches analyzing the possible substrates etiologic and phenotypic. Excluding some recently published articles on the role of rhinosinusitis as a possible "trigger" in PANS, we can state that at the moment there is no study in the literature that fully analyzes the various anatomical head and neck districts correlating these to the pathology, both etiologies, infectious, environmental or genetic (PANDAS o PANS) [7]. Our study, for the first time, has put his focus on the examination of patients suffering from PANDAS goal trying to analyze what could be more and / or associated with clinical evidence, also acting as a non-specific triggers, jointly interfere with pharyngo-tonsillar events with normal daily habits and health status of the patients themselves. Perform a physical examination it requires cooperation on the part of the young patient, which is often already less in patients without comorbidities. The presence of OCD, tics, anxiety, depression and fear often worsens the compliance of these patients who, if they are of school age, have reticence towards health care workers, starting to ask many explanations about the exams, and showing real and their own anxiety crises showing themselves so agitated, restless until hyperactivity. All this made the evaluation extremely complex and laborious. The analysis of the data in our possession shows a high percentage of male subjects PANDAS according to data already found in the literature. Most of the subjects in the study had streptococcal pharyngo-tonsillitis, but being a fundamental condition for patient enrollment we did not analyze all those children who had a positive streptococcal swab but without clinical evidence. Several studies have reported as neuropsychiatric symptoms raise not only an initial infection but can be slatentized over time [2]. Secondary infections are then used exclusively by activators of the disease itself. In addition, our study focused on patients with streptococcal disease at the first assessment. Few documents have had on previous pharyngo-tonsillaries infections of the subjects themselves and especially what pathogen they had as a substrate. The AOM is the finding of easier finding in pediatric subjects, and in our study were found high percentage of middle ear infections tend tympanograms results type "C" but often also of type "B". The transmissivity has certainly played a key role in the evidence in the field of audiology, where, in contrast to

the control group, the largest number of patients with tympanogram of type "B" also had mild conductive hearing loss. Only a small minority of patients (5.5%) had sensorineural hearing loss similar to age-related perinatal disorders (problems related to childbirth, prematurity, intensive care, hypoxia at birth) and difficult association with PANDAS. From this point of view to find evidence in the literature it was not possible. The evaluation of sleep respiratory disorders carried out through interviews with parents (perceived severity), and using objective tests, has shown that these patients have a significant presence of episodes with average type gravity variables paintings by partial obstruction of the upper airway and snoring to obstruction complete (apnea) that determine hypoxemia, disturbed sleep and daytime symptoms. These findings recognize the safe role of chronic and hyperplastic inflammation at the base of obstructive respiratory symptoms. In this context it should be clarified, as the adenotonsillar hypertrophy represents a major cause of OSA in children without comorbidities [14]. In our study, the rate of adenoid and tonsil hypertrophy in PANDAS group was recorded in 65.7% of patients. However, not all children who have adenotonsillar hypertrophy suffer from sleep-disordered breathing and is growing opinion that there is no absolute correlation between the degree of hypertrophy of the lymphatic structures and severity of obstructive respiratory framework, for the potential role played by other factors that must be recognized in surgical forecasting. In such circumstances it is understandable therefore the importance for a correct surgical indication, the knowledge of those anatomical and functional factors is able to predict the possibility of a not complete post-surgical resolution of the sleep respiratory disorders, with the need to resort to complementary treatments. However, the successful rate of adenotonsillectomy for pediatric OSAS is quite variable, ranging from 27.2 to 82.9 % [14]. Many pre-operative factors might influence the successful rate of the effect of adenotonsillectomy, including age, body mass index (BMI), tonsil size, adenoid size, pre-operative severity of OSAS, associated medical condition, such as allergic rhinitis or gastroesophageal reflux disease, pre-operative craniofacial features and surgical techniques.

The PSG data demonstrated the significant presence of sleep respiratory disorders in the group of patients PANDAS and this data can only find hypertrophy foundation adenotonsillar and morpho-structural modifications derived from it. Although the pathophysiology of childhood OSA is multifactorial, it is mainly due to enlarged adenotonsillar tissues, and the removal of the tonsils and adenoids is therefore widely considered the first-line therapy for childhood sleep apnoea [15-17]. Future studies on these conditions will be able to make further evidences the need for a surgical treatment tonsillar even today widely discussed in such pathology.

May be, also, genetic factors, alimentary diet, environmental factors such as xenobiotics or bacterial lipopolysaccharides [18,19] induction factors can be involved in the pathogenesis of this disease, but were not studied in this work, were probably behind the scope of our paper; moreover further study needs to be made for better clarify this issue.

Conclusions

We can affirm that this study can represent a "starter point" on ENT in PANDAS. There are numerous variables that have not been considered, as well as the final results are themselves dependent on the criteria for patient enrollment. We have, in fact, analyzed a population with already pharyngitis in PANDAS patients by excluding subjects with neuropsychiatric syndrome but without clinical evidence related to GABHS. Furthermore the other manifestations of the head and neck are inexorably related to the concomitant presence of strep throat excluding subjects with PANDAS syndrome and sporadic clinical manifestations and isolated. Our study, however, has for the first time focused on general otorhinolarygoiatric aspects in patients with PANDAS highlighting the significant presence of GABHS pharyngitis related, statistically significantly associated with sleep-disordered breathing. This latter condition, besides adding a significant finding in clinical-level goal, can determine on the basis of the guidelines for tonsillectomy (American Academy of Otolaryngology-Head & Neck Surgery) a secure positive input for the surgical therapeutic proposal rather than exclusively medical.

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