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Disorders of Humoral Immunity in Children with IgG Subclass Deficiency and Recurrent Respiratory Infections

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Abstract

Respiratory tract infections in children are one of the most common causes for medical consultations. When the infections are of recurring nature, they are a major reason for the diagnostics for primary immunodeficiency that is in about 65% of cases underlain by disorders of humoral immunity. This study seeks to retrospectively evaluate the history of recurrent respiratory tract infections in children with humoral disorders and the associations among deficiencies in the immune system components. We evaluated 394 children aged 3 months to 18 years. We found 49.5% (195 cases) of children with IgG deficiencies, all of whom had normal IgE levels. There were 8.4% (33 cases) of IgA deficiency, 7.4% (29 cases) of IgM insufficiency, and 4.1% (16 cases) of CD19+ cells deficiency. The elevated level of CD19+ cells was found in 27.7% (109 out of the 394 children). Immunoglobulin deficiencies often coexisted with a deficiency in another immunoglobulin class above outlined. There was an interdependence between IgA abnormality and IgG, IgG3, and IgG4 abnormalities as well as between IgM abnormality and IgG and IgG1 abnormalities. We conclude that respiratory tract infections in children are often underlain by a convergence of IgG with both IgA and IgM abnormal states. The physiopathological meaning of this convergence for the infection course and resulting functional respiratory changes remains elusive.

Keywords

Children · Humoral disorders · Humoral immunity · IgG deficiency · Immune deficiency · Respiratory infections

1 Introduction

Immunodeficiency is a state of impaired immunity balance in the body, which usually predispose to a variety of infections. Congenital immunodeficiency is rather rare, but when untreated may have a severe course, sometimes leading to death. Diagnostic tests and treatment should be undertaken as soon as possible to avoid serious infections that could cause a permanent damage. Humoral immunity is associated with

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circulating antibodies, notably involving IgA, IgG, IgM, and IgE classes. The immune system in children develops relatively slowly, as it starts functioning in the mature way around the age of 12 years. Younger children are, in the main, vulnerable to develop a disease when in contact with infectious agents (Nicholson 2016). The problem is potentiated when there exists a background humoral immunodeficiency, giving rise recurrent, severe, and difficult-to-treat infections. Such disorders go beyond and over the usual 6–8 benign upper airway infections *per* year, the frequency assumed as a customary norm for healthy preschool children. Normally, with increasing age of a child, there is a decrease in the incidence of infections. However, in children with primary immunodeficiency, infections may occur dramatically, often one after another, making it hard to treat, and without regaining full health in-between. Immunodeficient children notably suffer from chronic sinusitis and bronchitis. Recurrent or chronic infections can inhibit the growth and development of a child.

Humoral immunity disorders constitute the most frequent group of primary immune deficiency accounting for about 65% of related diseases. The group encompasses isolated IgA deficiency, a common congenital immunodeficiency, variable immunodeficiency syndrome, X-linked agammaglobulinemia, IgG subclass deficiencies, specific antibody deficiency, hyper-IgM and IgE syndromes, and other rare occurrences such as insufficient IgM or IgE deficiency (Carroll and Isenman 2012). In pediatric practice, 50% of children consulted for frequent respiratory infections have a normally functioning immune system. Another 30% suffer from various allergies, 10% have anatomical defects or inborn errors of metabolism, and 10% of children have abnormalities in the immune system (Glocker et al. 2007).

Respiratory infections are one of the most common reasons for medical consultations. When recurring nature, such infections are a major reason for the diagnostics toward primary immunodeficiency (Raby et al. 1996). Serum immunoglobulins are routinely determined in clinical practice as they provide key information on the status of the humoral immune system. On the other hand, low levels of immunoglobulins may indicate the presence of some of the humoral immunity deficiencies. For the interpretation of laboratory data, it is important to determine population-based reference intervals of immunoglobulin levels. That is particularly important for the physician to distinguish between the healthy and diseased patient when significant differences are encountered due to age, gender, or other, for instance, environmental factors (Horn and Pesce 2003; NCCLS 2000; Sasse 1992). Nonetheless, studies focusing on the possible influence of these factors on serum immunoglobulin levels are limited, particularly in the children population. In adults, IgM level has been shown higher in women than men. The concentration of immunoglobulins in the serum increases with age (Ichihara et al. 2004; Giltay et al. 2000; Stoica et al. 1980; Maddison and Relmen 1976).

Studies devoted to the deficiency of individual immunoglobulins and of IgG subclasses in children are scarce. Therefore, in this study we set out to evaluate the history of recurrent respiratory infections underlain by deficiency of specific immunoglobulins and the possible mutual associations between deficient immunoglobulins in the pediatric population.

2 Methods

The study was approved by the Ethics Committee of the Medical University in Wroclaw, Poland, and it was conducted according to the ethical principles for medical research as set by the Declaration of Helsinki of the World Medical Association. This retrospective study consisted of the evaluation of clinical history of children suffering from recurrent respiratory tract infections (RTI), indices of humoral immunity, and the interdependence between the immune system components. The study group consisted of 394 patients, aged from 3 months to 18 years, including 152 (38%) females and 242 (62%) males, all of whom were hospitalized with suspicion of primary immune deficiency disorders as the underlying cause if RTI. The serum level of four major classes of

immunoglobulins, IgA, IgG, IgM, and IgE, was measured with an immunoturbidimetric analyzer (Architect c-System; Abbott Laboratories, Lake Bluff, IL). The level of IgG subclasses was measured with a nephelometric analyzer (BN ProSpec System; Siemens Healthcare GmbH, Erlangen, Germany). Both automatic analyzers use a set of reagents provided by the manufacturers. Further, interdependence between deficient immunoglobulins and the association of immunoglobulin deficiency with demographic factors, such as age and gender, also was assessed. Children with a history of allergy or elevated IgE immunoglobulin were excluded from the study.

Continuous data were reported as means ±SD and categorical data as percentages of patients with each immunoglobulin deficiency. Statistical analysis was based on the Kruskal–Wallis or Mann-Whitney U test, and on Chi-square test for the respective data types. A p-value <0.05 defined statistically significant differences. The analysis was carried out using a commercial statistical package of Statistica v10 (StatSoft, Tulsa, OK).

3 Results

Overall, there were 12.2% of children (48 out of the 394) with RTI who had a deficiency in total IgG (IgGt). There also were deficiencies of IgA – 8.4% (33 cases), IgM – 7.4% (29 cases), or CD19 + cells – 4.1% (16 cases), whose percentage was small, not exceeding 10% (Fig. 1). There were significant differences among the children counts regarding each immunological deficiency ($p < 0.05$; Chi^2). The level of the immunoglobulins investigated in the absolute terms, including IgG subclasses, is presented in Table 1.

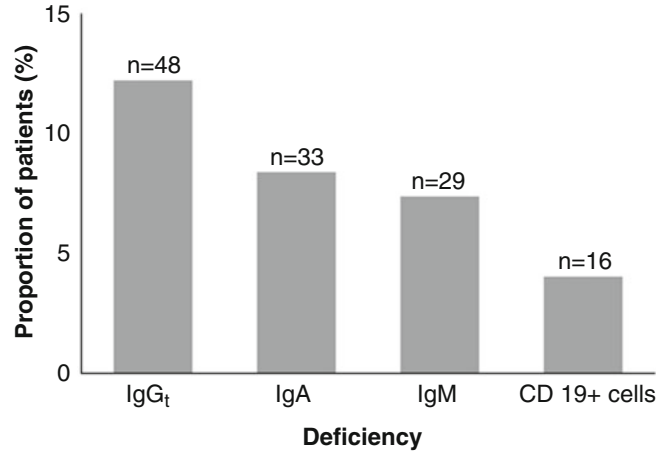

Fig. 1 Proportion of patients deficient in IgA, IgM, and CD19+ cells among the 394 children investigated

Table 1 Immunoglobulin levels (g/L) in children with respiratory tract infections

Immunoglobulin	Deficient	n	Non-deficient	n
IgA	0.06 ± 0.01	33	0.76 ± 0.46*	361
IgM	0.31 ± 0.06	29	0.81 ± 0.29*	365
IgGt	3.90 ± 0.87	48	7.30 ± 2.26*	346
IgG1	3.10 ± 0.95	108	5.51 ± 1.63*	286
IgG2	0.48 ± 0.38	24	1.46 ± 0.76*	370
IgG3	0.16 ± 0.07	70	0.32 ± 0.16*	324
IgG4	0.04 ± 0.08	79	0.26 ± 0.24*	315

Data are means ±SD; *IgG,* total immunoglobulin; *in the column Non-deficient indicate significant differences between deficient and non-deficient immunoglobulin level ($p < 0.0001$) according to Mann–Whitney U test

There often was a coexistence of multi-IgG subclass deficiencies as well as deficiency of IgG subclasses accompanying deficiencies in the other major immunoglobulin classes, which was subject to further evaluation. Overall, 196 (49.7%) out of the 394 children had some deficiency in IgG subclasses.

3.1 Deficiency in IgG Subclass in Children with Respiratory Tract Infections Deficient in IgA, IgM, and CD19+ Cells

Out of the 33 children with IgA deficiency, 33.3% (11 cases) had decreases in IgG1, 12.1% (4 cases) in IgG2, 27.5% (9 cases) in IgG3, and 39.4% (13 cases) in IgG4 (Fig. 2). The corresponding results on IgG subclass deficiency among the 29 children with IgM deficiency were shown in Fig. 3. Here, the largest subgroup of 34.5%

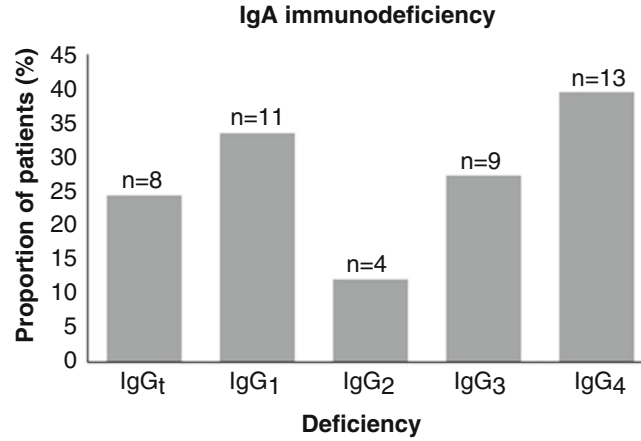

Fig. 2 Proportion of patients having deficiencies in IgG subclasses among the 33 children deficient in IgA

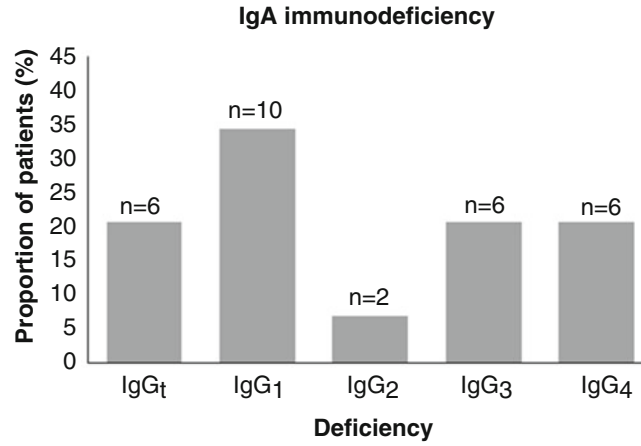

Fig. 3 Proportion of patients having deficiencies in IgG subclasses among the 29 children deficient in IgM

(10 cases) was with IgG1 deficiency, followed by 6.9% (2 cases) with IgG2, and 20.7% (6 cases) with IgG3 and IgG4 deficiencies each. Generally, proportion of children deficient in IgG subclasses was higher in IgM abnormality (9.6%) than in that in IgA abnormality (5.2%) ($p < 0.05$).

Figure 4 shows the proportion of IgG subclass deficiencies among the 16 children deficient in CD19+ cells. There were a relatively large number of children with deficiencies in all IgG subclasses, from 31.3% (5 cases) for IgG3 to 43.8% (7 cases) for IgG4.

The percentage of children with deficiency in total IgG was similar in IgA, IgM, and CD19+ deficient classes above outlined and amounted to about 19–23%.

Differences among the children counts, representing deficiency in individual IgG subclasses failed to reach statistical significance in the groups deficient in IgA, IgM, and CD 19+ cells ($p > 0.05$; Chi^2).

3.2 IgG Subclass Deficiency in Children with Non-deficient Levels of IgA, IgM, and CD19+ Suffering from Respiratory Tract Infections

More than one half of the children with RTI had the level of major immunoglobulin classes above the lower cut-off limit, although they may have been short of the normal level of IgG subclasses. A proportion of non-IgA deficient children but deficient in IgG subclasses is shown in Fig. 5. This proportion ranged from 26.9% for IgG1 to

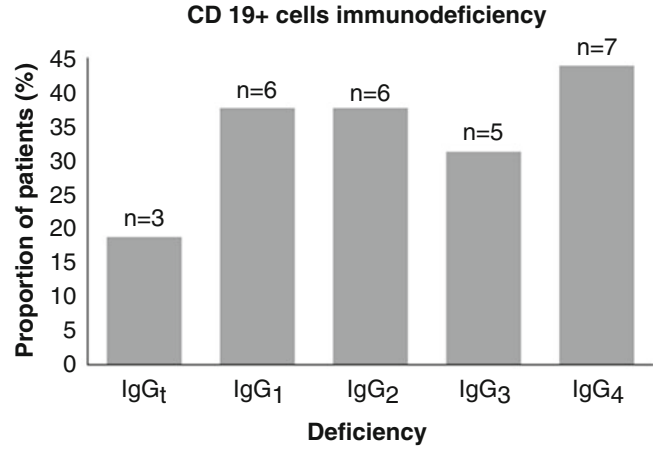

Fig. 4 Proportion of patients having deficiencies in IgG subclasses among the 16 children deficient in IgM

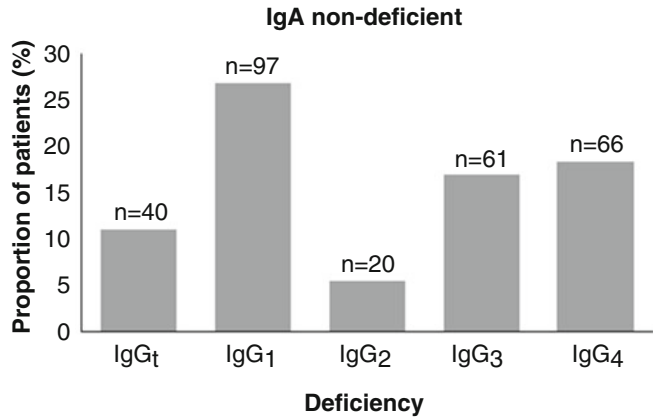

Fig. 5 Proportion of patients having deficiencies in IgG subclasses among the 33 non-IgA deficient children

5.5% for IgG2 and was smaller across all IgG subclasses compared to the IgA-deficient children, as shown in Fig. 2. Similar proportions of multi-IgG subclass deficiency were noticed in the non-IgM deficient children (Fig. 6); these proportions also were lower across all IgG subclasses compared to those in children with IgM deficiency, as shown in Fig. 3. Likewise, the proportion of IgG subclass deficiency was clearly lower in children who lacked deficiency in CD19+ cells (Fig.7) compared to those who were CD19+ cell deficient, as shown in Fig. 4. The difference was particularly distinct for IgG2 and IgG 4, whose proportions were severalfold lower in CD19+ non-deficient children. There were significant differences among the children counts, representing deficiency in individual IgG subclasses in the groups non-deficient in IgA, IgM, and CD19+ cells ($p < 0.05$; Chi^2), as opposed to those with insufficiency of major immunoglobulin classes outlined in the preceding subsection.

4 Discussion

The interdependence of immunoglobulin deficiency, underlying recurrent respiratory infections in children, has been rather rarely tackled in medical research. In this study, we found that deficiency of the IgG immunoglobulin class and its subclasses is clearly predominant and may be present in case of both deficient and non-deficient other immunoglobulin classes, as

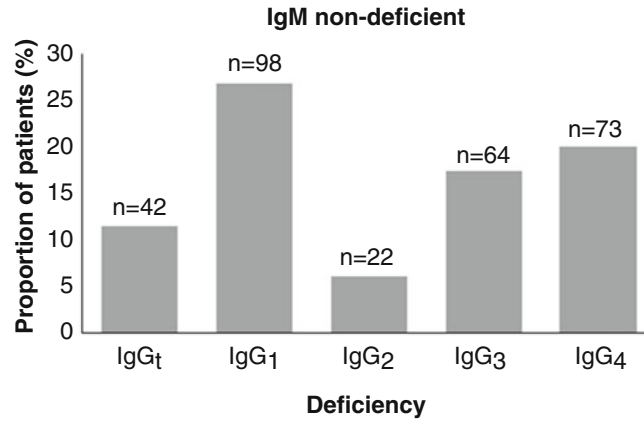

Fig. 6 Proportion of patients having deficiencies in IgG subclasses among the 33 non-IgM deficient children

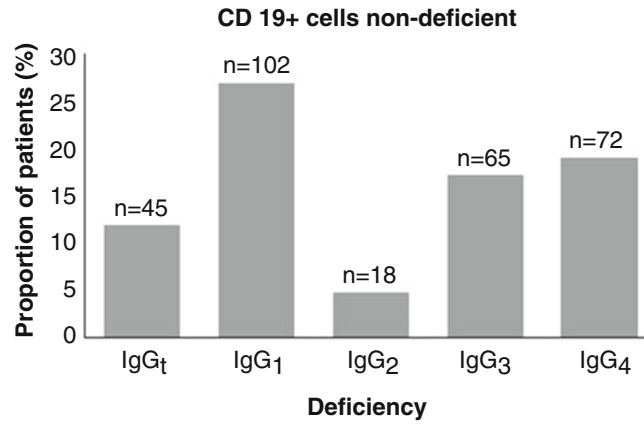

Fig. 7 Proportion of patients having deficiencies in IgG subclasses among the 33 non-CD19+ cells deficient children

well as CD19+ cells. These cells, belonging to B lineage cells in humans, are essential, inter alia, for the development and survival of the peripheral immune system in children. Dysfunction of CD19 + cells underlies immunodeficiency disorders characterized by diminished antibody production in response to infection. The present findings also demonstrate that IgG1 was the most often deficient immunoglobulin, whereas IgG2 most rarely deficient among IgG subclasses. We further found that a proportion of children deficient in IgG subclasses was higher in case of accompanying IgM abnormality than IgA abnormality. Of note, deficiency of IgG subclasses was clearly more expressed when it accompanied a deficiency in another major class of immunoglobulin, which suggests that insufficiency of immunity entails a mutually potentiating mechanism. Finally, the study confirms the presence of a substantial overlap of deficiencies of various types of major immunoglobulin classes, as well as the coexistence of multi-IgG subclass deficiencies during recurrent respiratory infections.

Bjorkander et al. (1988) have reported that IgA deficiency is usually accompanied by IgG2 and IgG4 deficiencies. The present study expands those findings by showing deficiency of total IgG, IgG3, and IgG4 in IgA deficient children. In case of selective IgM deficiency, a rare immunopathology, IgG subclass deficiency has been reported only in a few cases. Deficiency of IgG has so far been found unrestricted to a particular subclass, resulting in a variety of multi-immunodeficiency. That has also been confirmed for the association of IgG subclass deficiency with selective IgA deficiency (Yel et al. 2009; Ideura et al. 2008). In a study on serum immunoglobulins and lower respiratory tract infections in children with Down syndrome, Deepa et al. (2012) have shown a relationship between increased frequency of infections, on the one side, and reduced IgM and elevated IgG and IgA, on the other side. An understanding of production and mutual dependency of various immunoglobulin components remains an area of limited knowledge. Nonetheless, all the findings above outlined translate into the biological plausibility of a systemic impairment of the immune system maturity and function in children suffering from recurrent respiratory infections. The respiratory tract is the most common site of clinical manifestation of various immune deficiencies in children. Infectious and noninfectious respiratory complications determine the prognosis for such patients. The diagnostics directed at unraveling primary immune deficiencies could reduce morbidity and streamline the effectiveness of therapy, which would benefit the patient.

We conclude that respiratory tract infections in children are often underlain by a convergence of IgG with both IgA and IgM abnormal states. The meaning of this convergence for the infection course and thus functional respiratory changes remains to be explored in further studies.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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