

Chronic headache in children with meningism is caused by autoimmune inflammation of dura mater

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ABSTRACT

Tension headache is a common clinical diagnosis in children suffering from chronic headache, but little is known about this condition. We conducted clinical observation of 6100 patients (ages 5-18, citizens of Israel) suffering from “Tension Headache” and found meningeal symptoms and the whole complex of Meningism in 97% of them. This led us to the conclusion that chronic headache in children is a result of damage caused to brain membranes (Dura Mater). Next step was to look for the root cause of the brain membranes’ damage and we found it to be Streptococcal infection (80% of cases), Epstein–Barr virus (10% of cases), *Helicobacter Pylori* (HP) (2% of cases) and head trauma (8% of cases).

KEYWORDS: chronic-headache, brain, dura mater, meningism, children, treatment.

INTRODUCTION

In pediatric neurology, up to these days exists the term “chronic headache”, which includes two major subtypes: migraine and tension headache [1]. Tension headache is a common clinical diagnosis in children suffering from chronic headache, but little is known about this condition - there is no significant data on etiology, pathological process, or localization. The definition of “tension headache” was taken from the field of adult neurology, with same definitions and same mythology.

According to medical statistics [2], 20%-50% of children aged 5 to 18 years complain on headaches. Currently, the accepted practice among child neurologists is that if these children have “normal” neurological status, no pathological findings on CT and MRI, and no anamnestic findings of migraine, these children are diagnosed with “Tension Headache”. Their condition is attributed to stress and psychological issues, and accordingly it is considered that they should be treated with antidepressants. However, clinical practice that included questioning the parents showed that the use of antidepressants does not provide expected benefits and the children continue to suffer from headache, in some cases even severe. According to the parents, examinations by psychologists and psychiatrists showed that the children do not suffer from any psychological conditions.

The term “Tension headache” was introduced in pediatric neurology in “The International Classification of Headache Disorders”. Pediatricians well know that children are not “small adults” but completely different organisms. In this 21st century, “Tension headache” is a pediatric illness that still doesn’t have a known cause.

One of the most important parts of neurological diagnosis is thorough examination of the patient to determine patient’s neurologic status. In neurological guidelines, before the existence of imaging techniques, there were no additional tools to examine brain functions, and the diagnosis was established solely on clinical picture.

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Meningism [3-5] is a term describing the reaction of brain membranes (Dura) to trauma, inflammation or infection, presenting with symptoms of headache and meningeal symptoms, but without clinical picture of meningitis. The most important difference between meningism and meningitis is that in meningism in lumbar puncture (LP) there is no evidence of inflammation in cerebrospinal fluid (CSF).

Meningeal symptoms in patients previously diagnosed with “Tension Headache” include:

- Nuchal rigidity
- Kernig’s sign
- Brudzinski’s sign (upper)
- Brudzinski’s sign (middle)
- Tripod sign
- Guillain’s sign
- Facial sign

In addition, when the patient’s head is bent forward, pain appears in the following areas:

- Occiput
- Neck
- Epigastrium
- Back
- Chest

In the course of our work, we identified four major diseases that showed up as the cause of headache with meningeal syndrome:

1. Streptococcal infection

The most common cause of chronic headache was found to be Streptococcal infection (80%) [6, 7]. Streptococcus belongs to opportunistic pathogens (gram positive microorganism) existing as normal flora in human body. As any other opportunistic infections, it causes no symptoms in immunocompetent patients, but when immune status is being altered, Streptococcus may cause a range of clinical diseases.

Streptococcus Pyogenes is an important pathogen responsible for a variety of diseases, including erysipelas, scarlet fever, bronchitis, pneumonia, abscesses, sepsis and many more.

Infections in children may appear in several ways:

- a. Entrance through damaged skin in close contact with ill person or by using common objects (toys, tools, tableware, etc.).

- b. Air - droplets (aerosol) – coughing, speaking...

Besides, the risk of Streptococcal infections significantly increases during alterations in protective barriers of organism (chronic illness, immune suppression, hypothermia).

In order to determine the severity of the infection and to eliminate complications, blood tests and microbiologic tests should be conducted. These include cultures from sputum, throat and skin.

Mainstream therapy for Streptococcal infections is based on Penicillin (Rafapen, Pen–Rafa...).

PANDAS

In 1994 Dr. Swedo and her colleagues described a new medical condition and highlighted that in diseases such as tics disorders, Turret’s syndrome, and some other conditions, there is presence of streptococcal autoimmune response with Antistreptolysin–O (ASLO) levels above normal [8]. This condition was named as PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection). Initially, PANDAS was considered as a condition related to rheumatic fever and especially chorea, because of similar symptoms.

Development of PANDAS is more common in prepubertal children (chorea is more common in children 5-8 years of age). The disease is acute in onset and progression. Clinical picture for both, chorea and PANDAS, is diverse, but features of obsessive-compulsive disorders are common. One of the most common features of PANDAS include obsessive disorders, that appear with certain periodicity (average duration of the symptoms last about 12-15 weeks) and significantly impair patient’s life quality.

Diagnostic criteria for PANDAS:

1. Presence of obsessive-compulsive disorder and/or tics disorder.
2. Symptoms in children from 3 years old to pubertal age.
3. Disease is characterized by relapses, with sudden onset or exacerbation of the symptoms.
4. Exacerbation is associated with Streptococcal infection, meaning elevated ASLO levels.
5. Relation to neurological changes: chorea-like movements.

We would like to emphasize that in our observation, most of the children with PANDAS were also complaining about headaches, and neurological evaluation showed signs of meningism.

For treatment of PANDAS a prolonged course of antibiotic therapy is recommended.

2. Epstein–Barr Virus (EBV)

We discovered that chronic headache with signs of meningism can also be caused by EBV (subgroup of Herpes viruses). In our study we detected it in 10% of our patients with headache.

EBV infection usually appears in early childhood or teen ages. Some antibodies related to EBV remain in the child's body for the rest of the life [9]. Source of infection may be an infected individual. EBV has low infectious potential. Transmission occurs by the way of air-drops, but most common by sputum (as indicated by the commonly used other name of this disease – Kissing Disease/Mononucleosis). The virus can also be transmitted by blood transfusion. EBV can be secreted into environment for 18 months after primary infection (as proven by samples from nasopharynx). In patients recovered from EBV it still can be found in nasopharyngeal samples in 15-25% of cases.

The virus may cause variety of symptoms/diseases:

- Infectious mononucleosis
- Lymphogranulomatosis (Hodgkin's disease)
- Hepatitis
- Herpes – like lesions of skin and mucosal surfaces.
- Herpangina
- Chronic fatigue syndrome (common for many types of hidden infections) [10].

Infectious mononucleosis is the most common form of hidden EBV infection. Virus has the ability to selectively damage lymphoid and reticular tissues, clinically present as lymphadenopathy and hepatosplenomegaly. In many cases the disease is asymptomatic or with only mild non-specific symptoms. Antibodies to EBV are found in 50-80% of adults. Prolong existence of virus in the body, in the form of hidden infection, increases the risk of chronic mononucleosis, and in turn increases the risk of disease exacerbation in immunosuppressed or

immunocompromised states. Secondary/opportunistic infections (streptococci, staphylococci) play a role in pathogenesis of infectious mononucleosis.

Incubation period lasts 4-15 days (most common about a week), and is usually acute on onset. On 2nd-4th day of infection chorea and other symptoms of general "intoxication" reach their peak. Initial stages of the disease are characterized by general weakness, headache, myalgia and arthralgia; shortly later painful swallowing occurs. Usually body temperature rises to 38-40 degrees Celsius; it sometimes has a wave-like pattern and may last for 1-3 weeks or longer. However, in many individuals disease symptoms may be subfebrile with body temperature of 37-37.5 °C.

Chronic mononucleosis is a disease caused by EBV. Symptoms and clinical features may vary significantly. Almost all the patients complain of general weakness, headache, early fatigue, insomnia, myalgia, and some have fever, lymphadenopathy, pneumonia, pharyngitis, nausea, abdominal pain, diarrhea and vomiting. Not all patients have hepatosplenomegaly. Some patients have viral exanthemas, most common in the form of herpes-like lesions: oral in 26%, genital in 38%. At blood test leucopenia and thrombocytopenia are characteristic, but these findings are non-specific, because they appear in a wide variety of other chronic infectious diseases.

In mild cases of EBV disease it is possible to treat the symptoms by vitamins and symptomatic therapy alone.

For treatment of chronic headache caused by EBV, multfield team involvement may be necessary, including pediatric neurologist, infectious diseases specialist, immunologist, pediatrician, etc. Parents of the child should be aware and informed that headaches caused by EBV infection may last for long periods of time and reoccur in immunodeficient states, caused by other factors.

It is important to emphasize, that EBV is "related" to CMV (Cytomegalovirus) and both may coexist at the same time. A child has a very low risk to develop serious complications, even in coinfection by both these viruses. Besides, CMV, after primary infection, usually provides immunity. CMV infection may be dangerous only if appears

during pregnancy, because it may cause damage to multiple systems in fetus.

3. *Helicobacter Pylori*

Helicobacter Pylori [11] (HP) is a gram-negative, helically-shaped, microaerophilic bacterium. It was first discovered in 1875 by German scientists, but the relation between HP and gastritis was established only in 1983 by Australian scientists Robin Warren and Barry Marshall.

Interesting fact – for 23 years these scientists tried to convince scientific world about their theory of pathogenic features of HP, including deliberate self-infection of B. Marshall that caused him to develop gastritis. Their discovery revolutionized the approach to gastritis and gastric ulcers, and they were awarded the Nobel price at 2005.

In medical literature we found only a few cases describing headaches in patients with HP. These were mainly described as migraine headaches, somehow related to gastric ulcer [11, 12]. We were the first to discover that 2% of the patients with signs of meningism, have been suffering from diseases caused by HP.

4. Physical activity as a possible cause of chronic headache in children

Quite often (according to our data, about 8%) chronic headache in children results from sport activities, especially soccer, due to recurrent head traumas caused by headbutts used in this sport. These traumatic injuries cause damage to dura mater, which is the main source of pain receptors in the brain.

In these cases, the patient develops signs of meningism. Treatment of choice for these patients is bed rest (horizontal position, 24 hours a day for 7-10 days), until full resolution of headache. Analgesics can be used for symptoms relief. Sport activities such as martial arts, boxing and weightlifting may also contribute to the development of headaches. Rarely, headaches may also appear in children participating in dancing or gymnastics.

METHODS

From 1995 to 2020 we performed a clinical observation of 6100 patients suffering from

headache. In the multiple studies we conducted, our goal was to determine causes of chronic headache in children. Results of these studies showed that in 97% of the patients, who had been diagnosed with “Tension Headache”, meningeal symptoms and the whole complex of Meningism were present. This led us to the conclusion that chronic headache in children is a result of damage caused to brain membranes.

It is important to emphasize that the hard part of the brain membrane (dura mater) contains the highest concentration of pain receptors in the human body, while these receptors are absent in the brain tissue (white and gray matter). Also, it is important to distinguish Meningism from Meningitis, which is out of scope of this study. In meningism we do not expect to find inflammatory cells, which are characteristic of meningitis.

The outcomes of our study prove that the diagnosis of “Tension Headache” does not exist in pediatric neurology, instead there is Meningism syndrome which develops as a result of dura mater damage mostly caused by microorganisms. We were the first to study this subject and up until our discovery this fact did not appear in any medical literature.

In addition, we had MRI data for 414 children with chronic headache (without previous CT evaluation). These MRI data showed thickening of dura mater in 263 patients. These data support the argument that pathology of dura mater (pachymeningism) is the cause of chronic headache. We state that correct clinical and laboratory work up can exclude the need for performing imaging modalities, such as brain CT or MRI.

We tested our patients with meningism for the four potential causes of dura mater damage suggested above: Streptococcal infection, Epstein–Barr virus, *Helicobacter Pylori*, and head trauma.

1. Streptococcal infection

Streptococcal infection, past and present, can be diagnosed by Antistreptolysin–O (ASLO) or Antistreptolysin–O–Titer (ASOT) test. When streptococci enter the body, they produce the chemical component Streptolysin–O, which is used by the microorganism to destroy blood cells.

“O” in this term means that this compound is rapidly degenerates on exposure to oxygen. Human immune system immediately responds to Streptolysin–O by producing antibodies to block it. These antibodies are called Antistreptolysin–O. It is known that ASLO levels in the blood do not increase simultaneously with onset of streptococcal disease, but only 1-3 weeks later. Normal levels of ASLO are considered to be up to 200 IU/ml.

2. Epstein–Barr Virus (EBV)

Diagnosis of EBV is based on several parameters in blood tests. This includes elevated lymphocytes levels (15% above upper limit normal) and presence of atypical mononuclear cells (higher than 10% of all the leukocytes). Antibodies to EBV appear in the blood after 3-6 weeks following primary infection (in 100% of patients) and remain for life.

3. *Helicobacter Pylori*

Diagnosis of HP was performed by blood test for HP antigen or breath test (C13 urea breath test).

4. Physical activity and head trauma

Patients were questioned about their participation in sport activities and about head traumas.

RESULTS AND DISCUSSION

When analyzing the data from our patients with chronic headache with signs of meningism we found the following:

80% had higher than normal ASLO levels (normal levels up to 200 IU/ml), which led us to the conclusion that these children suffered from Streptococcal infection. In these patients ASLO levels were 200-1790 IU/ml.

10% of patients were diagnosed with Epstein–Barr Virus. In medical literature we did not find recommendations regarding chronic headache caused by EBV infection. We are the first to describe headaches caused by EBV infection.

2% of patients have been suffering from diseases caused by *Helicobacter Pylori*. If HP was found in a child with headache, it is possible to state with high degree of certainty that the headache is due to autoimmune meningism, caused by HP antigen. In our study we found that treatment of

HP by a gastroenterology specialist resulted in the resolution of headache and symptoms of meningism.

8% of patients reported recent head trauma or participation in sport activity that could cause head injury.

Less than 1% of patients could not be classified to any of the groups above.

CONCLUSION

This study is based on 25 years of our experience in this field.

The data we collected from 6100 children allows to conclude that chronic headaches in children are not at all related to the “Tension Headache” diagnosis that doctors use for almost 100 years to describe headache in children and adults. This type of headache was thought to be related to psychological issues and was treated with antidepressants.

Instead, the headache is a result of damage to dura mater, clinically present as meningism. Most often the cause is an autoimmune reaction involving dura mater caused by Streptococcal infection. Other causes appeared to be Epstein–Barr Virus, *Helicobacter Pylori* and head trauma related to physical activity.

We certainly hope that our discovery would change the attitude to chronic headaches experienced by 20-50% of children. We found the real causes of chronic headache in children and we hope that child neurologists around the world would treat children according to our findings that gave positive results.

CONFLICT OF INTEREST STATEMENT

The authors of this manuscript certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. No funding was received.

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