Bulut F, Cumbul A, Ballica B. Clinical Importance of Family History in Recurrent Chronic Tonsillitis Pediatric Patients: Review. J Pediatrics & Pediatr Med. 2020; 4(3): 1-5

Journal of Pediatrics and Pediatric Medicine

Journal of Pediatrics and Pediatric Medicine

Mini-Review Open Access

Clinical Importance of Family History in Recurrent Chronic Tonsillitis Pediatric Patients: Mini-Review

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Article Info

Article Notes
Received: September 21, 2020
Accepted: December 03, 2020

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Keywords:
Recurrent/chronic tonsillitis
PFAPA syndrome
Persistent Fever
Halitosis
Biofilm Volume
Family Inheritance
Tonsillectomy

Abstract

Introduction: In pediatric patients with a history of recurrent chronic tonsillitis in both their mother and father, they may show an excessive immune response due to genetic inheritance.

Method: Family history in immune defense mechanism predispose to tonsil disorders. Biofilm formation theory explains that the underlying factor of recurrent/ chronic tonsillitis formation is the bacterial biofilm on the surface of the tonsils.

Results: Although recurrent chronic tonsillitis is a clinical diagnosis, patient's symptoms and signs should be monitored carefully. The history of each patient and family members should be taken carefully. Since the clinical presentation of PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis) syndrome can be confused with pediatric patients with a history of recurrent chronic tonsillitis in both parents, must follow a multidisciplinary approach before starting a treatment.

Conclusions: Family history determines the severity of tonsillar damage with immune response in pediatric patients with a history of recurrent chronic tonsillitis in both their mother and father.

Introduction

Recurrent / chronic tonsillitis, a common childhood disease, is a parenchymal infection of the palatine tonsils. Recurrent tonsilitis is diagnosed when tonsilitis occurs at least 5 times in a year and diagnosis of recurrent chronic tonsillitis has been done based on clinical criteria[1]. It is reported that more than 65% of human bacterial infections comprise bacterial biofilm, and connection between bacterial biofilms[2] and human disease has been established long ago.

Formation of biofilms is associated with many otolaryngological infections and closely related to the recurrence and chronicity of these infections. Biofilm formation theory argues that the underlying factor of recurrent / chronic tonsillitis is bacterial biofilms on the surface of the tonsils[3]. Bacteria uses the biofilm formation for communication signals sent from cell to cell. In bacterial pathogenesis, bacteria can detect the population density and stimuli from the environment and activates a mechanism called "quorum sensing" (QS) that enables it to develop a response by coordinating gene regulation[4]. Changes in genetic information and the ability of QS in bacteria residing in biofilm are important mechanisms explaining antibiotic resistance of many pathogens. Genetic variations in immune defense mechanism predispose to tonsil disorders. While

the etiology of PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis) syndrome remains uncertain. Some candidate genes have been suggested to be factors contributing to the etiology of the disease [5]. Some studies have shown different immunological aspects of tonsils and tonsil microbiota in children with PFAPA syndrome[6].

This article provides an overview of current information on the clinical role of genetics and mucosal biofilm volume in pediatric recurrent chronic tonsillitis patients with a parental history, and underlines the similarity between the clinical symptoms of these and with PFAPA syndrome. It also highly recommends a careful clinical examination and history taking, including hereditary conditions and genetic screening, before PFAPA is diagnosed.

Role of Genetics in Recurrent Tonsillitis

Genetic inheritance determines the severity of tonsillar damage with immune response in pediatric patients with a history of recurrent chronic tonsillitis in both parents[7]. Martin et al. previously reported the effects of genetics on the incidence of tonsillectomy[8]. In another clinical study, importance of genetic clustering in the family was elucidated in tonsillectomy cases[9]. In a genetic analysis on recurrent/chronic tonsillitis patients with at least one copy of the IL1B-31*C allele (both homozygous and heterozygous) are found at higher risk to develop the disease[10]. Also, it was reported that two host immunity related polymorphisms complement factor (CFH) and (TLR) 4-T399I play role in GAS tonsilitis[11-12].

Group A streptococcus is the major bacterial pathogen of tonsilitis. It was shown that streptococcal tonsillitis can stimulate psoriasis attacks, which is explained by molecular mimicry between human and bacterial antigens. Most substantial polymorphisms were detected in the intron of the MUC22 gene close to PSORS1 and HLA-C and -B loci. MUC22 was also seen within the TRIM10-TRIM15 locus[13]. TRIM family proteins are known to be involved in the regulation of inflammatory and innate immune signaling[14] and a nearby locus with the TRIM39 gene has been associated with Behcet's disease[15] an autoimmune disease also known to be triggered by streptococcal infections. Also in patients having recurrent tonsillitis episodes, integration host factor (IHF) is reported as a bacterial protein, which can stimulate transcription and regulate gene expression[16]. Also in patients having recurrent tonsilitis episodes, IHF is reported as a bacterial protein, which can stimulate transcription and regulate gene expression[17].

Significance of Mucosal Biofilm Volume in Recurrent Tonsillitis

Biofilms prefer moist environments, which make respiratory system and related mucosal surfaces particularly attractive for their development[18]. Some recurrent infections accompanied with biofilm formation, including chronic rhinosinusitis, chronic otitis media, and chronic Aden tonsillar diseases, lead to myriad of morbidities[19]. Biofilm formation theory explains that the underlying factor of recurrent / chronic tonsillitis is the bacterial biofilm on the surface of the tonsils [20]. Moreover, bacteria contain a large and accessible gene pool. As more bacteria colonize, the production of signaling molecules continues until a threshold level is exceeded, QS mechanism gets activated [21]. QS and extracellular signallings between bacteria residing in biofilm are important mechanisms that explain both antibiotic resistance of many pathogens, alterations in genetic information[22]. Bacteria can exist in several forms: free-floating, individual planktonic or in biofilm organization containing millions of bacteria. Biofilm bacteria have alternative gene expression models compared to planktonic bacteria, and many novel genes have been reported in biofilm formations. The importance of biofilm thickness has been reported in previous studies[1]. Deeper biofilm [23] layers are better protected from a myriad of antibacterial methods, including host immune reactions, detergents, and antimicrobial agents. Bacteria are surrounded by a major structural component of biofilm referred to as extracellular polymer substances (EPS) enriched with polysaccharides, glycolipids, proteins and nucleic acids[2]. The first study related to histomorphometric examination of the tonsillar tissues of children with a history of recurrent / chronic tonsillitis in both parents and the biofilm volume in tonsillar tissue were performed by us. Bacterial biofilm thickness and volume in pediatric patients with a history of recurrent chronic tonsillitis in both parents were measured higher in light microscopy examinations[24]. Furthermore, the effects of different drugs on biofilms have been reported so far[25]. Our previous research also displayed the effect of n-acetylcysteine and acetylsalicylic acid on bacterial biofilm[26].

Differential Diagnosis of PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis) Syndrome From 3-Year-Old Children with a History of Recurrent Chronic Tonsillitis in Both Their Mother and Father

We observed persistent fever despite antibiotic treatment, halitosis and frequent recurrent episodes of chronic tonsillitis in children under 3 years of age with the recurrent chronic tonsillitis story in both in both parents. Unlike PFAPA, recurrent tonsilitis attacks along with fever were found in patients before the age of 1 and we did not observe aphthous stomatitis. Halitosis was experienced just before and during episodes. Clinical findings show similarity with symptoms of PFAPA. PFAPA syndrome is the most common periodic fever syndrome among children and it was first recognized with an antibiotic-resistant fever with unknown origin, pharyngitis, stomatitis and

cervical adenitis between the ages of 2 and 5[27]. On the other hand, PFAPA syndrome presenting with recurrent chronic tonsillitis has been reported to have a strong relationship with familial inheritance[28]. PFAPA is characterized by different febrile attacks with a regular periodicity, however, PFAPA is one of the most difficult disease to distinguish from hereditary periodic fevers[29]. PFAPA exacerbations are mediated by activated T lymphocytes, GM-CSF, G-CSF and some proinflammatory cytokines such as IL-1β, IL-6 and IL-8. During PFAPA attacks, genes associated with complement system, IL-1, and IFN are markedly overexpressed, also evidences showed that there is an increased IL1RN and TNF expression in the tonsillar tissue taken from tonsillectomy performed during the asymptomatic periods[30]. The percentage of IL-1β positive B cells is higher in tonsils with PFAPA and most of the intracellular IL-1β positive cells are found to be memory B cells[29]. Also, TLR stimulation increases the TNF production. Indeed, saliva cytokines (protein or RNA) have been examined as a potential diagnostic marker when seems promising technique even for young children[31].

Persistent colonization with GAS may also occur, but does not appear to cause frequent recurrent infection or transmission of the disease to contacts[32]. Both host factors and bacterial factors appear to play a role in determining the severity of the infection[33]. And some candidate genes have been suggested to be factors contributing to the etiology of periodic fever and PFAPA syndrome. It has been shown that tonsils from PFAPA patients have a different cellular structure compared to tonsils of patients with recurrent streptococcal pharyngitis (RP). In histological examination, both PFAPA and RP tonsils have been reported to show variable expansion of the follicles and epithelium, displaying multifocal inflammatory events distinguished with neutrophils infiltrating the squamous mucosa[6]. Some studies have shown different immunological aspects of tonsils and tonsil microbiota in children with PFAPA syndrome and there is not yet an international consensus on this matter[5]. In another study, histological features of adult-onset PFAPA has been shown to be very similar to pediatric-onset PFAPA[34]. PFAPA syndrome is an immune-mediated disease characterized by cytokine dysfunction[30].

Diagnosis

A recent study reported that glycogen synthase kinase 3β (GSK-3β) activation index is a clinically applicable method for pediatric recurrent chronic tonsillitis patients[35]. Pediatric patients under 3 years of age with a history of recurrent chronic tonsillitis in both the parents present antibiotic resistant fever, halitosis and frequent recurrent episodes of tonsillitis. Diagnostic criteria's in PFAPA; regular recurrent fevers with an early onset age (<5 years), principal symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs: a) aphtous stomatitis, b) cervical lymphadenitis, c) pharyngitis, a complete asymptomatic period between attacks, normal growth and development[36]. Typically, over a 3 to 5 day period, body temperature reaches 40.5 °C, it occurs within almost constant intervals every 3-6 weeks. Comprehensive studies in PFAPA patients have not revealed any evidence of an infectious cause. Also, its cyclic nature of diseases is not consistent with classical infection and suggests an immunological disorder caused by inappropriate congenital immune responses[27, 37].

Persistent Fever in Recurrent / Chronic Tonsillitis

Many theories have been proposed to explain colonization of antibiotic-resistant GAS, such as; biofilm formation[38-40] and intracellular bacterial[41]. A relevant study conducted by us shows that children under age of 3 with a history of recurrent / chronic tonsillitis in parents have resistant fever despite antibiotic treatment[24]. PFAPA syndrome occurs with recurrent drug resistant fever attacks between the age 2-5 and it is recognized as an autoinflammatory disease[42]. Another study presents a serious case of chronic EBV infection caused by a novel CD70 mutation, which is manifested with periodic fever[43]. Current pharmacological treatment of PFAPA often includes corticosteroids that are effective in treating fever attacks[5]. Effectiveness of corticosteroid usage against antibiofilm has been reported [25]. Oral glucocorticoids dramatically alleviate the symptoms of PFAPA[44]. Cimetidine, an H2 antagonist with immunomodulating properties, was proposed by Feder in 1992 as an effective prophylactic treatment for PFAPA as it inhibits chemotaxis and T cell activation[45]. A single dose of prednisone (1-2 mg / kg) or betamethasone (0.1-0.2 mg / kg) administered at the beginning of an attack can excellently stop fever attacks within a few hours. Apremilast may have great efficacy in the treatment of PFAPA patients as it reduces the production of proinflammatory cytokines, including IL-12p70 and IFN from human PBMCs[46,47]. Additionally, since IL-12 is important in the pathogenesis of PFAPA, ustekinumab, a monoclonal antibody targeting the p40 subunit of IL-12 and IL-23, could be a potential treatment for resistant cases[48]. PFAPA is described as a clinical entity, with a beneficial effect of tonsillectomy operations but the underlying mechanism of success is still unclear[5].

Conclusion

There is a similarity between the clinical symptoms of pediatric patients under 3 years of age with a parental history of recurrent chronic tonsillitis, and those with PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis) syndrome. Patients with clinical symptoms such as halitosis and fever which do not decrease despite treatment, should be monitored carefully. In pediatric patients with a history of recurrent chronic tonsillitis in both parents, they may show an excessive immune

response due to genetic inheritance. It is important to reveal the relationship between biofilm volume-thickness and genetic predisposition in these patients. With a better understanding of the biofilm structure, it will have a significant contribution in both treatment and prevention of complications in patients who are clinically diagnosed at an early stage in recurrent chronic tonsillitis. Since the clinical presentation of PFAPA syndrome can be confused with pediatric patients with a history of recurrent chronic tonsillitis in both their mother and father, must follow a multidisciplinary approach before starting a treatment. Genetic studies to be conducted in the future will better reveal the tonsillar immunology and will make easy to differentiate chronic/recurrent tonsillitis and PFAPA syndrome.

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