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ENT involvement and orobuccal movements' disorders in Pandas patients: assessment and rehabilitations tools

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Abstract. – OBJECTIVE: PANDAS are known as the spectrum of autoimmune pathologies related to a previous or current infection by group A beta-hemolytic streptococcus (SBEGA), dealing with several neuropsychiatric manifestations that mainly affect pediatric age. The main features consist of behavioral disease or movement disease characterized by acute-onset, presenting especially through infant period or adolescence. Specific manifestations, occurring during the progression of the disease, are the presence of otorhinolaryngologic symptoms (ENT) and orofacial movement disorders associated with temporomandibular joint pain.

PATIENTS AND METHODS: We enrolled 130 children (5-15 years) with a clinical diagnosis of PANDAS between 2012 and 2018. Participants were assessed using ENT specific parameters, PSG to examine respiratory disorders and conventional audiological evaluation. Descriptive and comparative statistical analyses were performed with a control group of 51 healthy patients.

RESULTS: The prevalence of ENT symptoms associated was significantly detected in 88 patients of 130 in Group A (relative frequency (%) 67.6; *p*=0.041) and in 51 patients of 130 in the control Group B (relative frequency (%) 39.2; *p*=0.063). In relation to prevalence of SDB, 54 subjects have presented nocturnal respiratory obstructive symptoms from mild to severe (relative frequency (%) 61.3; *p*=0.033) *vs.* 20 patients of Group B (relative frequency (%) 39.2; *p*=0.055). The obstructive severity average type was correlated to the consensual adenotonsillar development (size 3-4), (relative frequency (%) 45.4; *p*=0.047). The audiological deficits found were mostly of transmissive type with OME correlated and linked to the presence of occasional episodes of AOM. The four PANDAS patients who presented orobuccal dystonia (relative frequency (%) 4.54; *p*=0.091) achieved an improvement of the algic symptoms through the exercises of self-rehabilitation.

CONCLUSIONS: Findings from our study show that respiratory diseases, characterizing a group of patients with pandas, are the direct consequences of the malformed or hypertrophic condition and suggesting in these conditions surgical therapy as an approaching tool.

Key Words
PANDAS, ENT, Orobuccal disorders, Infection.

Introduction

PANDAS syndromes represent a group of acute-onset neuropsychiatric disorders consisting of obsessive convulsive disorder (OCD) or movement disorders typically of the late pediatric age, usually between 5 and 15 years [1]. The disease recognizes his etiology in a previous or current triggered infection by *"group A beta-haemolytic streptococcus"* (GABHS). Initially, it has a relapsing/remitting clinical course with a specific symptomatic trait of TIC (either movement or vocal disorders), OCD and eventually interesting upper digestive tract. PANDAS were firstly described in 1998 by the National Institute of Mental Health. Recently, new

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studies [2-4] provided a different vision including PANDAS as a subgroup of a more comprehensive framework of neuropsychiatric disorders in acute onset, leading to the concept of PANS (Pediatric Acute Onset Neuropsychiatric Syndrome). It differs for the unspecified causative agent according to the observation that similar syndromes can be a consequence either of a streptococcal or other different infective agent, environmental factors or, not least, metabolic diseases[5]. It has been described a set of PANS with acute OCD onset in which concurrent increasing of anti-streptococcal antibody rate (with or without a clear infective manifestation) seems to cause a worsening in symptomatic OCD features or even comorbidities as behavior regression, anxiety, and depression with wanderings of suicide. This suggests multiple etiology of trigger agents involved in PANS including immunological or genetic causes[6-10]. Literature has widely treated about the clinical aspect of PANS and PANDAS connected with pharyngeal inflammation, though no other clinical study has been conducted to clarify the presence of upper aerodigestive symptoms linked with streptococcal infection. Mahony et al[7] paid significant attention to the role of rhinosinusitis as a possible trigger in the onset of PANS disorders. This was upheld by following animal researches suggesting the presence of specific Th17 cellular antigen, raised up in nasal lymphatic tissue, can migrate through the nasopharynx. Thus, prosecuting its way through the nasal cavity and reaching anterior cranial fossa, it would lead to a subversion of the synaptic mechanism by generating inflammatory reaction and activating microglial cells[8]. The identified findings focused on the correlation between rhinosinusitis and PANS and how adequate treatment can lead to the remission of clinical manifestations. This study aimed to specify the impact of upper airway obstruction with ENT related diseases, including respiratory sleep disorders (SDB), middle ear pathology and orofacial movement disorders (including temporomandibular joint pain) and to recognize a potential role of oropharyngeal streptococcal infection.

Materials and Methods

Our work was set as a non-randomized descriptive observational study, in which was enrolled a court of 88 patients with a recognized diagnosis of PANDAS through a multicenter research study conducted between March 2012 and June 2018. Patients were selected from a larger group of about 130 PANDAS patients using inclusion and exclusion parameters (Group A). After collecting general demographic information's, were assessed specific parameters as adenotonsillar objectivity, etiological factors, respiratory disorders, etc. For statistical purposes, we compared the prevalence of ENT disorders in a group of 130 healthy patients received at a routine pediatric visit (Group B).

Sleep-Associated Breathing Disorders (SDB)[11-17]

SDB were evaluated according to the Guidelines of the American Academy of Otolaryngology- Head and Neck Surgery (AAO-HNS). Using a polysomnographic study (PSG) we identified and recorded the different sleep patterns and performed the AHI index (Apnea- Hypopnea Index). The diagnosis of Obstructive Sleep Apnea Syndrome (OSA) was defined with an AHI value $\geq$ 1/h. The degree of severity was determined considering the number of obstructive apnea and hypopnea episodes per hour of sleep. Finally, we divided patients into three groups according to the AHI's severity (1–5, 5–15 and >15/h).

Adenoid and Tonsil Size[13-18]

The adenoid degree was measured by nasofibroscopy examination and divided into four grades:

a) Grade 1, adenoid tissue occupies only the upper segment of the rhinopharyngeal cavity;
b) Grade 2, adenoid tissue is confined to the upper half of the rhinopharyngeal cavity;
c) Grade 3, adenoid tissue is extended over the rhinopharynx with choanal obstruction and partial closure of tubal ostium;
d) Grade 4, tube ostium and lower choanal border could not be observed).

Tonsils were graded as follows:

a) Small tonsils confined to the tonsillar pillars;
b) Tonsils that extend just outside the pillars;
c) Tonsils that extended outside the pillars but did not meet in the midline;
d) Large tonsils that met in the midline.

Etiologic Agent[18]

According to standard procedures, the microbiological diagnosis was made in all patients through a throat swab culture.

Middle Ear Pathology[13,14]

We evaluated a condition of effusive otitis media (OME) or acute otitis media (AOM) detecting

the simultaneous presence of different diagnostic elements. OME was identified by the presence of an effusion, glue-like fluid behind an intact tympanic membrane in the absence of signs and symptoms of acute inflammation, abnormal color (yellow/amber/ blue), retracted/concave tympanic membrane, and air-fluid levels. At hearing testing, we detected a mild conductive hearing loss. Tympanogram revealed an immobile ear drum or negative middle ear pressure. AOM was suspected in the presence of mild bulging of the tympanic membrane with otalgia and intense tympanic membrane erythema, subjective hearing symptoms sharply elevated in the last 48-72 hours and middle ear exudate detection.

Rhinosinusal Involvement[15,16]

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

Sensorineural/Transmission Hearing Loss

The choice of techniques for audiological evaluation was age-dependent, considering the pediatric patient and his motor skills. Participants underwent conventional tonal audiometry, analyzing the air threshold (at 125, 250, 500, 1000, 2000, 3000, 4000 and 8000 Hz frequencies). Moreover, the bone via conduction threshold was examined with a mastoid vibrator (to 250-4000 Hz) frequencies to specify the degree of hearing loss both from a quantitative and a qualitative point of view. We considered the Guidelines 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, were used objective examinations as acoustic otoemissions and impedance test.

Movement's Disorders with Temporomandibular Joint Pain[10]

This evaluation was performed in order to identify dystonic mandibular movements (temporomandibular hyperkinesia) with persistent pain in the temporomandibular joint. The outcome measure was the intensity of oromandibular pain using a numerical rating scale (NRS) from 0 to 10 (0 = no pain, 10 = worst pain imaginable). The Burke-Fahn Marsden Disability Scale (BFM) was used to classify the grade of mandibular temporal movement disorders. Then, patients with temporomandibular joint disorders have undergone rehabilitation treatment and have been trained to perform exercises at home. The exercises consisted of ten repetitions, twice a day, of protrusion-retrusion (antero-posterior) of the mandible, lateralization of the jaw to the right and lateralization movements of jaw to the left, maximum opening and closing of the mouth excluding the contextual contraction of the tongue and of the other chewing muscles[9]. The protrusion-retrusion movements were performed with a spacer (cotton roll) between the incisors while the lateralization movements with a spacer between the canines (positioned homolaterally to the direction of the lateral displacement). The exercises, performed twice a day with the help of a mirror, aimed to correct the anomalous postures that arose during the last repetitions. Before home rehabilitation exercises, patients underwent training exercises in the hospital to correctly execute it and without evoking pain. Therefore, it was a sort of "guided home self-rehabilitation". Inclusion criteria were (a) confirmed diagnosis of PANDAS, (b) age between 5 and 15 years with a current or history of ENT diseases with associated symptoms and signs. Exclusion criteria were (a) patients in/ or previous orthodontic or orthognathic treatment, (b) craniofacial anomalies, (c) genetic disorders, neuromuscular diseases, cognitive deficits and or mental retardation, (d) children younger than 36 months of age, (e) obesity, (f) lingual tonsil hypertrophy and (g) previous history of any adenotonsillar surgery. We had also established inclusion criteria for the control group, selecting patients with (a) no suspected or confirmed diagnosis of PANDAS, (b) age between 5 and 15 years, (c) current or history of ENT diseases not related to other disorders. The Ethics Committee approval (no: 15-20/2012) and informed consent of the caregivers and children were obtained accordingly.

Statistical 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), concerning the categorical variables, 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 lipopoly-

Table I. Demographic data of patients.

	Total (N=88)	n (%)	*p*-value
Gender			
Male	60	68.2	0.043*
Female	28	31.8	
Age (years)			
5-8	2	31.8	
8-10	37	42.0	0.073
>10	23	26.2	

saccharides induction factors may be involved in the pathogenesis of this disease were not studied in this manuscript.

Results

The prevalence of ENT symptoms associated was significantly detected in 88 patients of 130 (relative frequency (%) 67.6; p=0.041) and in 51 patients of 130 in the control group (relative frequency (%) 39.2; p=0.063). In relation to demographic factors, significant differences have emerged regarding the sex with a significant prevalence of the male sex in PANDAS' patients compared to the control (60 male *vs.* 28 female) (relative frequency (%) 68.2 *vs.* 31.8; p=0.043). However, no significant differences were found considering the age (p=0.073) (Table I). In relation to prevalence of SDB, 54 subjects have presented nocturnal respiratory obstructive symptoms from mild to severe (relative frequency (%) 61.3; p=0.033) *vs.* 20 patients of group B (relative frequency (%) 39.2; p=0.055) (Table II). In relation to above, the obstructive severity average type was correlated to the consensual adenotonsillar development, especially in 40 subjects with size 3-4 (relative frequency (%) 45.4; p=0.047) (Table III-IV). In the relationship of etiological agent causal, among positive patients at previous controls to *GABHS*, during the acute episodes were found positive 77.7 % in PANDAS' group *vs.* 28.3 % of group B (p=0.073). Not to be underestimated, although not significant in this study, the presence of still other etiologic agents both in PANDAS group that in healthy Group, was probably related to a temporary super infection EBV (relative frequency (%) 17.4; p=0.076) and *Mycoplasma Pneumoniae* as coinfection (relative frequency (%) 4.9; p=0.082). The presence of rhinosinusitis did not show any significant results for observational purposes in both groups – 12 patients in Group A and 6 in Group B (relative frequency (%) 14.2 *vs.* 12,5% p=0.067) (Table IV). The audiological deficits found were mostly transmissive type (Group A: 68 patients relative frequency (%) 78.2 *vs*. Group B: 22 patients relative frequency (%) 41.3; p=0.039) with OME correlated and linked to the presence of occasional episodes of AOM (relative frequency (%) 25.4 *vs.* 17.5%; p=0.079). In group A six cases with sensorineural hearing loss have been reported unrelated to causal prenatal or perinatal phenomena rather than the pathology itself (relative frequency (%) 6.8 *vs.* 3.4; p =0.082) (Table IV). The four PANDAS patients who presented orobuccal dystonia (relative frequency (%) 4.54; p=0.091) achieved an improvement of the algic symptoms through the exercises of self-rehabilitation, an improvement in the particularity of the temporomandibular joint and, at the same time, a clear reduction of the hyperkinetic movements. No patient of the control group presented orobuccal dystonia or temporomandibular joint disorders. The assessment scales used for pain and movement disorder (numerical rating scale or NRS and Burke-Fahn Marsden Disability Scale)[9] showed marked improvement or even the resolution of symptoms. Any disturbances or worsening have been reported after the self-rehabilitation treatment performed. According to current literature, the prevalence of ENT disorders in the control group was found in about 39.2% of patients. Among these, SDB were the most common (39.2%), with OME (41.3%) and adenotonsillar disorders

Table II. Respiratory Sleep Disorders (RSD).

AHI (Severity of OSA)	Total (N=88)	n (%)	*p*-value
< 1 (Absence)	26	29.5	0.061
1-5 (Mild)	27	30.7	0.047*
5-15 (Moderate)	32	36.3	0.043*
>15 (Severe)	3	3.5	0.085

Abbreviations: AHI (apnea/hypopnea index).

Table III. Relationship between RSD and abnormal adenotonsillar size.

AHI (Severity of OSA)	Size 1-2 (%)	Size 3-4 (%)	*p*-value
< 1 (Absence) (26)	20 (22.7)	6 (6.8)	0.071
1-5 (Mild) (27)	8 (9.1)	19 (21.6)	0.047*
5-15 (Moderate) (32)	4 (4.6)	28 (31.8)	0.034*
>15 (Severe) (3)	0 (-)	3 (3.5)	0.001
Total	32 (36.4)	56 (63.6)	0.043*

Abbreviations: AHI (apnea/hypopnea index); OSA (Obstructive Sleep Apnea); Adenotonsillar Size 1-2 (Normal); Adenotonsillar Size 3-4 (Abnormal).

(19.2%) (Table IV). Hearing problems (SNHL) were found in 3.4% of cases (Table IV).

Discussion

PANDAS disease is a complex nosological entity with several clinical features, including even ENT manifestation. Therefore, it is of particular interest not only for pediatricians but also for neuropsychiatrists and otolaryngologists. In the context of these multiple district disorders, head and neck regions are an important site possibly affected by localized manifestation, usually requiring a specific otolaryngologic consultation. Thus, ENT disorder should always be considered in pediatric patients considering the high incidence of recurrent streptococcal infections in children. The analysis of the results showed ENT manifestations may be divided into three groups: otological problems, adenotonsillar hypertrophy and airways problems. Previous different studies focused on a possible role of rhinosinusitis in the trigger of PANS. Other different works analyzed the role of the tonsillar system, especially during tonsillopharyngitis, and considered tonsillectomy as a possible therapeutic target [17]. Nonetheless, no other article at the moment widely describes the correlated etiologies or pathogenetic causes of ENT districts [7]. This work aims to evaluate for the first time the whole ENT specter and the oromandibular joint pain in children affected by PANDAS. In particular, one of our attempts was to identify, through an accurate analysis of the patients, which factors could interact with pharyngo-tonsillar events causing an altered health status, even focusing the attention on those ones apparently acting as a non-specific trigger. Unfortunately, often it is not possible to complete and adequate clinical evaluation due to the lack of collaboration of pediatric patients, showing a lack of compliance in executing exams and asking many explanations about the practice not showing confidence in the care. Moreover, children's fear can worsen the state, especially with the concurrent presence of neuropsychiatric disorders (tics, anxiety, depression), with manifestation as crying, agitation, and restless or frank hyperactivity. As previously reported in the literature, male children composed most percentage of PANDAS patients from our data analysis. Despite many subjects were affected by streptococcal pharyngo-tonsillitis, fundamental criteria to be recruited was both laboratory and clinical evidence of streptococcal infection, so positive swab patients without clinical evidence were not admitted. Particularly, we collected the subgroup of patients manifested clinical features of PANDAS following the first event of streptococcal disease. As a matter of fact, neuropsychiatric symptoms can develop either throughout an initial infection or slatentize subsequently, often requiring a

Table IV. ENT pathology in PANDAS's patients.

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	62	26 (30.2)	0.067
Hearing problems (SNHL)	69	6 (6.84)	0.082
Temporomandibular joint disorders	84	4 (4.54)	0.091

secondary infection as activator of the disease[2]. Among the observations of our study, it should be noted that the temporomandibular rehabilitation, applied to subjects with disorders of the temporomandibular movement, reduced pain, the intensity and the number of hyperkinetic movements in all our patients. In particular, temporomandibular hyperkinesia appears to be improved due to the consequent greater awareness and post-exercise motor control. No cases of temporomandibular disorders were found in the control group. As regards to the super-specific field of audiology, the most recurrent finding is Acute Otitis Media (AOM). From our study emerges that a high percentage of patients with middle ear infection shows tympanograms's results with altered motility of the ossicular chain and scarring of tympanic membrane till perforation. Most cases resulted as a type "C", followed by type "B". Patients with phlogosis of middle ear also present interest in the audiological sphere, obviously confirmed by the presence in these patients of mild conductive hearing loss with tympanogram of type B. In such an important period for the complete development of the sensory and cognitive function, repercussions in the acquisition of language are also possible. Nevertheless, in a small minority (6.8%) of cases of PANDAS' group, the hearing loss is consequent to a sensorineural cause, very similar to those deafness syndromes with natal/perinatal onset, often due to ischemic accidents at birth or in prematurity. Unfortunately, literature about it is very lacking and no correlation with PANDAS can be assessed. Reversely, the hearing loss in the control group was due to a transmissive pathology in all the patients. Respiratory disorders are the main protagonist among the manifestations of the head and neck disorders. In pediatric age they are, as mentioned, an unpleasant consequence of frequent infective episodes characterizing upper respiratory trait, of course due to an anatomical predisposition (reduction of diameter for age). SDB can present different grades of obstruction till the complete apnea and causing hypoxemia, sleep disorders and daylight symptoms. A precise estimation of episodes' severity is possible thanks to parents' interview jointly with objective tests as polysomnography. Moreover, in the evaluation of these findings, a certain role is played by chronic and hyperplastic phlogosis, seeing specifically adenotonsillar hypertrophy as the main cause of OSA in children with no other intercurrent disturbances[17-20]. The frequency of hypertrophy in the tonsil or adenoid tissue in PANDAS patients analyzed in our work was estimated at 45.4% *vs*. 19.2% in Group B. However, since the presence of hypertrophy is not stable in children suffering from OSA, there is a potential role of several other factors and severity of obstructive episodes. For this reason, in the choice of surgical indication, must be observed all those factors potentially implicated in the successful rate of surgery (adenotonsillectomy). Therefore, clinical features like age, adenoid and tonsil size, preoperative grade of obstructions, BMI, comorbidities such as gastroesophageal reflux disease, allergic rhinitis or recurrence of audio-otological disease and anatomic findings have to be considered. However, despite extensive preoperative evaluation of the patient's clinical features is essential for the surgery's execution, the successful range of adenotonsillectomy in pediatric patients with OSA is still inconstant from 27.2% to 82.9%[18]. This range in most cases requires the provision of ulterior treatments. Despite this, the high prevalence of sleep breathing disorders in PANDAS' patient's group emerges from PSG data suggesting an important role of adenotonsillar hypertrophy. Therefore, even if OSA is considered as a multifactorial condition, the surgical excision of hypertrophic tissue of tonsils and adenoids is still considered the gold standard for therapy in children with sleep obstructive apnoea[17-24]. Since it concerns such a debated matter, it is necessary to reach further evidence to clarify the role and the indication of surgery in the tonsillar pathology. Specific attention should be paid to these factors probably implicated in the pathogenesis of OSA, like genetic arrangement, alimentary disorders, presence of xenobiotics or lipopolysaccharides, together with all those elements not treated in our study[18,22].

Conclusions

This study may be considered a first attempt to analyze ENT symptoms in PANDAS patients. One of the limits of our work is related to the recruitment modality: we do not consider the wide range of patients with neuropsychiatric symptoms unless it was not documented clinical or laboratory evidence of GABHS. Thus, limiting the feasibility of our results only to those patients with already documented strep throat. Our main aim was, anyway, to evaluate general otolaryngologic features in patients with PANDAS,

paying attention to important consequences as sleep obstructive apnea related to GABHS pharyngitis. Especially, the presence of a severe grade of OSA can represent a particular indication for tonsillectomy, as indicated by guidelines of the American Academy of Otolaryngology-Head and Neck Surgery. Considering the poor relative frequency of orobuccal dystonia PANDAS related found in our study, temporomandibular disorders didn't reach statistical significance. The role of the otolaryngologist in the ongoing care of PANDAS patients cannot finish with the diagnosis but the specialist should see the patient after intervals of 3-6 months to exclude or treat major and minor significant complications like middle ear effusion. Subsequent visits may be at longer intervals but allow to regard symptoms of hearing loss or fluctuation and to detect first signs of other otorhinolaryngology pathologies.

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Conflict of Interests

The Authors declare that they have no conflict of interest.

References

1) Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, Lougee L, Dow S, Zamkoff J, Dubbert BK. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry 1998; 155: 264- 271.
2) Murphy TK, Parker-Athill EC, Lewin AB, Storch EA, Mutch PJ. Cefdinir for recent-onset pediatric neuropsychiatric disorders: a pilot randomized trial. J Child Adolesc Psychopharmacol 2015; 25: 57-64.
3) Chang K, Frankovich J, Cooperstock M, Cunningham MW, Latimer ME, Murphy TK, Pasternack M, Thienemann M, Williams K, Walter J, Swedo SE; PANS Collaborative Consortium. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. J Child Adolesc Psychopharmacol 2015; 25: 3-13.
4) Murphy TK, Patel PD, Mcguire JF, Kennel A, Mutch PJ, Parker-Athill EC, Hanks CE, Lewin AB, Storch EA, Toufexis MD, Dadlani GH, Rodriguez CA. Characterization of the pediatric acute-onset neuropsychiatric syndrome phenotype. J Child Adolesc Psychopharmacol 2015; 25: 14-25.
5) Hesselmark E, Bejerot S. Biomarkers for diagnosis of Pediatric Acute Neuropsychiatric Syndrome (PANS) - sensitivity and specificity of the Cunningham Panel. J Neuroimmunol 2017; 312: 31-37.
6) Toufexis J, Hommer R, Gerardi DM, Grant P, Rothschild L, D'Souza P, Williams K, Leckman J, Swedo SE, Murphy TK. "Disordered eating and food restrictions in children with PANDAS/PANS." J Child Adolesc Psychopharmacol 2015; 25: 48-56.
7) Mahony T, Sidell D, Gans H, Brown K, Farhadian B, Gustafson M, Sherr J, Thienemann M, Frankovich J. Improvement of psychiatric symptoms in youth following resolution of sinusitis. Int J Pediatr Otorhinolaryngol 2017; 92: 38-44.
8) Dileepan T, Smith ED, Knowland D, Hsu M, Platt M, Bittner-Eddy P, Cohen B, Southern P, Latimer E, Harley E, Agalliu D, Cleary PP, Group A. Streptococcus intranasal infection promotes CNS infiltration by streptococcal-specific Th17 cells. J Clin Invest 2016; 126: 303-317.
9) Makino I, Arai YC, Aono S, Hayashi K, Morimoto A, Nishihara M, Ikemoto T, Inoue S, Mizutani M, Matsubara T, Ushida T. The effects of exercise therapy for the improvement of jaw movement and psychological intervention to reduce parafunctional activities on chronic pain in the craniocervical region. Pain Pract 2014; 14: 413-418.
10) Krystkowiak P, Du Montcel ST, Vercueil L, Houeto JL, Lagrange C, Cornu P, Blond S, Benabid AL, Pollak P, Vidailhet M. Reliability of the Burke-Fahn-Marsden scale in a multicenter trial for dystonia. Mov Disord 2007; 22: 685-689.
11) Marcus CL, Omlin KJ, Basinki DJ, Bailey SL, Rachal AB, Von Pechmann WS, Keens TG, Ward SL. Normal polysomnographic values for children and adolescents. Am Rev Respir Dis 1992; 146: 1235-1239.
12) Kitamura K, Iino Y, Kamide Y, Kudo F, Nakayama T, Suzuki K, Taiji H, Takahashi H, Yamanaka N, Uno Y. Clinical practice guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan - 2013 update. Auris Nasus Larynx 2015; 42: 99-106.
13) Walls A, Cubangbang M, Wang H, Raiji M, Knight J, Steehler M, Latimer E, Harley EH. JR. Pediatric autoimmune neuropsychiatric disorder associated with streptococcus immunology: a pilot study. Otolaryngol Head Neck Surg 2015; 153: 130-136.
14) Bhutta MF. Epidemiology and pathogenesis of otitis media: construction of a phenotype landscape. Audiol Neurotol 2014; 19: 210-223.
15) Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaert P, Georgalas C, Goossens H, Harvey R, Hellings P, Hopkinsc, Jones N, Joos G, Kalogjera L, Kern B, Kowalski M, Price D, Riechelmann H,Schlosser R, Senior B, Thomas M, Toskala E, Voegels R, Wang De Y, Wormald PJ. European position paper on rhi-

nosinusitis and nasal polyps 2012. Rhinol Suppl 2012; 23: 1-298.

16) Bhattacharyya N, Grebner J, Martinson Ng. Recurrent acute rhinosinusitis: epidemiology and health care cost burden. Otolaryngol Head Neck Surg 2012; 146: 307-312.

17) Witmans MB, Keens TG, Davidson Ward SL, Marcus CL. Obstructive hypopneas in children and adolescents: normal values. Am J Respir Crit Care Med 2003; 168: 1540.

18) Pavone P, Rapisarda V, Serra A, Nicita F, Spalice A, Parano E, Rizzo R, Maiolino L, Di Mauro P, Vitaliti G, Coco A, Falsaperla R, Trifiletti RR, Cocuzza S. Pediatric autoimmune neuropsychiatry disorder associated with group a streptococcal infection: the role of surgical treatment. Int J Immunopathol Pharmacol 2014; 27: 371-378.

19) Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, Schechter MS, Ward SD, Sheldon SH, Shiffman RN, Lehmann C, Spruyt K; American Academy of Pediatrics. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2012; 130: 714-755.

20) Martins IJ. Bacterial lipopolysaccharides and neuron toxicity in neurodegenerative diseases. Neurol Neurosurg 2018; 1: 1-3.

21) Kang KT, Chou CH, Weng WC, Lee PL, Hsu WC. Associations between adenotonsillar hypertrophy, age, and obesity in children with obstructive sleep apnea. PLoS One 2013; 8: e78666.

22) Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. Otolaryngol Head Neck Surg 2009; 140: 800-808.

23) Martins Ij. Increased risk for obesity and diabetes with neurodegeneration in developing countries. CHAPTER 01. Top 10 Contribution on Genetics. Book Chapter. 2018. (www.avidscience.com)

24) Pavone P, Falsaperla R, Nicita F, Zecchini A, Battaglia C, Spalice A, Iozzi L, Parano E, Vitaliti G, Verrotti A, Belcastro V, Cho SY, Jin DK, Savasta S. Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection (PANDAS): clinical manifestations, IVIG treatment outcomes, results from a cohort of Italian patients. Neuropsychiatry (London) 2018; 8: 854-860.

25) Campanella V, Syed J, Santacroce L, Saini R, Ballini A, Inchingolo F. Oral probiotics influence oral and respiratory tract infections in pediatric population: a randomized double-blinded placebo-controlled pilot study. Eur Rev Med Pharmacol Sci 2018; 22: 8034-8041.