

# Could recurrent otitis media predict primary antibody deficiencies in Egyptian children?

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## Background

Recurrent ear infection is a significant warning sign of primary immunodeficiency diseases.

## Objective

To estimate the frequency of IgA deficiency among children presenting to the outpatient clinic with recurrent otitis media (ROM > 4 times/year) and identify other possible risk factors of ROM in our community.

## Materials and methods

Three hundred children (154 males and 146 females), who presented to the outpatient clinic of Children's Hospital, Ain Shams University with ROM, were consecutively enrolled in the study over a 1-year period. According to the age of enrollment, children were classified into two groups: group A (1–6 years) and group B (>6–12 years). The demographic features of both groups were evaluated together with assessment of serum IgA level.

## Results

Of all patients studied, only two (0.7%) had a low serum IgA level for normal age-reference values. None of the patients had neutropenia or lymphopenia. Iron-deficiency anemia was diagnosed in 76 cases, with higher rates among the patients in group A than group B. All patients received several courses of various empirical broad-spectrum antibiotics, but with either an incomplete course ( $n = 192$ ) or a poor response ( $n = 49$ ).

## Conclusion

The current study showed a relatively low incidence of IgA deficiency among children with ROM and indicated other environmental risk factors that participated in the occurrence of OM in our community.

## Keywords:

children, immunoglobulin A deficiency, recurrent otitis media

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## Introduction

Otitis media (OM) is the second most frequently diagnosed infection in infants and young children after rhinitis [1,2]. The pathogenesis of acute otitis media (AOM) involves complex interactions between bacteria, viruses, and the host inflammatory response. Viral upper respiratory tract infection increases the risk of bacterial AOM by promoting the replication of bacteria and increasing inflammation in the nasopharynx and Eustachian tube, which subsequently facilitates bacterial entry into the middle ear space [3–6]. Respiratory viruses can coinfect the middle ear with bacterial AOM pathogens and have been identified as the sole causative agent of AOM [7]. The most common viruses that cause AOM are rhinovirus, adenovirus, bocavirus, and respiratory syncytial virus [8], whereas the most commonly isolated bacteria in AOM with effusion are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [9,10].

The upper respiratory tract is an obvious portal of entry for microorganisms and an adequately functioning immune system is required to prevent the establishment

of infections in the ear, nose, and throat. Host defense depends on cellular and humoral immunity mechanisms that are active throughout the body and have specialized functions restricted to mucosal surfaces involving mucociliary clearance and IgA antibody secretion [11]. Selective immunoglobulin A (IgA) deficiency is considered the most common primary immunodeficiency (PID) disease, affecting one in 300–700 individuals [12]. The majority of cases are asymptomatic; however, some may present with respiratory tract and gastrointestinal infections, allergies, or autoimmune diseases [11,13]. Recurrent otitis media (ROM) is one of the common clinical manifestations of selective IgA deficiency [14]. We have reported previously that approximately a quarter of PID children had ROM before diagnosis [15], and the highest incidence of ROM was found among cases with predominantly antibody deficiency including those with serum IgA deficiency. However, the underlying immunodeficiency was not suspected in almost all patients, except late after the occurrence of other severe infections that indicated referral to a tertiary hospital for immunological evaluation [16]. In this study, we aimed to evaluate the frequency of IgA deficiency among

children presenting to the outpatient clinic with ROM and to identify other possible risk factors of ROM in our community.

## Materials and methods

During the period from December 2010 to February 2012, children between 1 and 12 years of age with ROM who presented to outpatient clinics of Pediatrics and Ear, Nose, and Throat (ENT) at Ain Shams University Hospitals, Cairo, Egypt, were consecutively enrolled in the study. The exclusion criteria included patients with known anatomical or functional abnormality that may lead to ROM such as cleft palate, Down syndrome, primary ciliary dyskinesia, and nasal allergy, chronic diseases such as diabetes mellitus and chronic renal failure, and patients with malignancy or receiving immunosuppressive drugs. The clinical evaluation included assessment of demographic data of patients including age, sex, age at first episode of AOM, frequency of AOM and other respiratory infections per year, history of immunization during infancy, family history of similar conditions or PID, previous sibling death of infection, and parents' consanguinity. A detailed assessment of history of the management of previous AOM events was performed for every patient, with a special focus on the type of antibiotic, route of administration, compliance and response to treatment, and history of previous surgical intervention on the ears, tonsils, or adenoids. Every patient was subjected to a clinical examination of all body systems and an otoscopic evaluation of the ears was performed by ENT specialist. The laboratory investigations included complete blood count by a Coulter LH750 cell counter (Coulter, Electronics, Hialeah, Florida, USA) and measurement of serum IgA by nephelometry (Behring Nephelometer, Behring Werke, Marburg, Germany); values below 33 mg/dl (lowest value detected by nephelometry) were evaluated by a radioimmunoassay test to confirm IgA deficiency. Serum values of IgA of the patients studied were compared with age-matched reference values for the normal range [17]. Selective IgA deficiency was defined as serum IgA level less than 7 mg/dl and normal or elevated levels of IgG and IgM in children over 4 years, and partial IgA deficiency was indicated by serum IgA level below the age-matched

normal range. Culture and sensitivity testing of ear discharge was performed in some cases with otorrhea. This study was approved by the ethics committee of Ain Shams University, and an informed consent was obtained from the parents or the legal guardian of each patient.

## Statistical analysis

Statistical analysis of data was carried out using SPSS, version 19.0 (IBM Corp., Endicott, New York, USA), 2010 for Windows XP. The  $\chi^2$ -test was used to compare qualitative variables between groups. *P* value less than 0.05 was considered significant.

## Results

### Demographic characteristics of the cohort

During the study period, 300 patients (154 males and 146 females) were identified with ROM. Their ages ranged between 13 and 144 months. These patients were living in rural and suburban areas of Egypt and all were exposed to passive smoking. None of the patients had received *H. influenzae* type B or conjugate pneumococcal vaccines. Only two patients (0.66%) had a family history of ROM. Consanguinity was evident in 13% (*n* = 39) of patients.

According to age at enrollment, patients were classified into two groups: group A included 158 patients who presented during early childhood (1–6 years) and group B included 142 patients who presented during late childhood (>6–12 years); the characteristic demographic features of both groups are listed in Table 1.

### Clinical presentation

All the cases studied presented with ROM. Otolgia was the presenting symptom in 270 cases (90%) and high fever (>38.5°C) was elicited in 150 cases (50%). Otorrhea was found in 10% of patients; ear swab for culture testing was not available to all cases because of malpractice by some physicians who focused on performing ear suction and cleansing before taking a swab. Adenoid hypertrophy was elicited in 49 patients (16.3%) in group A. A history of recurrent infections other than OM was elicited

**Table 1 Demographic features of the sample studied**

Variables	Group A [ <i>n</i> (%)]	Group B [ <i>n</i> (%)]	$\chi^2$	<i>P</i>
Male ( <i>n</i> =154)	88 (57)	66 (43)	4.63	0.031
Female ( <i>n</i> =144)	68 (47)	78 (53)		
Consanguinity ( <i>n</i> =39)	25 (64)	14 (36)	2.48	0.115
Parenteral antibiotics ( <i>n</i> =98)	50 (51)	48 (49)	0.1	0.7
Antibiotics >2 months ( <i>n</i> =27)	13 (48)	14 (52)	0.2	0.6

in 111 patients (37%). Of these patients, 25 (8%) had a history of recurrent bronchopneumonia, 44 (15%) had persistent oral thrush, and 32 (11%) had recurrent skin abscesses.

### Antibiotic treatment

All patients had received empirical antibiotic therapy in which amoxicillin/clavulonic acid had been received at least once during an episode of AOM. In general, treatment with antibiotics indicated considerable differences between patients in terms of improper dosage, route of administration, course duration, and compliance (Fig. 1). Parenteral antibiotics including ceftriaxone or cefotaxime were administered for less than 5 days in 64% of cases ( $n = 192$ ), and in 23% of patients ( $n = 69$ ), the intake of parenteral/oral antibiotics was interchanged for no obvious reason. In 16% of cases ( $n = 48$ ), antibiotics were administered without previous medical consultation. Moreover, poor response to medical treatment was recorded in 49 cases.

In terms of surgical intervention, eight patients had undergone grommets tube insertion for persistent effusion.

### Laboratory parameters of the cases studied

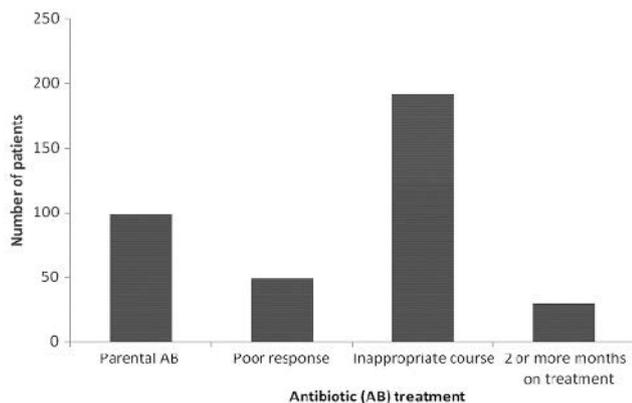
In the current study, iron-deficiency anemia was diagnosed in 76 cases (25.5%) and a significantly high rate of anemia ( $\chi^2: 4.6; P: 0.031$ ) was observed in group A ( $n: 48; 63.1\%$ ) as compared with group B ( $n: 28; 36.8\%$ ). Meanwhile, none of the patients had persistent neutropenia or lymphopenia to suggest other immunodeficiency diseases. Ear swabs for culture and sensitivity testing were obtained from only 12 patients and showed *Staphylococcus aureus* in four patients,

*Pseudomonas* spp. in four patients, *Escherichia coli* in one patient, *Klebsiella* spp. in another patient, and no growth in two patients. Of the 300 cases enrolled, only two patients (0.66%) had partial IgA deficiency. These two patients were a girl and a boy aged 11 and 12 years, respectively. Both cases were born to non consanguineous parents and did not have any history of infection other than ROM. The girl had anemia and the serum IgA level was decreased (20 mg/dl; normal range for age is 33–236 mg/dl) but serum levels of IgM and IgG were within normal for age (42 and 960 mg/dl, respectively). The second patient had a low serum level of IgA (18 mg/dl; normal range for age is: 33–236 mg/dl), IgM was normal (142 mg/dl), and IgG was high (2158 mg/dl).

### Discussion

OM is a major health concern in children, and is a leading cause of physician visits and antibiotic intake in developed and developing countries [18]. Our results clearly showed the disease burden of OM in our community as 300 cases with ROM were identified during a short period of one year. ROM is considered a significant warning sign to suspect primary antibody deficiency [19]. However, despite the extreme selectivity of cases, our results showed a relatively low incidence of serum IgA deficiency among children with ROM (0.7%), which may be an underestimated figure in view of the relatively higher rates reported in other similar studies (1.3%) [14] and (4.8%) [20], and the high prevalence rate of IgA among asymptomatic individuals [12]. In this respect, ethnic and geographic variations in the prevalence of IgA deficiency must be addressed [21–23]. PID registries and reports from several Middle Eastern countries showed considerable variations in the prevalence of symptomatic IgA deficiency between different countries [15,20,24] and different ethnic groups [25]. It is further possible that in our study, environmental factors might have had a considerable influence on the occurrence of ROM. Analysis of demographic characters of patients with ROM and normal IgA level showed that all the patients studied were from rural or suburban areas with suboptimal living conditions and were exposed to smoking, which supports the notion that OM is a heritage of poverty and occurs more prominently among poor children [26]. Therefore, ROM could be attributed to environmental factors such as overcrowding, inadequate hygiene, inattention to symptoms, limited compliance to prescribed regimes, limited access to health care services of optimal quality, and suboptimal nutritional status. Anemia has been reported as a significant finding in children with ROM [27], which

Figure 1



Antibiotic treatment of the sample studied: treatment with antibiotics showed considerable differences between patients in terms of improper dosage, route of administration, course duration, and compliance.

was elicited in 76 cases (26%) of studied patients, especially the group of young children.

Undoubtedly, the poor management of AOM, especially in marginalized or illiterate communities, and the increased healthcare costs of management OM in Egypt had, at least in part, contributed toward the frequent recurrence of AOM and subsequent morbidity. In a 10-year period study on 3,364 cases with suppurative OM (acute/chronic) in Egypt, the reported morbidity and mortality rates were 12.54 and 1.42%, respectively. The onset of complications was insidious and most cases developed complications while receiving treatment, which indicates that OM is not a benign disease in Egypt [28].

The current view of AOM management is that observation (watchful waiting) be used rather than immediate prescription of antibiotics [29,30]. On the basis of joint decision making with the parents, unilateral, nonsevere AOM in children aged 6–23 months or nonsevere AOM in older children may be managed either with antibiotics or with close follow-up and withholding antibiotics unless the child worsens or does not improve within 48–72 h of symptom onset [30].

Definitely, the inappropriate use of antibiotics reported in the present study had a negative impact on the response to antibiotic intake and had also facilitated the emergence of resistant strains such as *Pseudomonas* spp., *S. aureus*, *Klebsiella* spp., and *E. coli* that were detected in the ear swabs.

In the current study, none of the patients had received *H. influenzae* type B and Pneumococcal conjugate vaccines

because these two vaccines are not yet scheduled in the free-of-charge compulsory immunization of infants in Egypt. Several international surveys have reported that the incidence of AOM has been reduced to 33% since the use of these two vaccines [31–33]. Therefore, it is possible that the ROM recorded especially among the young group of studied patients could be a result of lack of vaccination against high-risk pathogens of OM.

OM is a multifactorial disease. It seems that the susceptibility to AOM has a genetic background, despite the fact that it is an infectious disease that is influenced by various environmental factors [34]. To date, several genes that could influence the risk of OM had been identified. In candidate gene studies, a number of genes that are part of the immune system have been associated with a risk of OM [35,36]. These genes include tumor necrosis factor- $\alpha$ , interleukin 6 and 10 (IL-10), toll-like receptor 4 (TLR 4), surfactant, CD14, Fc $\gamma$ -receptor II $\alpha$ , and interferon- $\gamma$  [37,38]. In fact, we could not confirm the influence of genetic predisposition because such investigations were beyond the scope of our study. Although parent consanguinity was elicited in 13% of studied cases, only 1% of cases reported OM in other family members.

We were concerned that the low incidence of IgA deficiency among ROM observed in this cohort might discourage pediatricians and otolaryngologists from suspecting primary antibody deficiency diseases while dealing with cases of OM. To avoid this misconception, we have described from our previous reports [15,16] the clinical data of ROM patients with an established diagnosis of predominantly antibody deficiency and compared it with patients who had normal IgA levels in the current study (Table 2). The significant

**Table 2 Clinical features of recurrent otitis media patients with primary antibody deficiency vs. normal serum IgA level**

Factors	Primary antibody deficiency (N = 11) <sup>a</sup>	Normal IgA level (N = 298)	Test value	P value
Age (months)				
Mean $\pm$ SD	51.09 $\pm$ 40.26	83.30 $\pm$ 50.5	-2.8	0.005
Median (range)	40 (2–144)	72 (13–216)		
Sex				
Male/female	6/5	145/153	0.565	0.5
Consanguinity				
Yes/no	5/6	39/259	6.5	0.02
Retarded growth				
Yes/no	7/4	5/292	66.58	0.000
Concomitant infection (URI, GE, skin, oral thrush)				
Yes/no	9/2	137/161	0.077	0.825
Two pneumonia/year				
Yes/no	10/1	25/273	80.5	0.000
Antibiotics >2 months				
Yes/No	10/1	27/271	85.2	0.000
Intravenous antibiotics				
Yes/no	10/1	95/203	34.16	0.000

GE, gastroenteritis; URI, upper respiratory infections. <sup>a</sup>Data are from Reda *et al.* [15,16]

characteristics in ROM patients that should alarm physicians to suspect primary antibody deficiency are young age at presentation, parental consanguinity, retarded growth, recurrent pneumonia, and prolonged courses of oral and parenteral antibiotics.

Finally, our study has some limitations. First, although none of the patients had persistent leukopenia or lymphopenia that would indicate further investigational steps to identify severe forms of PID, yet, other immunodeficiency diseases such as complement deficiency or Ig G subclass deficiencies were not investigated. Second, being a cross-sectional study, past incidences of AOM were not evaluated by specialists, the recurrence rate was based on history, and hence, the possibilities of over-reporting of AOM remained a concern.

In conclusion, the current study showed a relatively low incidence of IgA deficiency among children with ROM and indicated other environmental risk factors that may have participated in the occurrence of OM in our community. The high rate of ROM and OM complications observed in our patients indicates suboptimal management of AOM that poses additional challenges in the identification of PID in the domain of ear infections.

## Acknowledgements

### Conflicts of interest

None declared.

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