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Prevalence of humoral immunodeficiency in adult patients with recurrent tonsillitis

Osama G. Abdel-Naby Awad*

Otolaryngology, Head and Neck Department, Minia University Hospital, Minia, Egypt

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ABSTRACT

Purpose: Recurrent tonsillitis in adults has a significant impact on patients' daily life and healthcare costs. Humoral immunodeficiency increases the susceptibility to recurrent infections. The purpose of this study was to investigate the prevalence and contribution of humoral immunodeficiency in adult patients with recurrent tonsillitis.

Material and methods: A prospective cross-sectional study conducted over 3 years duration with two groups of subjects. Group 1: included 50 normal adult subjects and group 2: included 50 adult patients with recurrent tonsillitis. Recruitment occurred in a tertiary care hospital in Egypt. Different immunoglobulins (Ig A, Ig M and Ig G isotypes) were quantitatively assessed and compared in 2 groups. Incidence of different infections was also compared in patients with humoral immunodeficiency versus patients with intact immunity.

Results: 4 (8%) subjects in group 1 had selective humoral Immunodeficiency versus 13 (26%) patients in group 2. Patients with recurrent tonsillitis had significantly lower mean of most assessed immunoglobulins: IgA ($P = 0.002$), IgM ($P = 0.003$), IgG ($P < 0.0001$), IgG1 ($P < 0.0001$) and IgG3 ($P < 0.0001$) compared to normal subjects; with no significant difference in mean of IgG2 ($P = 0.395$) and IgG4 ($P = 0.105$). Patients with humoral immunodeficiency had significantly higher incidence of tonsillitis ($P < 0.0001$) and rhinosinusitis ($P < 0.0001$) attacks compared to patients with normal immunity.

Conclusion: Adult patients with recurrent tonsillitis may have higher prevalence of humoral immunodeficiency compared to normal subjects. These findings suggest that assessment of immune function should be undertaken routinely in these patients.

1. Introduction

Tonsillitis is an inflammation of the pharyngeal tonsils. The inflammation usually extends to the adenoid and the lingual tonsils; consequently, the term tonsillopharyngitis is usually used. Tonsillitis is a common condition, especially in childhood due to viral or bacterial [1]. Recurrent tonsillitis is defined as repeated episodes of acute tonsillitis followed by periods with only very few, or without any, symptoms [2]. Recurrent tonsillitis in adults has a significant impact on families' daily life and healthcare costs secondary to frequent episodes of sore throat, fever, sleepless nights, general illness, impaired daily functioning and absence from school or work associated [3–5]. Frequency of group A Streptococcus is significantly higher in children aged 0–9 years and in adults aged 30–39 years [6].

Tonsillectomy is a widely applied procedure as a treatment for recurrent tonsillitis [3]. Tonsillectomy is recommended when a patient had 6 or more acute tonsillitis attacks during last 12 months and not indicated if a patient had < 3 attacks [2]. Risk of tonsillectomy is considered as it is associated with significant risk of primary and secondary hemorrhage, in addition it is painful procedure particularly for adults [7]. Inflammation of other pharyngeal lymphoid tissues makes patients with tonsillectomy still suffer from sore throat. Studies recommend more randomized controlled trials with adequate long-term follow-up to clarify the benefits of tonsillectomy versus non-surgical treatment in patients with recurrent tonsillitis [8].

Antibiotics are still commonly prescribed for acute and for recurrent throat infection. Antibiotic use reduces incidence of tonsillitis-associated complications like rheumatic fever and acute glomerulonephritis. However; reduction of unnecessary use of antibiotics is a major task to overcome the problem of antibiotic resistance [9]. In the light of these discussions, the use of alternative medicine in treatment of recurrent tonsillitis especially in adults may be an interesting option.

Immunoglobulins (Igs), also known as antibodies, comprise a family of proteins that occur in five major forms, also termed classes or

* 122 Kornish El-Neel Street, Minia City, Minia 61111, Egypt.
E-mail address: Usama.abdelnabi@mu.edu.eg.

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isotypes: IgM, IgD, IgG, IgE and IgA. Igs are produced by vertebrate animals as part of the normal immune response to microbial, e.g. bacterial or viral infection. Binding of Igs to a microbe can have immediate effects such as blocking and mobilizing other components of the immune system to destroy or inactivate the microbes, thereby providing protection against infectious diseases [10]. Subramaniam et al. [11] reported significant increase of IgG, A and M in children with chronic adenotonsillitis and levels of three immunoglobulins decreased to normal one month post-tonsillectomy, this decrease has been attributed to the removal of infected tissue and antigenic stimulation. On the contrary, no significant variation in serum IgG, IgA and IgM levels before and after tonsillectomy has been noted by some authors [12].

Alqudah et al. [13] reported some kind of humoral immunodeficiency and decrease in serum Igs in up to 54.8% of patients with recurrent rhinosinusitis; these results modified their standard practice and measurement of immunoglobulins levels in patients with recurrent rhinosinusitis is now undertaken routinely at their institution. From this point; the aim of this study was to assess humoral immunodeficiency in adult patients with recurrent tonsillitis in a hope to help such difficult to treat patients.

2. Patients and methods

2.1. Recruitment and classification of subjects

Participants were prospectively recruited from patients attending Minia University Hospital outpatient clinic, Minia City, Egypt, between May 2015 and September 2018. The study was approved by the Committee for Medical Research Ethics in Egypt, 2015NBA5413234. All patients signed a written consent prior to inclusion in the study. No pharmaceutical companies funded the study or contributed to the study design, outcome evaluation or writing of this study.

A total of 100 adult subjects were divided into: group 1; control group (50 adult subjects attending hospital clinic for a cause other than recurrent tonsillitis) and group 2; study group (50 patients with recurrent tonsillitis defined as having at least 3 episodes of acute tonsillitis in year and for 3 successive years of study duration). Clinically significant sore throat is defined as acute tonsillitis with one or more of the following features [14]: 1 – temperature > 38.3 °C, 2 – cervical lymphadenopathy (tender cervical lymph nodes or nodes > 2 cm), 3 – tonsillar exudate or 4 – a positive culture for group A B-Haemolytic streptococcus.

We assessed smoking index in tobacco cigarettes smokers [15] plus alcohol consumption intensity in alcohol drinkers [16]; and compared results in 2 groups.

2.2. Exclusion criteria

We excluded from the study patients with the following: suspected or proven tonsillar neoplasm, immune system disorders or with family history of immunodeficiency diseases, human immunodeficiency virus, and other causes of secondary immunodeficiency (including history of chemotherapy or other immunosuppressive drugs), any condition that may acutely or chronically influence immunoglobulin levels such as patients with hepatitis B, liver cirrhosis, chronic allergic disorders or presence of allergy at the time of inclusion in the study.

2.2.1. Subjects' assessment

Subjects were followed for 3 successive years with recording number of acute tonsillitis, rhinosinusitis, pneumonia, otitis media and skin infection attacks during period of the study with detailed ear, nose and throat examination.

2.2.2. Immunoglobulins assay

Five milliliters of venous blood samples were drawn from the antecubital veins with all aseptic precautions for immunoglobulin estimation from all participating subjects. The specimen was allowed to clot for 10 min and then centrifuged at 3000 rpm for 5 min to separate the serum. The serum was then transferred to another test tube and used for immunoglobulin estimation. Total serum IgG, A and M estimation was done by quantitative immunoturbidometry method and values expressed as mg/mL. IgG subclasses were determined by radioimmunodiffusion with monoclonal antibodies. Low immunoglobulin levels were considered to be those < 2 SD below the age-adjusted mean.

2.3. Statistics

Software package SPSS® version 16.0 (Chicago, U.S.) was used in the statistical analysis of the data. Parametric data were analyzed using the unpaired *t*-test. Categorical data were analyzed by the chi-square test or the Fisher's exact test, as appropriate. A value of $p \leq 0.05$ was considered.

3. Results

In group 1, of the 50 subjects, 60% (30/50) were men and 40% (20/50) were women, with an average age of 25.33 years (19–48 years). In group 2, of the 50 patients, 50% (25/50) were men and 50% (25/50) were women, with an average age of 30.08 years (19–45 years). There was no significant difference between both groups with respect to sex, age. Characteristics and comorbidities of study patients are presented in Table 1.

Difference in immunoglobulin levels of 2 groups.

Four (8%) subjects in group 1 had some immunoglobulins deficiency compared to 13 (26%) patients in group 2 classified as follow (Table 2):

1- Difference in IgA level: No subjects had Immunoglobulin levels < 2 SD from the mean in group 1 compared to 2 (4%) patients in group 2. (Mean 250 mg/dL, range: 60–490 mg/dL) in group 1 compared to (Mean: 190 mg/dL, range: 20–470 mg/dL) in group 2; ($P = 0.002$).
2- Difference in IgM level: No subjects had Immunoglobulin levels < 2 SD from the mean in group 1 compared to 2 (4%) patients in group 2. (Mean: 120 mg/dL, range: 38–270 mg/dL) in group 1 compared to (Mean: 95 mg/dL, range: 15–240 mg/dL) in group 2 ($P = 0.003$).
3- Difference in IgG level: Immunoglobulin levels < 2 SD from the mean were found in 2 (4%) subjects in group 1 compared to 5 (10%) patients in group 2. (Mean: 850 mg/dL, range: 400–1700 mg/dL) in

Table 1
Characteristics of study subjects.

Characteristic	Group 1 Control group (n = 50)	Group 2 Recurrent tonsillitis (n = 50)	*P* value
Age			
19–30 years	20	22	0.734
31–40 years	22	18	
41 + years	8	10	
Sex			
Male	30	25	0.899
Female	20	25	
Duration of cigarette smoking (years)	14 (5–20)	15 (5–25)	0.453
Comorbidities (number of patients)			
Hypertension	10	12	0.442
Tobacco pack-years, mean	40 (7–120)	36 (8–115)	0.624
Alcohol consumption (number of patients)			
Mild	2	3	0.432
Moderate	1	1	
None	47	46	

Table 2
Difference in immunoglobulins levels in 2 groups.

Immunoglobulins level Mean ± SD	Group 1 Control group (n = 50)	Group 2 Recurrent tonsillitis (n = 50	*P* value
Ig A	250 ± 125.2 mg/dL	190 ± 45.3 mg/dL	0.002*
Ig M	120 ± 45.4 mg/dL	95 ± 30.4 mg/dL	0.003*
Ig G	850 ± 300.6	570 ± 230.2	< 0.0001*
Ig G1	800 ± 324.5	350 ± 121.2	< 0.0001*
Ig G2	400 ± 215.1	370 ± 125.2	0.395
Ig G3	70 ± 30.3	40 ± 23.4	< 0.0001*
Ig G4	70 ± 36.4	60 ± 24.1	0.105

Data presented as mean ± standard deviation.
* $P < 0.05$ (Student's *t*-test for paired samples): represents significant difference.

group 1 compared to (Mean: 570 mg/dL, range: 350–1700 mg/dL) in group 2 ($P < 0.0001$).

4- Difference in IgG subclass level:
   A- No subjects had isolated IgG1 deficiency in group 1 compared to 2 (4%) patient in group 2, (Mean: 800 mg/dL, range: 400–1200 mg/dL) in group 1 compared to (Mean: 350 mg/dL, range: 250–1250 mg/dL) in group 2 ($P = 0.034$).
   B- No subjects had isolated IgG2 deficiency in group 1 compared to 2 (4%) patients in group 2, (Mean: 400 mg/dL, range: 120–640 mg/dL) in group 1 compared to (Mean: 370 mg/dL, range: 100–650 mg/dL) in group 2 ($P = 0.395$).
   C- One (2%) subject had isolated IgG3 deficiency in group 1 compared to 2 (4%) patients in group 2, (Mean: 70 mg/dL, range: 10–120 mg/dL) in group 1 compared to (Mean: 40 mg/dL, range: 10–130 mg/dL) in group 2 ($P < 0.0001$).
   D- One (2%) subject had isolated IgG4 deficiency in group 1 compared to 2 (4%) patients in group 2, (Mean: 70 mg/dL, range: 40–160 mg/dL) in group 1 compared to (Mean: 60 mg/dL, range: 20–140 mg/dL) in group 2 ($P = 0.105$).
   E- No subjects had deficiency of all IgG isotypes in group 1 compared to 3 (6%) patients in group 2.
   F- Three (6%) patients in group 2 had deficiency of IgA, IgM and IgG; and thus qualified for the diagnosis of common variable immunodefiency (CVID). No subjects had CVID in group 1.
5- Difference in incidence of recurrent infection attacks in group 2 (Table 3): Patients with immunodeficiency had significantly higher incidence of acute tonsillitis and rhinosinusitis attacks compared to patients with normal immunity during study duration. However; there was no significant difference regarding incidence of pneumonia, otitis media and skin infection attacks.
6- Difference in incidence of infection attacks according to type of immunoglobulin deficiency in group 2 (Table 4): Patients with CVID had higher incidence of infections and patients with Ig A deficiency had lower incidence of infections compared to other patients with immunodeficiency.

Table 3
Difference in different clinical presentations in patients with immune dysfunction vs. subjects with normal immunity during 3 years duration in group 2.

Clinical presentation (mean ± SD)	Subjects with immune dysfunction (n = 13)	Subjects with normal immunity (n = 37)	*P* value
Recurrent tonsillitis	20 ± 9.1	10 ± 3.4	< 0.0001*
Recurrent sinusitis	7 ± 3.2	3 ± 1.2	< 0.0001*
Recurrent pneumonia	1 ± 0.1	1 ± 0.2	0.950
Recurrent otitis media	3 ± 0.3	2 ± 0.8	0.768
Recurrent skin infection	3 ± 0.4	2 ± 0.7	0821

Data presented as mean ± standard deviation.
* $P < 0.05$ (Student's *t*-test for paired samples): represents significant difference.

4. Discussion

Acute tonsillitis has a real effect on patients and healthcare systems because it is considered one of the most common otolaryngological disorders. Increase the tonsil volume may compromise upper airways patency, whereas associated active inflammation may lead to local and systemic reactions [16]. > 11 million patients with acute tonsillitis annually seek medical services with a high antibiotic prescription rate ranging between 47% and 73% [2–4]. Antibiotic resistance increased healthcare costs by 61% for each patient encounter [17].

Tonsillectomy is an option for treatment recurrent tonsillitis in some cases, while antibiotic therapy is considered the standard treatment. Tonsillectomy complications in adults are not uncommon, reaching up to 20% mostly related to postoperative pain, dehydration, and hemorrhage. These complications have additional healthcare expenses of thousands of dollars per patient [18]. Many health professionals recommend natural remedies for management of recurrent tonsillitis [19]. Homeopathy reported as a supportive therapy for recurrent tonsillitis by 59%, phytotherapy by 28% and vitamins/nutritional supplementation by 37% by a survey respondents [20]. Some homeopathic medicinal products or Chinese herbal preparations may reduce symptoms of acute tonsillitis or pharyngitis [21,22]. In a randomized controlled double-blind trial in children with recurrent tonsillitis; homeopathic treatment significantly reduced the number of tonsillitis attacks [23].

Immunoglobulin G represents approximately 75% of serum antibodies in humans and it is considered as the most common type of antibody found in blood circulation. It controls tissues infection through several mechanisms [24]. Immunoglobulin A plays a crucial role in the immune function of mucous membranes [25–27]. IgM is the largest antibody and it is the first antibody to appear in the response to initial exposure to an antigen. IgM can bind complement component C1 and activate the classical pathway leading to opsonization of antigens and cytolysis [24].

The underlying mechanism of humoral deficiencies may be due to abnormal T and B cell communication, resulting in a dysfunction in T helper cells, B cell heavy chain switching, or antigen presentation [28]. Primary immunodeficiencies (PID) are divided according to the part of the immune system that they affect, there are many different phenotypes from relatively common conditions to extremely rare [29]. Certain phenotypes are completely asymptomatic and others fatal. There are 8 categories of PID [29], > 50% of PID are due to humoral immunity abnormalities [28]. In United States, as many as 500,000 persons have one of the > 80 PID [30] with about 50,000 cases diagnosed each year [28]. PID appears to affect males and females equally; these patients have increased susceptibility to infection with the possible exception of asymptomatic IgA deficiency. With the rapid use of antibiotics, it is rare today to see osteomyelitis, meningitis or consolidated

Table 4
Difference in different clinical presentations according to type of immunoglobulin deficiency during 3 years duration in group 2.

Type of immunoglobulin deficiency	Tonsillitis (mean ± SD)	Sinusitis (mean ± SD)	Pneumonia (mean ± SD)	Otitis media (mean ± SD)	Skin infection (mean ± SD)
Selective Ig A deficiency	9 ± 3.1	3 ± 0.2	0	0	0
Selective Ig M deficiency	12 ± 5.8	5 ± 2.8	0	0	1 ± 0.1
Selective Ig G deficiency	10 ± 4.1	5 ± 2.7	1 ± 0.1	2 ± 0.3	2 ± 0.2
CVID	22 ± 9.4	7 ± 2.2	1 ± 0.2	1 ± 0.2	3 ± 0.1

Data presented as mean ± standard deviation. CVID: common variable immunodeficiency.

pneumonia as the presenting feature [31]. The most common offending organisms generally are encapsulated bacteria, such as Hemophilus influenzae and *Streptococcus pneumoniae*. Indeed, a common presenting symptom in adults may be chronic fatigue with little infections [32]. Selective antibody deficiency can be considered as a diagnosis in patients with normal Ig levels who are older than 2 years of age and present with recurrent upper and/or lower respiratory tract infections [33].

This study was conducted to assess if there is subtle humoral immunodeficiency in adult patients with recurrent tonsillitis presented to our institution. We found significant selective immunoglobulin deficiency of most of tested immunoglobulins in patients with recurrent tonsillitis compared to normal subjects. Three (6%) patients in the study group had low level of IgG, IgM and IgA, and thus qualified for the diagnosis of CVID. These patients had higher incidence of acute tonsillitis and rhinosinusitis attacks compared to other patients with humoral immunodefiency. In United States, CVID is the most frequently diagnosed PID [31]. The term CVID encompasses a heterogeneous group of disorders that cause hypogammaglobulinemia [34]. Onset can occur after two years of age, but the average age of onset is the middle to late 20s [35]. Patients with CVID have a poor response to vaccines (decreased IgG antibody response) and an increased risk of developing auto-immune disorders and malignancy [35].

Study group had significant lower mean of IgA compared to control group, these patients had a lower incidence of tonsillitis and rhinosinusitis attacks compared to other patients with humoral immunodefiency. Of the PID disorders, selective IgA deficiency may have the highest incidence (one case per 300 to 700 persons, according to estimates based on blood donation analyses), but the disorder is often asymptomatic and undiagnosed [36]. Patients with symptoms often have sinusitis and respiratory tract infections, along with gastrointestinal involvement. All patients with IgA deficiency are at increased risk for allergies and autoimmune diseases. In contrast to patients with CVID, patients with IgA deficiency have a normal IgG response to vaccinations [36].

Also, study group had significant lower mean of IgM compared to control group. The importance of low serum IgM is controversial; patients with IgM deficiency may present with a wide spectrum of clinical manifestations, from asymptomatic to life-threatening infections, including recurrent infections. Yel et al. [37] conducted a retrospective chart review to assess clinical and immunologic features of 15 symptomatic adult (6 male and 9 female patients) IgM-deficient patients. On their initial evaluation, 80% presented with increased susceptibility to infections, 33% had atopic manifestations such as asthma and allergic rhinitis, 20% had both infections and atopy and 20% had autoimmune manifestations. Patients in our study group had significant lower IgG levels with significant lower levels of IG1 and IG3. The significance of lower IgG subclasses has been controversial; the current recommendations are that low levels of IgG subclasses are not considered clinically significant unless they are associated with poor specific antibody response [38].

Studies conducted to assess humoral immunity in patients with tonsillitis are sparse. These studies evaluated the changes in humoral immunity in pediatric patients with chronic adenotonsillitis and the effect of adenotonsillectomy on humoral immunity as measured by serum immunoglobulin levels. Observations of these studies showed significantly higher serum IgG, A and M levels in patients with chronic adenotonsillitis, pre-operatively, as compared to age- and sex-matched controls with significant decrease of these levels postoperatively compared to the respective pre-operative values [11]. Our study is the first study (up to our knowledge) to assess humoral immunity in adult patients with recurrent acute tonsillitis compared to age- and sex-matched controls. In this study, 3 (6%) normal subjects had specific antibody deficiency. There are no generally accepted estimates for the incidence of specific antibody deficiency in the general population, up to 20% of subjects with IgG subclass deficiency and 90% of IgA deficient patients are asymptomatic [32].

The concept of immunodeficiency as a risk factor for upper respiratory tract infection especially refractory CRS has gained attention in recent years although the true incidence is still unknown. CRS may be the initial presentation of an immunocompromised state in adults [39] and should be considered in cases of patients with refractory CRS who fail appropriate medical therapy [40,41]. Approximately 25% of patients presenting to a tertiary immunology clinic with IgG immunodeficiency presented with CRS as the primary finding [42,43]. According to the Modell Foundation and the American Red Cross, two or more serious sinus infections within 1 year are one of ten warning signs of PID [44]. Alqudah et al. [13] reported different hormonal dysfunction patterns in their patients with refractory CRS and they used these findings to change their standard practice where these patients are routinely screened for quantitative immunoglobulins, in their study [13]; some patients with normal or slightly decreased immunoglobulin levels were unable to mount a specific antibody response to unconjugated polysaccharide antigens, which are T-independent type 2 antigens. The major characteristics of antibody response against T-independent type 2 antigens are the delayed maturation of response, the restricted immunoglobulin isotype, and the lack of establishment of memory [45,46], they concluded that it is conceivable that a patient may have a normal antibody response to T-dependent antigens and normal immunoglobulin levels and still be unable to mount an anti-polysaccharide antibody response illustrating the importance of not relying on the static measurement of serum immunoglobulin but depending instead on the dynamic assessment of functional antibody responses. The consensus recommendation is that a normal response in adults is a fourfold increase in antibody titers to 70% of the serotypes tested and a normal response in children is a fourfold increase in antibody titers to 50% of tested unconjugated polysaccharide antigens [38]. Pneumococcal vaccine is the only unconjugated polysaccharide vaccine that is readily available for which antibody titer determinations are commercially available; unfortunately this vaccine is not easily available in our area, so it was hard to use it in our study.

The National Institute of Child Health and Human Development recently initiated an educational program to raise awareness of primary immunodeficiencies. As a part of this program, the Jeffrey Modell Foundation developed a list of warning signs for primary immunodeficiency [30,47]. These warning signs are listed in Table 5. Recurrent tonsillo-pharyngitis is not one of these signs; we think this sign should be added to this warning list based on this study results.

It is very difficult to do reliable comparative clinical studies due to a range of modifying factors. The main limitations of this study were that

Table 5
Warning signs of a primary immunodeficiency in adults. Presence of ≥2 of the following warning signs is diagnostic.

1	> 2 ear infections in one year
2	> 2 sinus infections in one year in the absence of allergies
3	1 pneumonia per year for more than one year
4	Chronic diarrhea with weight loss
5	Repeat viral infections (colds, herpes, warts, condyloma)
6	Recurrent need for intravenous antibiotics to clear infections
7	Recurrent, deep abscesses of the skin or internal organs (ex.: liver, lungs)
8	Persistent thrush or fungal infection on skin or elsewhere
9	Infection with normally harmless tuberculosis-like bacteria
10	Family history of a primary immunodeficiency

Adapted from http://immunodeficiency.ca/primary-immunodeficiency/10-warning-signs.

we didn't make a detailed immunologic workup including immunization with protein and polysaccharide-based vaccines to exclude a functional humoral defect. However; the main strengths of this study that it is a prospective study with a control group and there was a difference in the clinical characteristics of those with and without immunoglobulins deficiency with a possible clinical usefulness. In reality, such diagnosis may change the whole therapeutic approach. It is imperative to identify patients with antibody abnormalities because their clinical management would be different from those with normal immune function. We think it is cost-effective to do a complete immunological work up for adults patients with recurrent tonsillitis compared to possible cost and complications of tonsillectomy. Surgical management shouldn't be the gold standard for patients with suspected immunodeficiency because tonsillectomy doesn't seem to resolve the predisposition of these patients to infection and probably they will continue to battle other types of infectious process. Patients diagnosed with immunoglobulins deficiency should be considered for long-term antibiotic prophylaxis and/or immunoglobulin replacement therapy [13]. Based on this study results; we suggest consideration for further immunological workup for adult patients with recurrent tonsillitis starting with serum immunological levels assessment as a part of the whole workup.

5. Conclusion

Adult patients with recurrent tonsillitis have a high incidence of humoral antibody deficiency compared to age and sex-matched controls. These data may suggest an algorithm be adopted for immunological evaluation of such patients for better management.

References

[1] Bathala S, Eccles R. A review on the mechanism of sore throat in tonsillitis. J Laryngol Otol 2013;127:227–32.
[2] Salatino S, Gray A. Integrative management of pediatric tonsillopharyngitis: an international survey. Complement Ther Clin Pract 2016;22:29–32.
[3] Burton MJ, Glasziou PP, Chong LY, Venekamp RP. Tonsillectomy or adenotonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis. Cochrane Database Syst 2014;11.
[4] Roos K, Claesson R, Persson U, Odegaard K. The economic cost of a streptococcal tonsillitis episode. Scand J Prim Health Care 1995;13:257–60.
[5] Stewart MG, Friedman EM, Sulek M, et al. Quality of life and health status in pediatric tonsil and adenoid disease. Arch Otolaryngol Head Neck Surg 2000;126:45–8.
[6] Klug TE. Incidence and microbiology of peritonsillar abscess: the influence of season, age, and gender. Eur J Clin Microbiol Infect Dis 2014;33:1163–7.
[7] Georgalas CC, Tolley NS, Narula PA. Tonsillitis. BMJ Clin Evid 2014;22:1–14.
[8] Windfuhr JP. Evidenz basierte Indikationen der Tonsillektomie [Evidence-based indications for tonsillectomy]. Laryngorhinootologie 2016;95:S38–87.
[9] G.J. Ng, S. Tan, A.N. Vu, C.B. Del Mar, M.L. van Driel, Antibiotics for preventing recurrent sore throat. Cochrane Database Syst Rev. 7, 2015.
[10] Solomon A, Weiss DT. Structural and functional properties of human lambda-light-chain variable-region subgroups. Clin Diagn Lab Immunol 1995;2:387–94.
[11] Subramaniam V, Pai V, Mazumdar MR. Effects of adenotonsillectomy on humoral immunity. International Journal of Otorhinolaryngology and Head and Neck Surgery 2016;2:230–3.
[12] Nasrin M, Miah MR, Datta PG, Saleh AA, Anwar S, Saha KL. Effect of tonsillectomy on humoral immunity. Bangladesh Med Res Counc Bull 2012;38:59–61.
[13] Alqudah M, Graham SM, Ballas ZK. High prevalence of humoral immunodeficiency patients with refractory chronic rhinosinusitis. Am J Rhinol Allergy 2010;24:409–12.
[14] Windfuhr JP. Indications for tonsillectomy stratified by the level of evidence. GMS Curr Top Otorhinolaryngol Head Neck Surg 2016;15.
[15] Budney A, Vandrey R, Hughes J, Thostenson J, Bursac Z. Comparison of cannabis and tobacco withdrawal: severity and contribution to relapse. J Subst Abuse Treat 2008;5:362–8.
[16] National Institute on Alcohol Abuse and Alcoholism. Overview of alcohol consumption, drinking levels defined. http://www.niaaa.nih.gov. Published 2015.
[17] Jerome A, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev 2010;90:47–112.
[18] Schmidt R, Herzog A, Cook S. Complications of tonsillectomy, a comparison of techniques. Arch Otolaryngol Head Neck Sur 2007;133:925–8.
[19] Slatino S, Gray A. Integrative management of pediatric tonsillopharyngitis: an international survey, complement. Ther Clin Pract 2016;22:29–32.
[20] Billings KR, Maddalozzo J. Complementary and integrative treatments: adenotonsillar disease. Otolaryngol Clin North Am 2013;46:329–34.
[21] Huang Y, Wu T, Zeng L, Li S. Chinese medicinal herbs for sore throat. Cochrane Database Syst Rev 2012(3).
[22] Malapane E, Solomon EM, Pellow J. Efficacy of a homeopathic complex on acute viral tonsillitis. J Altern Complement Med 2014;20:868–73.
[23] Rau E. Treatment of acute tonsillitis with a fixed-combination herbal preparation. Adv Ther 2000;17:197–203.
[24] Luiz JC, Carneiro J. Basic histology. McGraw-Hill; 2003.
[25] Falkenburg WJ, van Schaardenburg D, Ooijevaar-de Heer PJ, et al. Anti-hinge antibodies recognize IgG subclass- and protease-restricted neoepitopes. J Immunol 2017(1):82–93.
[26] Fred FD. Anaphylaxis: lessons from mouse models. J Allergy Clin Immunol 2007;120:506–15.
[27] Khondoun MV, Strait R, Armstrong L, Yanase L, Finkelman NFD. Identification of markers that distinguish IgE-from IgG mediated anaphylaxis. Proceedings of the National Academy of Sciences, USA 2011;108:12413–8.
[28] Srinvasa BT, Alizadehfar R, Desrosiers M, et al. Adult primary immune deficiency: what are we missing? Am J Med 2012;125:779–86.
[29] Ocampo CJ, Peters AT. Antibody deficiency in chronic rhinosinusitis: epidemiology and burden of illness. Am J Rhinol Allergy 2013;27:34–8.
[30] Modell V, Quinn J, Ginsberg G, Gladue R, Orange J, Modell F. Modeling strategy to identify patients with primary immunodeficiency utilizing risk management and outcome measurement. Immunol Res 2017;64:713–20.
[31] Tencer T, Friedman HS, Li-McLeod J, Johnson K. Medical costs and resource utilization for hemophilia patients with and without HIV or HCV infection. J Manag Care Pharm 2007;13:790–8.
[32] Cooper MA, Pommering TL, Korányi K. Primary immunodeficiencies. Am Fam Physicia 2001-2008;15(2003).
[33] M. Frieri. Good's syndrome, CVID, and selective antibody deficiency in patients with chronic rhinosinusitis. Curr Allergy Asthma Rep 14, 2014, 438.
[34] Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol 1999;93:190–7.
[35] Ballow M. Primary immunodeficiency disorders: antibody deficiency. J Allergy Clin Immunol 2002;109:581–91.
[36] Clark JA, Callicoat PA, Brenner NA, Bradley CA, Smith DM. Selective IgA deficiency in blood donors. Am J Clin Pathol 1983;80:210–3.
[37] Yel L, Ramanuja S, Gupta S. Clinical and immunological features in IgM deficiency. Int Arch Allergy Immunol 2009;150:291–8.
[38] Lane PJ, MacLennan IC. Impaired IgG2 anti-pneumococcal antibody responses in patients with recurrent infection and normal IgG2 levels but no IgA. Clin Exp Immunol 1986;65:427–33.
[39] Sergio E, Grammer LC. Immune deficiency in chronic rhinosinusitis: screening and treatment. Expert Rev Clin Immunol 2017;13:117–23.
[40] Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinology 2012;50:S23.
[41] Bernatowska E, Mikoluc B, Krezeski A, et al. Chronic rhinosinusitis in primary antibody immunodeficient patients. Int J Pediatr Otorhinolaryngol 2006;70:1587–92.
[42] Ocampo CJ, Peters AT. Antibody deficiency in chronic rhinosinusitis: epidemiology and burden of illness. Am J Rhinol Allergy 2013;27:34–8.
[43] Srinvasa BT, Alizadehfar R, Desrosiers M, et al. Adult primary immune deficiency: what are we missing? Am J Med 2012;125:779–86.
[44] Vanlerberghe L, Joniau S, Jorissen M. The prevalence of humoral immunodeficiency in refractory rhinosinusitis: a retrospective analysis. B-ENT 2006;2:161–6.
[45] Mosier DE, Subbarao B. Thymus-independent antigens: complexity of B-lymphocyte activation revealed. Immunol Today 1982;3:217–22.
[46] Sanders LA, Rijkers GT, Kuis W, et al. Defective antipneumococcal polysaccharide antibody response in children with recurrent respiratory infections: a controlled study with follow-up. Clin Exp Immunol 2013;172:238–44.
[47] Paul ME, Shearer WT. The child who has recurrent infection. Immunol Allergy Clin North Am 1999;19:423–36.