

Diagnosis of Nervous System Disorders in Children

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Abstract Damage to the nervous system in children is observed in various diseases, including neurological syndromes involving the central nervous system (CNS), peripheral NS, autonomic NS and the development of mental disorders. Timely diagnosis of the etiological causes and nature of the lesion will allow for adequate therapy and preventive measures.

Keywords Rheumatic chorea, PANS - syndrome, PANDAS - syndrome

1. Introduction

Damage to the nervous system in children is observed in various diseases, including neurological syndromes involving the central nervous system (CNS), peripheral nervous system, autonomic nervous system and the development of mental disorders. In many diseases in children, against the background of the clinical symptoms of the underlying disease, symptoms of damage to the nervous system are observed, which decrease and disappear during the treatment, but in some cases neurological symptoms persist or recur, which requires a complete clinical and laboratory examination, differential diagnosis of diseases with manifestations neurological and mental symptoms, consultations of rheumatologists, neurologists.

2. Etiology

A large number of studies point to the relationship of streptococcal infection with the development of lesions of the nervous system.

Group A beta-hemolytic streptococcus (GABHS, *Streptococcus pyogenes*) causes a variety of bacterial infections in humans [1,2]. The clinical forms of streptococcal (group A) infection are diverse with the development of superficial lesions (tonsillopharyngitis, otitis, sinusitis, erysipelas) and invasive forms of diseases (cellulitis, myositis, meningitis, pneumonia, peritonitis, endocarditis, arthritis, scarlet fever, sepsis), and also contributes to the development immunopathological diseases (acute rheumatic fever, poststreptococcal glomerulonephritis, poststreptococcal autoimmune diseases of the central nervous system.

GABHS has a pathogenic effect, can persist in infected

tissues due to the surface M-protein, which allows the microorganism to escape phagocytosis by polymorphonuclear leukocytes in the absence of antibodies specific to this type of protein, providing colonization on the mucosa [1,3]. GABHS contributes to the development of autoimmune complications [4]. Streptococcal infection plays a significant role in the pathogenesis of various lesions of the central nervous system, including Sydenham's chorea (chorea minor), neuropsychiatric disorders (PANDAS), and possibly tics, impulsive-compulsive disorders) [2,5,6].

The literature describes cases of acute onset tics and obsessive-compulsive disorders without prior GABHS infection. Children have also been described in whom acute onset or exacerbation of tics and OCD occurred after an infection (viral and/or bacterial).

Timely study of anamnesis, identification of genetic predisposition, clinical examination and laboratory and instrumental studies play an important role in making a diagnosis and conducting appropriate therapy. Symptoms of CNS damage depend on the etiology of the disease and the nature of the damage.

3. Clinical Manifestations

Rheumatism is an infection caused by group A β -hemolytic streptococcus. In recent years, there has been a tendency towards an increase in the incidence of rheumatism in all age groups, and more intensively in children. This trend is also due to the presence of secular rhythms characteristic of aggressive streptococcal infection and a decrease in the sensitivity of streptococci to penicillins. For childhood rheumatism, chorea is characteristic, occurring in 12-17% of cases, mainly in early puberty and in girls.

Rheumatic chorea (small chorea or Sydenham's chorea) - due to the involvement in the pathological process of various brain structures (striated body, subthalamic nuclei, cerebellum). The latent period can last up to several months from a previous streptococcal infection. In some cases, after a streptococcal infection, signs of rheumatic brain damage

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begin gradually, when health worsens, school performance decreases, sleep is disturbed, the child becomes irritable, sometimes signs of heart damage are detected later. Chorea minor is often associated with carditis, the symptoms of which come to light later.

Rheumatic chorea is characterized by a pentad of symptoms:

- distal hyperkinesias
- muscle hypotension (up to muscle flabbiness with imitation of paralysis)
- disorders of statics and coordination
- vegetative-vascular dysfunction
- psycho-emotional disorders (mood instability, irritability, tearfulness, etc.).

Hyperkinesias increase with excitement, disappear during sleep, are more often bilateral, less often unilateral. There is a violation of handwriting, slurred speech, it is difficult for the child to eat and drink on his own. Against the background of adequate therapy, the manifestations disappear after 1-2 months. It is necessary to differentiate with other diseases, in the clinical picture of which there are signs of damage to the nervous system [7-9].

At the end of the last century, in 1998 Swedo S.E. and a group of scientists from the National Institute of Mental Health (USA) for the first time described a new disease characterized by an undulating course with obsessive-compulsive disorders and/or tics in children over 5 years of age with a history of streptococcal infection [10-12]. The disease has been named.

The disease was called "pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection", or PANDAS syndrome.

Subsequently, the researchers drew attention to the clinical heterogeneity of PANDAS (different severity and polymorphism of clinical manifestations), the difficulties in establishing the relationship between streptococcal infection and acute tics and obsessive-compulsive disorders without previous GABHS infection, the lack of association between the clinical exacerbation of PANDAS and changes in autoantibody titer and the lack of reliable diagnostic markers [13-18], which led to the introduction of a new name for the disease - "pediatric acute neuropsychiatric syndrome" (English Pediatric Acute Neuropsychiatric Syndrome, PANS), the key phenomenon of which is the acute onset of symptoms, the presence in the clinic of recurrence of symptoms with tics and obsessive-compulsive syndrome, the pathogenesis of PANS is not always associated with infectious factors [19,20]. PANS can have a variety of etiologies, including genetic and immunological, with or without prior infection [21]. It was noted that all cases of PANDAS are associated with streptococcus and are a subtype of PANS [22].

Diagnostic criteria for PANDAS syndrome [11]:

- 1) the presence of obsessive-compulsive disorders and / or tics;
- 2) debut in childhood: symptoms appear between 3 years

of age and puberty;

- 3) paroxysmal type of the course of the disease, characterized by a sudden onset or a sharp increase in symptoms. Often the onset of symptoms or their aggravation can be associated with a specific day or week. Symptoms usually decrease significantly, and sometimes completely disappear between episodes of exacerbation;
- 4) connection with streptococcal infection - exacerbation should be associated with the detection of streptococcus in the nasopharynx and / or with an increase in the titer of antibodies to streptococcus;
- 5) connection with neurological disorders.

During an exacerbation, patients find changes in neurological status. Hyperactivity and hyperkinesias (including choreiform) are most often observed. The PANDAS syndrome is characterized by the severity of psychiatric aspects, as well as a much faster and complete regression of neuropsychiatric symptoms only with adequate antistreptococcal therapy.

Diagnostic criteria for PANS [6]:

- 1) a sharp, dramatic onset of obsessive-compulsive syndrome or a sharp restriction in food intake;
- 2) the presence of neuropsychic symptoms (≥ 2 simultaneously) with an acute onset:
 - anxiety;
 - emotional lability and/or depression;
 - irritability, aggression and/or oppositional behavior;
 - behavioral regression;
 - decreased school performance (associated with attention deficit/hyperactivity disorder);
 - sensory or motor abnormalities;
 - somatic symptoms, including sleep disturbance, enuresis, frequent urination;
- 3) the symptoms are not explained by other known diseases.

Thus, the clinical symptoms of chorea minor (one of the manifestations of acute rheumatic fever) and PANDAS syndrome are similar (beginning after a streptococcal infection, clinical manifestations). The development of PANDAS syndrome is typical for children of prepubertal age (in contrast to chorea, for which the typical age group is children 5-8 years old). Chorea minor is combined with other clinical criteria for acute rheumatic fever (carditis, polyarthritis, rarely erythema annulare, rheumatic nodules) [23]. Chorea minor is characterized by a subacute onset of the disease, fever, and carditis, while PANDAS has an acute onset of the disease without systemic manifestations [24-27].

Despite the variability of the clinical symptom complex, the presence of obsessive-compulsive disorders (OCD) is common for both chorea and PANDAS syndrome. Tics and OCD are often observed in the prodromal period of chorea, and hyperkinesias join later [28-32]. Handwriting impairment and irritability are also seen in these conditions. Chorea often has a monophasic course.

PANDAS syndrome is characterized by the severity of psychiatric aspects, a much faster and complete regression of neuropsychiatric symptoms only with adequate antistreptococcal therapy. Such conditions occur with a certain frequency (the average duration of an attack is 12-15 weeks on average) and significantly reduce the patient's quality of life. For RANDAS, cardiac disorders are uncharacteristic [30].

It should be noted that there is a return of symptoms after streptococcal or other infection, which is an important criterion for PANDAS.

In PANDAS syndrome, unlike rheumatism, there are no classic symptoms of ARF (rheumatic nodules, annular erythema, arthritis, carditis), an older age of the onset of the disease, an undulating course, the occurrence of exacerbations of the disease often after a psycho-emotional event, the mandatory presence of neurological symptoms in the acute period, favorable forecast. In acute rheumatic fever, in most cases, the symptoms of minor chorea are often combined with symptoms of carditis, changes in the heart valves are observed, which is confirmed by electrocardiogram and echocardiogram [27].

Some authors express the opinion that the development of PANDAS may be associated not only with streptococcus, but also with other infections [20,33–37].

Conducted observations and studies indicate that patients with RANS syndrome have a genetic predisposition to certain infections and are prone to a pathological immune response with the production of cross-antibodies to microbial and brain antigens [37,38]. The clinical picture of PANS is characterized by the presence of an obsessive-compulsive syndrome with or without tics, emotional lability, anxiety, behavioral changes, etc. One of the manifestations of PANS is Tourette's syndrome, the prevalence of which is 5–7 cases per 100,00 children [38,39]. This pathology is characterized by transient tic disorders in the form of motor tics and auditory tics: echolalia (repetition of other people's words) and palilalia (repetition of one's own word), sometimes coprolalia (spontaneous utterance of socially undesirable or forbidden words or phrases) [40]. Tics in Tourette's syndrome are of a monotonous nature, temporarily suppressed, non-rhythmic, aggravated by emotional arousal, often they are preceded by an irresistible impulse, when the child experiences a feeling of tension and the need to perform certain movements, after which he feels better.

Recently, a large number of studies have been carried out on the pathophysiology of tics, Tourette's syndrome and ACS. A theory has been proposed to increase the activity of the supplementary motor area before the onset of tics, which plays an important role in the formation of sensory phenomena preceding the execution of tics (prodromal urges) [41]. Magnetic resonance imaging of the brain showed a decrease in the size of the caudate nucleus in children and adults with Tourette's syndrome [42], with a negative correlation between the size of the caudate nucleus in childhood and the severity of symptoms in older age [43].

In a study by E. Sowell et al. a decrease in the size of the cortex in the sensorimotor region, as well as in other regions (ventral frontal cortex, dorsal parietal cortex) was found in children with Tourette's syndrome [44].

4. Diagnostics

A sudden change in the child's behavior, the appearance of stereotyped actions and movements (obsessions, tics, hyperkinesis) indicates a specific lesion of the nervous system, which can be observed in ARF and various variants of the PANS syndrome, which requires consultation with a neurologist, rheumatologist.

When studying a family history, take into account the presence of neurological, mental disorders, autoimmune and autoinflammatory diseases in the patient's relatives, as well as frequent past infections, including streptococcal etiology in a child.

All children need a microbiological examination of the pharynx to confirm a previous nasopharyngeal infection. It is recommended to make a throat swab, regardless of the presence or absence of clinical pharyngitis, in case of exacerbation of neuropsychiatric symptoms [32,45]. For the diagnosis of infection, the determination of the level of antibody titer is used: antistreptolysin O (ASLO) and antideoxyribonuclease B (aDNase B) in the dynamics of observation, as well as other biochemical blood parameters indicating the presence of an inflammatory process. An electro- and echocardiogram will confirm the development of ARF, encephalography, and magnetic resonance imaging will reveal changes in the brain.

5. Conclusions

Features of the nervous system damage in ARF and PANS / PANDAS syndrome, the presence of neuropsychiatric symptoms require differential diagnosis, laboratory and instrumental studies to diagnose the nature of the CNS lesion and appropriate treatment and observation by a rheumatologist and neurologist depends on the established diagnosis. Timely diagnosis of the nature of the damage to the nervous system will allow for adequate therapy, preventive measures and monitoring of the identified pathology, respectively, which is of decisive importance in the prevention of persistent and severe lesions of the nervous system.

REFERENCES

- [1] Pokrovsky VI, Briko NI, Kleymenov DA. Prevalence and clinical and epidemiological characteristics of diseases caused by group A streptococci in Russia. Therapeutic archive. 2009; 81(11): 5–9.
- [2] Stevens DL, Bryant AE. Severe Group A Streptococcal

- Infections. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations* [Internet]. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK333425/> (Accessed 20 January 2018).
- [3] Nasser W, Beres SB, Olsen RJ, Dean MA, Rice KA, Long SW, Kristinsson KG, Gottfredsson M, Vuopio J, Raisanen K, Cagant DA, Steinbakk M, Low DE, McGeer A, Darenberg J, Henriques-Normark B, Van Beneden CA, Hoffmann S, Musser JM. Evolutionary pathway to increased virulence and epidemic group A *Streptococcus* disease derived from 3,615 genome sequences. *Proc Natl Acad Sci U S A*. 2014; 111(17): E1768–76. doi: 10.1073/pnas.1403138111.
 - [4] Zhu L, Olsen RJ, Nasser W, de la Riva Morales I, Musser JM. Trading capsule for increased cytotoxin production: contribution to virulence of a newly emerged clade of emm89 *Streptococcus pyogenes*. *MBio*. 2015; 6(5): e01378–15. doi: 10.1128/mBio.01378-15.
 - [5] Krasnova EI. streptococcal infection. Clinical-diagnostic and treatment-and-prophylactic aspects. Novosibirsk: Sibmedizdat NGMU; 2015. 160 p.
 - [6] 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 acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. *J Child Adolesc Psychopharmacol*. 2015; 25(1): 3–13. doi: 10.1089/cap.2014.0084.
 - [7] Dauksh I.A., Murathodzaeva A.V., Khakimova U.R. Clinic and course of acute rheumatic fever in children at the present stage. *Pediatrics*. Tashkent. 2016. - No. 3. - S. 62 - 65.
 - [8] Dauksh I.A., Muratkhodzaeva A.V. Damage to the nervous system in rheumatic fever in children. *Pediatrics*. Tashkent. 2017. - No. 1. - S. 73 - 76.
 - [9] Muratkhodzaeva A.V., Dauksh I.A., Pirnazarova G.Z., Khakimova U.R. Rheumatic fever in children. *Tutorial*. Tashkent. 2020. S. - 113.
 - [10] Allen AJ, Leonard HL, Swedo SE. Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry*. 1995; 34(3): 307–311. doi: 10.1097/00004583-199503000-00015.
 - [11] Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry*. 1998; 155(2): 264–271. doi: 10.1176/ajp.155.2.264.
 - [12] Snider LA, Seligman LD, Ketchen BR, et al. Tics and problem behaviors in schoolchildren: prevalence, characterization, and associations. *Pediatrics*. 2002; 110 (2 Pt 1): 331–336. doi: 10.1542/peds.110.2.331.
 - [13] Morer A, Lazaro L, Sabater L, Massana J, Castro J, Graus F. Antineuronal antibodies in a group of children with obsessive-compulsive disorder and Tourette syndrome. *J Psychiatrist Res*. 2008; 42: 64–68. <https://doi.org/10.1016/j.jpsychires.2006.09.010>.
 - [14] Singer HS, Giuliano JD, Zimmerman AM, Walkup JT. Infection: a stimulus for tic disorders. *Pediatric Neurol*. 2000; 22: 380–383. [https://doi.org/10.1016/S0887-8994\(00\)00131-4](https://doi.org/10.1016/S0887-8994(00)00131-4).
 - [15] Singer H.S. Tourette's syndrome: from behavior to biology. *Lancet Neurol*. 2005; 4(3): 149–159. [https://doi.org/10.1016/S1474-4422\(05\)01012-4](https://doi.org/10.1016/S1474-4422(05)01012-4).
 - [16] Brilot F, Merheb V, Ding A, Murphy T, Dale RC. Antibody binding to neuronal surface in Sydenham chorea, but not in PANDAS or Tourette syndrome. *Neurology*. 2011; 76: 1508–1513. <https://doi.org/10.1212/WNL.0b013e3182181090>.
 - [17] Hoekstra PJ, Manson WL, Steenhuis MP, Kallenberg C, Minderaa RB. Association of common cold with exacerbations in pediatric but not adult patients with tic disorder: a prospective longitudinal study. *J Child Adolesc Psychopharmacol*. 2005; 15: 285–292. <https://doi.org/10.1089/cap.2005.15.285>.
 - [18] Singer HS, Hong JJ, Yoon DY, Williams PN. Serum autoantibodies do not differentiate PANDAS and Tourette syndrome from controls. *Neurology*. 2005; 65(11): 1701–1077. <https://doi.org/10.1212/01.wnl.0000183223.69946.fl>.
 - [19] Morris CM, Pardo-Villamizar C, Gause CD, Singer HS. Serum autoantibodies measured by immunofluorescence confirm a failure to differentiate PANDAS and Tourette syndrome from controls. *J Neurol Sci*. 2009; 276: 45–48. <https://doi.org/10.1016/j.jns.2008.08.032>.
 - [20] Chang K, Frankovich J, Cooperstock M, et al. Clinical evaluation of youth with acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. *J Child Adolesc Psychopharmacol*. 2015; 25(1):3–13. doi: 10.1089/cap.2014.0084.
 - [21] Toufexis MD, Hommer R, Gerardi DM, et al. Disordered eating and food restrictions in children with PANDAS/PANS. *J Child Adolesc Psychopharmacol*. 2015; 25(1): 48–56. doi: 10.1089/cap.2014.0063.
 - [22] Zibordi F, Zorzi G, Carecchio M, Nardocci N. CANS: Childhood acute neuropsychiatric syndromes. *Eur J Paediatr Neurol*. 2018; 22(2): 316–320. doi: 10.1016/j.ejpn.2018.01.011.
 - [23] Belov B.S., Nasonova V.L., Kuzmina N.N. Acute rheumatic fever: modern etiopathogenetic aspects. *Scientific and practical rheumatology*. 2008; 5:51–58. Belov B.S., Nasonova V.L., Kuzmina N.N. Acute rheumatic fever: modern etiopathogenetic aspects. *Nauchno-prakticheskaya Revmatology*. 2008; 5:51–58. (In Russ.)
 - [24] Seliverstov Yu.A., Klyushnikov S.A. Differential diagnosis of chorea. *Nervous diseases*. 2015; 1:6–15. Seliverstov Yu.A., Klyushnikov S.A. Differential diagnosis of chorea. *Nervous pains*. 2015; 1:6–15. (In Russ.)
 - [25] Kharitonov V.I., Vinnik Yu.M., Selyukov G.I. Diagnosis and treatment of PANDAS syndrome. Description of the case. *Russian Journal of Child Neurology*. 2014; 3: 48–50. Kharitonov V.I., Vinnik Yu.M., Selyukov G.I. Diagnosis and treatment of PANDAS syndrome. Description of the case. *Russkij Zhurnal Detskoy Nevrologii*. 2014; 3: 48–50. (In Russ.)
 - [26] Cardoso F., Vargas A.P., Oliveira L.D., Guerra A.A., Amaral S.V. Persistent Sydenham's chorea. *Movement Disorders*.

1999; 14(5): 805-807.

- [27] Snider LA, Sachdev V, MacKaronis JE, et al. Echocardiographic findings in the PANDAS subgroup. *Pediatrics*. 2004; 114(6): e748–e751. doi: 10.1542/peds.2004-0308.
- [28] Snider LA, Swedo SE. PANDAS: current status and directions for research. *Mol Psychiatry*. 2004; 9(10): 900–907. DOI: 10.1038/sj.mp.4001542.
- [29] Macerollo A., Martino D. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): an evolving concept. *Tremor Other Hyperkinet Mov (NY)*. 2013.
- [30] Uspenskaya T. L., Vinogradova T. V., Ipatova S. L., Sitnikova E. P., Kasatkin D. S. Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS syndrome): world practice and clinical observation. / *Children's infections*. - 2019. -18 (3). – P. 53-56.
- [31] Makeeva N. I., Odinets Yu. V., Sergienko E. V., Gubar S. O., Osmachko I. E., Boyko O. N. Rheumatism or a new nosological form? (clinical case). *Bulletin of problems of biology and medicine* - 2017 - VIP. 2 (136). - S. 153 - 155.
- [32] Kostik I.A., Kostik M.M. Modern approaches to the diagnosis and treatment of PANS/PANDAS. Questions of modern pediatrics. - 2019. - T.-19. - No. 5. - S. 324 - 338.
- [33] Ercan TE, Ercan G, Sevrage B, et al. Mycoplasma pneumoniae infection and obsessive-compulsive disease: a case report. *Journal of child neurology*. 2008; 23(3): 338–340. doi: 10.1177/0883073807308714.
- [34] Caruso JM, Tung GA, Gascon GG, et al. Persistent preceding focal neurologic deficits in children with chronic Epstein-Barr virus encephalitis. *J Child Neurol*. 2000; 15(12): 791–796. doi: 10.1177/088307380001501204.
- [35] Fallon BA, Kochevar JM, Gaito A, Nields JA. The underdiagnosis of neuropsychiatric Lyme disease in children and adults. *Psychiatr Clin North Am*.
- [36] Krause D, Matz J, Weidinger E, et al. Association between intracellular infectious agents and Tourette's syndrome. *Eur Arch Psychiatry Clin Neurosci*. 2010; 260(4): 359–363. doi: 10.1007/s00406-009-0084-3.
- [37] Muller N, Riedel M, Blendinger C, et al. Mycoplasma pneumoniae infection and Tourette's syndrome. *Psychiatry Res*. 2004; 129(2): 119–125. doi: 10.1016/j.psychres.2004.04.009.
- [38] Munasipova S.E., Zalyalova Z.A. Clinical and laboratory characteristics of pediatric acute neuropsychiatric syndrome. *Journal of Neurology and Psychiatry*. 2017. - No. 11; Issue. 2. - From 47 - 53.
- [39] Snider LA, Seligman LD, Ketchen BR, et al. Tics and problem behaviors in schoolchildren: prevalence, characterization, and associations. *Pediatrics*. 2002; 110 (2 Pt 1): 331–336. doi:10.1542/peds.110.2.331.
- [40] Cubo E, Gabriel y Galan JM, Villaverde VA, et al. Prevalence of tics in schoolchildren in central Spain: a population-based study. *Pediatric Neurol*. 2011; 45(2): 100–108. doi: 10.1016/j.pediatrneurol.2011.03.003.
- [41] Hampson M, Tokoglu F, King RA, et al. Brain areas coactivating with motor cortex during chronic motor tics and intentional movements. *Biol Psychiatry*. 2009; 65(7): 594–599. doi: 10.1016/j.biopsych.2008.11.012.
- [42] Peterson B, Riddle MA, Cohen DJ, et al. Reduced basal ganglia volumes in Tourette's syndrome using three-dimensional reconstruction techniques from magnetic resonance images. *Neurology*. 1993; 43(5): 941–949. doi: 10.1212/wnl.43.5.941.
- [43] Bloch MH, Leckman JF, Zhu H, Peterson BS. Caudate volumes in childhood predict symptom severity in adults with Tourette syndrome. *Neurology*. 2005; 65(8): 1253–1258. doi: 10.1212/01.wnl.0000180957.98702.69.
- [44] Sowell ER, Kan E, Yoshii J, et al. Thinning of sensorimotor cortices in children with Tourette syndrome. *Nat Neurosci*. 2008; 11(6): 637–639. doi: 10.1038/nn.2121.
- [45] Cooperstock MS, Swedo SE, Pasternack MS, Murphy TK; PANS/PANDAS Consortium. Clinical management of pediatric acute-onset neuropsychiatric syndrome: Part III - Treatment and Prevention of Infections. *J Child Adolescent Psychopharmacol*. 2017; 27(7): 594–606. doi.org/10.1089/cap.2016.0151. 594–606. doi.org/10.1089/cap.2016.0151.