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The prevalence of humoral immunodeficiency in refractory rhinosinusitis: a retrospective analysis

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Abstract. *The prevalence of humoral immunodeficiency in refractory rhinosinustis: a retrospective analysis. Objective*: To evaluate the prevalence of humoral immunodeficiency in patients with refractory rhinosinusitis.
Methodology: All patients with refractory rhinosinusitis, who were treated at or referred to the ENT Dept of the University Hospital in Leuven between January 2002 and December 2004, were retrospectively identified. Patient charts that contained information on humoral immunity testing were selected to calculate the prevalence of IgA deficiency, common variable immunodeficiency (CVID) and IgG2/3 subclass deficiency.
Results: A total of 307 subjects (261 adults and 46 children) were included. Overall, 67 patients (21.8%) with refractory rhinosinusitis had laboratory evidence of a humoral immunodeficiency. We found an IgA deficiency in 7 patients (2.2%); CVID was not found in any patient (0%); IgG2 subclass deficiency in 6 patients (2.0%) and IgG3 subclass deficiency in 55 patients (17.9%). Nine patients (2.9%) had combined deficits of major and/or subclass serum immunoglobulin levels. There was no significant difference in the prevalence of humoral immunodeficiency between adults and children.
Conclusion: Humoral immunodeficiency is present in a significant proportion of patients with refractory rhinosinusitis. The majority of these deficiencies are subtle IgG subclass deficits, whereas more severe humoral immune disorders are a rare finding. A laboratory evaluation of humoral immune function, including measurement of serum levels of IgA, total IgG and IgG subclasses, should be part of the evaluation of patients with refractory rhinosinusitis.

Introduction

Chronic or recurrent rhinosinusitis is an immense world-wide health problem, affecting up to 15% of the population.[1] The aetiology of rhinosinusitis is diverse and includes non-host factors (e.g. pollution, infections), general host factors (e.g. genetic, allergy, immunity) and local host factors (e.g. anatomical abnormalities).[2] Most cases of rhinosinusitis can be treated succesfully with medication and/or surgery. In 5-25% of patients however, response to these classical treatment regimens is not satisfactorily and rhinosinusitis persists.[3] These patients with refractory disease often pose a diagnostic and therapeutic challenge.

Risk factors for refractory rhinosinus disease include atopy, medical conditions affecting the sinonasal tract mucosa and defects in the immune response.[4] Indeed, immune disorders are known to have a profound effect on the respiratory tract.[5,6] The studies on the incidence of humoral immune deficiencies in patients with refractory rhinosinusitis are heterogeneous, with humoral immune deficiencies detected in 5-63 % of patients. Moreover, there are considerable differences in the reported prevalence of specific immunodeficiencies, such as IgA deficiency, common variable immune deficiency (CVID) and IgG subclass deficiency.[7-12] These divergent results underscore the current lack of data on the prevalence and importance of immune defects in patients with refractory rhinosinusitis.

The objective of our study was to evaluate the prevalence of humoral immune deficiencies in a Belgian population of patients with refractory rhinosinusitis. We specifically investigated the prevalence of IgA deficiency, CVID and IgG subclass deficiency in these patients, and compared our results to the literature.

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Materials and Methods

A retrospective analysis of patient charts was performed. Patients with refractory rhinosinusitis, who were treated at or referred to the ENT clinic of the University of Leuven between January 2002 and December 2004 were identified. Refractory rhinosinusitis was considered when rhinosinusitis symptoms (facial/frontal headache, nasal/postnasal discharge, hyposmia/anosmia, nasal blockage) and signs (nasal endoscopy +/- computed tomography) persisted despite classical treatment regimens (long term nasal steroids, intermittent courses of oral steroids +/- antibiotics and endoscopic sinus surgery). The patient charts were reviewed and those which contained information on humoral immunity testing were selected. The charts of patients, who received oral steroids before laboratory testing, were not excluded.

The following features were recorded for each case: (1) patient age; (2) patient gender and (3) serum concentrations of IgA, total IgG, IgG2 and IgG3. Quantitative major and subclass immunoglobulin levels were assessed by nephelometry, Beckman Instruments Inc. (Brea, California, USA). These serum concentrations were compared with age-adjusted reference values from the same laboratory. Immunoglobulin deficiency was defined as a serum concentration of more than two standard deviations below the geometric mean.

On the basis of immunologic findings, patients were categorized into the following groups: (1) normal humoral immunity; (2) isolated IgA deficiency; (3) CVID or (4) IgG subclass deficiency. CVID was considered when there was a marked reduction in serum levels of both total IgG and IgA.

The prevalence of different humoral immune deficiencies was calculated for the entire data set. The results were compared with those of previously published studies.

Results (Table 1)

A total of 569 patients with refractory rhinosinusitis were treated at or referred to the ENT clinic. The 307 charts (54%) containing documentation on humoral immunity tests were selected for further analysis. There were 261 adults (85%; 110 men and 151 women) and 46 children (15%; 21 boys and 25 girls) with refractory rhinosinusitis included in our analysis.

Normal or increased humoral immunity

The serum concentrations of the tested immunoglobulins fell within normal ranges for most of the patients. Normal IgA was found in 244 adults (93.5%) and 41 children (89.1%); normal total IgG in 232 adults (88.9%) and 40 children (87.0%); normal IgG2 in 242 adults (92.7%) and 43 children (93.5%) and normal IgG3 in 205 adults (78.5%) and 39 children (84.8%). All tests were normal for 169 adults (65.8%) and 31 children (67.4%).

An increased serum concentration of at least one immunoglobulin was found in 42 adults (16.1%) and 6 children (13.0%). There was an increased IgA in 14 adults (5.4%) and 1 child (2.2%); increased total IgG in 19 adults (7.3%) and 6 children (13.0%); increased IgG2 in 15 adults (5.7%) and 1 child (2.2%) and increased IgG3 in 7 adults (2.7%) and 1 child (2.2%).

IgA deficiency

Three adults (1.1%) and 4 children (8.7%) had a decreased serum concentration of IgA. Two of the children had an undetectable serum IgA, the other 5 patients had a subnormal serum IgA level. The difference in the prevalence of IgA deficiency between adults and children is not significant ($p = 0.25$).

Table 1

Overview of selective and combined immunoglobulin deficiencies in children and adults with refractory rhinosinusitis

Immunoglobulin	**Number of patients n (%)**	
	Children (<18 y) *(n = 46)*	**Adults (≥18 y) *(n = 261)***
IgA	3 (6.3)	2 (0.8)
Total IgG	0	5 (1.9)
IgG2	1 (2.2)	0
IgG3	4 (8.7)	43 (16.5)
IgA + IgG3	1 (2.2)	0
Total IgG + IgG2	0	1 (0.4)
Total IgG + IgG3	0	3 (1.2)
IgG2 + IgG3	1 (2.2)	1 (0.4)
Total IgG + IgG2 + IgG3	0	1 (0.4)
IgA + IgG2 + IgG3	0	1 (0.4)

In 2 patients (0.7%) the decrease in serum IgA was associated with an IgG subclass deficiency. Namely, one adult also had a decreased IgG2 and IgG3, and one child had an associated lowering of serum IgG3.

Common variable immune deficiency

None of the patients had a combined deficiency of serum IgA and total IgG.

IgG subclass deficiency

Fifty-five adults (21.1%) and 7 children (15.2%) had an IgG subclass deficiency. A total IgG deficiency was found in 10 adults (3.8%) and 0 children.

Two children (4.3%) and 4 adults (1.5%) had an IgG2 deficiency. The difference in prevalence of IgG2 deficiency between adults and children is not significant. One of these children also had an IgG3 deficiency; 4 adults showed associated deficiencies of IgG3 *(n = 1)*, total IgG *(n = 1)*, total IgG and IgG3 *(n = 1)* and IgA and IgG3 *(n = 1)*.

Six children (13.0%) and 49 adults (18.8%) had a decreased serum IgG3 level. The difference in prevalence of IgG3 deficiency between adults and children is not significant (p = 0.18).

Two of these children had associated deficiencies of other immunoglobulins, namely one with IgA deficiency and one with IgG2 deficiency. Six of these adults showed associated immunoglobulin deficits of total IgG *(n = 3)*, IgG2 *(n = 1)*, total IgG and IgG2 *(n = 1)* and IgA and IgG2 *(n = 1)*.

A decreased serum concentration of at least one immunoglobulin was found in 57 adults (21.8%) and 10 children (21.7%).

Discussion

The most important finding of this retrospective study is that humoral immune deficiencies are a relatively common finding in patients with refractory sinusitis. Immunoglobulin deficits are present in 21.8% of the patients. IgG3 subclass deficiency is the most frequent humoral immune deficiency, with a prevalence of 17.9%. IgA and IgG2 deficiencies are rarer at a prevalence of 2.3% and 2.0% respectively. This study did not identify patients with CVID. Normal or increased serum concentrations of IgA, IgG and IgG2/3 were detected in 78.2% of patients with refractory sinusitis.

IgA deficiency is one of the most common antibody deficiencies, with an incidence of up to 1/400 subjects in the general population.[13] It is found in association with IgG subclass deficiencies in about 20% of patients.[14] The majority of individuals with IgA deficiency will be clinically asymptomatic for life. Those with symptoms have sinopulmonary infections, gastro-intestinal problems and an increased risk for auto- immune disorders.[6] An IgA deficiency was detected in 2.3% of patients with refractory rhinosinusitis; 2 (28%) of them had an associated IgG subclass deficiency. These results are similar to those of most other studies, in which IgA deficiency was present in 1.3%[10] to 16.7%[12] of patients with chronic sinusitis (Table 2).

Common variable immune deficiency, also called acquired hypogammaglobulinemia, affects about 1/25 000 Caucasians and is characterised by a marked reduction of both IgA and total IgG serum concentrations. Asymptomatic CVID does not exist, and patients are prone to recurrent bacterial infections of the sinopulmonary tract, gastrointestinal problems, auto- immune disorders and malignancies. The average age of onset of CVID is 25 years, and the mortality rate over a 25-year period is 24%, mostly due to lymphoma and chronic pulmonary disease.[15] No patients with CVID were found in our study population. This is in accordance with 3 other reports on humoral immune deficiencies in patients with chronic rhinosinusitis,[8-10] but contrasts to the findings of May *et al.*[11] and Chee *et al.*,[12] who reported CVID to be as prevalent as 2.0% to 10.3% respectively.

IgG subclass deficiency is a relatively common finding in patients with recurrent sinopulmonary infections. However, healthy subjects can have low levels of IgG subclasses as well. Therefore, the controversy about the clinical significance of these subtle immunoglobulin deficits continues, and clinical immunologists have questioned whether IgG subclass deficiency represents a true immunodeficiency disease.[16] Because IgG2 plays an important role in the response to polysaccharide antigens, IgG2-deficient patients may typically have recurrent infections with *Haemophilus influenzae* and/or *Streptococcus pneumoniae*. They may be unable to respond adequately to immunization with purified polysaccharide antigens (e.g. Pneumovax®).[11] IgG3 is the predominant subclass in the primary response to various viral agents, thus, its deficiency can be associated with recurrent viral upper respiratory infections.[17] An IgG2 deficiency was detected in 2.0% of chronic rhinosinusitis patients in this study in agreement with the published

Table 2
Prevalence of humoral immunodeficiency in patients with chronic rhinosinusitis (CVID: common variable immune deficiency; NR: not reported)

Authors	**Patients** ***(n =)***	**Immunoglobulin deficiency**			
		IgA	**CVID**	**IgG2**	**IgG3**
Shapiro *et al.*[7]	Children *(n = 61)*	1	1	2	9
Scadding *et al.*[8]	Adults *(n = 74)*	5	0	3	19
Armenaka *et al.*[9]	Adults (n = 30)	1	0	0	18
Hoover *et al.*[10]	Adults *(n = 80)*	1	0	0	3
May *et al.*[11]	Adults and Children *(n = 245)*	NR	5	10	1
Chee *et al.*[12]	Adults *(n = 78)*	13	8	NR	NR
This study	Adults *(n = 261)*	3	0	4	48
	Children *(n = 46)*	4	0	2	5
Total	***n = 875***	**28/630 (4.4%)**	**14/875 (1.6%)**	**21/797 (2.6%)**	**103/797 (12.9%)**

3.3%[7] to 4.1%.[8,11] Similarly, an IgG3 deficiency was present in 17.9% of this study population compared to the reported 0.4%[11] to 60%.[9] The IgG2 subclass is the most common reported deficiency among children whilst it is the IgG3 subclass amongst adults.[7,9,18] This study also found IgG3 deficiency (18.8%) to be more common than IgG2 deficiency (1.5%) in adults. However in contrast to previous studies on children, 13% were IgG3 deficient whilst only 4.3% IgG2 deficient.

These results support the concept of immune dysfunction as a potential risk factor for refractory rhinosinusitis and the recommendation for humoral immunity testing in these patients. Not only the major idiotypes but also the IgG subclasses should be examined. This is of particular importance for IgG2 and IgG3, as these represent only 20% and 10% of total IgG serum concentrations respectively, and partial or complete deficiency of these subclasses might thus not influence total IgG levels. In this study, 50 patients (16.3%) with IgG2/3 subclass deficiencies would have been overlooked if only the major idiotypes had been investigated, as these patients all showed normal serum concentrations of total IgG. Some authors have advocated the extension of humoral immunity testing with active immunization (protein and polysaccharide antigens) to investigate serotype-specific antibody production.[11,19] Recently, Chee *et al.*[12] showed that T-lymphocyte function was commonly disturbed in adults with refractory rhinosinusitis. Therefore, they suggested that cellular immunity tests should also be included in any diagnostic work-up of immune system function.

The identification of a chronic rhinosinusitis patient with a humoral immune deficiency raises important questions about the appropriate management. Treatment options include repeated immunizations (to boost antibody production), culture-directed antibiotics, prophylactic antibiotics, endoscopic sinus surgery and immunoglobulin replacement therapy. A multidisciplinary approach including specialists in immunology, ENT and respiratory diseases is recommended.

This study did not report on IgM and IgG1/4 subclasses. The clinical significance of a deficiency of these immunoglobulins is still under much debate. IgM deficiency has sporadically been reported in association with recurrent infections.[20] IgG1 is the predominant IgG subclass, amounting to approximately 70% of serum IgG. Therefore, variations

in the serum IgG1 concentration are always represented by identical variations of the total serum IgG level.[21] IgG4 subclass levels are commonly undetectable, even in normal individuals, and the accurate detection of very low levels of IgG4 is technically difficult to achieve. Therefore, the clinical relevance of IgG4 evaluation remains unclear.[20]

Routine immunization tests were not performed in this study population. This probably would have provided interesting information, as patients with recurrent infections and normal IgG levels may show an abnormal response to immunization.[22] Therefore, this study may underestimate the true prevalence of humoral immune disorders in patients with refractory rhinosinusitis. On the other hand, the majority of immunoglobulin deficits in this study were decreases of IgG subclass antibodies, which are of questionable clinical significance. As yet, no information on the (spontaneous) evolution of antibody levels in these patients is available. Major humoral immune disorders, such as IgA deficiency or CVID, were rare or absent in this study population.

In future studies, it would be interesting to compare the evolution of rhinosinusitis between patients with and those without humoral immune deficits. Also, further studies can investigate the differences in prevalence of humoral immune disorders between patients with isolated refractory rhinosinusitis and patients with rhinosinusitis and recurrent pulmonary infections.

Conclusions

Humoral immunodeficiency is present in a significant proportion of patients with refractory rhinosinusitis. The majority of these deficiencies are subtle IgG subclass deficits, whereas more severe humoral immune disorders are a rare finding. A high index of suspicion for humoral immune deficiency is indicated in these patients, especially when persistent respiratory problems are also present. A laboratory evaluation of humoral immunity function, including measurement of serum levels of IgA, total IgG and IgG subclasses, should be part of the evaluation of patients with refractory rhinosinusitis.

References

1. Tripathi A, Conley DB, Grammer LC, *et al*. Immunoglobulin E to staphylococcal and streptococcal toxins in patients with chronic sinusitis/nasal polyposis. *Laryngoscope*. 2004;114: 1822-1826.
2. Kennedy DW. Pathogenesis of chronic rhinosinusitis. *Ann Otol Rhinol Laryngol Suppl*. 2004;193:6-9.
3. Palmer JN, Kennedy DW. Medical management in functional endoscopic sinus surgery failures. *Curr Opin Otolaryngol Head Neck Surg*. 2003; 11:6-12.
4. Lund VJ, Scadding GK. Immunologic aspects of chronic sinusitis. *J Otolaryngol*. 1991;20:379-381.
5. Bernatowska E, Mikoluc B, Krzeski A, Piatosa B, Gromek I. Chronic rhinosinusitis in primary antibody immunodeficient patients. *Int J Pediatr Otorhinolaryngol*. 2006; 70:1587-1592.
6. Ballow M. Primary immunodeficiency disorders: antibody deficiency. *J Allergy Clin Immunol*. 2002;109: 581-591.
7. Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. *Pediatrics*. 1991;87:311-316.
8. Scadding GK, Lund VJ, Darby YC, Navas-Romero J, Seymour N, Turner MW. IgG subclass levels in chronic rhinosinusitis. *Rhinology*. 1994;32: 15-19.
9. Armenaka M, Grizzanti J, Rosenstreich DL. Serum immunoglobulins and IgG subclass levels in adults with chronic sinusitis: evidence for decreased IgG3 levels. *Ann Allergy*. 1994;72:507-514.
10. Hoover GE, Newman LJ, Platts-Mills TA, Phillips CD, Gross CW, Wheatley LM. Chronic sinusitis: risk factors for extensive disease. *J Allergy Clin Immunol*. 1997;100:185-191.
11. May A, Zielen S, von Ilberg C, Weber A. Immunoglobulin deficiency and determination of pneumococcal antibody titers in patients with therapy-refractory recurrent rhinosinusitis. *Eur Arch Otorhinolaryngol*. 1999; 256:445-449.
12. Chee L, Graham SM, Carothers DG, Ballas ZK. Immune dysfunction in refractory sinusitis in a tertiary care setting. *Laryngoscope*. 2001;111:233-235.
13. Bachmann R. Studies on the serum gamma-A-globulin level. 3. The frequency of A-gamma-A-globulinemia. *Scand J Clin Lab Invest*. 1965;17: 316-320.
14. Oxelius VA, Laurell AB, Lindquist B, *et al*. IgG subclasses in selective IgA deficiency: importance of IgG2-IgA deficiency. *N Engl J Med*. 1981;304: 1476-1477.
15. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol*. 1999; 92:34-48.
16. Shackelford PG, Granoff DM, Madassery JV, Scott MG, Nahm MH. Clinical and immunologic characteristics of healthy children with subnormal serum concentrations of IgG2. *Pediatr Res*. 1990;27:16-21.
17. Daele J, Zicot AF. Humoral immunodeficiency in recurrent upper respiratory tract infections. Some basic, clinical and therapeutic features. *Acta Otorhinolaryngol Belg*. 2000;54:373-390.
18. Soderstrom T, Soderstrom R, Avanzini A, Brandtzaeg P, Karlsson G, Hanson LA. Immunoglobulin G subclass deficiencies. *Int Arch Allergy Appl Immunol*. 1987;82:476-480.
19. Sethi DS, Winkelstein JA, Lederman H, Loury MC. Immunologic defects in patients with

chronic recurrent sinusitis: diagnosis and management. *Otolaryngol Head Neck Surg*. 1995;112:242-247.
20. Finocchi A, Angelini F, Chini L, *et al*. Evaluation of the relevance of humoral immunodeficiencies in a pediatric population affected by recurrent infections. *Pediatr Allergy Immunol*. 2002;13:443-447.
21. French MA, Harrison G. Serum IgG subclasses in patients with an increased susceptibility to respiratory tract infections. *Aust N Z J Med*. 1987; 17:402-406.
22. Hidalgo H, Moore C, Leiva LE, Sorensen RU. Preimmunization and postimmunization pneumococcal antibody titers in children with recurrent infections. *Ann Allergy Asthma Immunol*. 1996;76:341-346.

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