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Main Article

ENT manifestations in Iranian patients with primary antibody deficiencies

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Abstract

Objective: One hundred and nine patients with primary antibody deficiencies were selected in order to determine the frequency of ENT complications.

Method: Demographic information and ENT medical histories were collected for each patient. Duration of study for each patient was divided into two periods of before diagnosis and after diagnosis and the initiation of treatment.

Results: Eighty-two of 109 patients (75.2 per cent) experienced ENT infections during the course of the disease (63: otitis media, 75: sinusitis and nine: mastoiditis). At the time of diagnosis, 52 (47.7 per cent) out of 109 patients presented with an ENT symptom. The frequencies of episodes were 27 for sinusitis and 25 for otitis media (one complicated with mastoiditis). After immunoglobulin replacement therapy the incidence of otitis media was reduced from 1.75 before treatment to 0.39 after treatment per patient per year ($p = 0.008$). The incidence of sinusitis also significantly decreased from 2.38 to 0.78 (p value $= 0.011$).

Conclusion: ENT infections are common medical problems in primary antibody deficiency patients. Persistent and recurrent ENT infections should be suspected as originating from a possible underlying immunodeficiency.

Key words: Antibody Deficiency Syndromes; Otolaryngology; Sinusitis; Otitis Media; Iran

Introduction

Primary antibody deficiency is the most common form of primary immunodeficiencies which comprises a heterogeneous inherited group of disorders ranging from a severe reduction in all serum immunoglobulin isotypes with absent B cells to selective antibody deficiency with normal serum immunoglobulins.[1,2] The most common symptomatic forms of primary antibody deficiencies are common variable immunodeficiency, X-linked agammaglobulinaemia and Hyper IgM syndrome. Hypogammaglobulinaemia is the main characteristic of these diseases. In contrast to the patients with X-linked agammaglobulinaemia who have a low number of B cells (<1 per cent),[3,4] the number of B cells in common variable immunodeficiency and Hyper IgM syndrome are normal.[5] Patients with primary antibody deficiency are more susceptible to pyogenic infections, particularly to encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* compared to healthy individuals.[6,7] These organisms are responsible for upper and lower respiratory tract infections including ENT infections and pneumonia.[8]

Several documented studies show that ENT infections occur in 70–98 per cent of patients with antibody deficiency during the course of their diseases.[7,9] In some instances, ENT infections can be the initial presenting symptom of the underlying disease[10] and affected patients are frequently seen by ENT specialists. Delay in diagnosis, especially in those presenting with ENT infections, can result in severe complications and the need for surgical procedures.[11]

In order to evaluate the frequency and severity of ENT infections in patients with primary antibody deficiency, this historical cohort study was performed.

Patients and methods

The Children's Medical Center Hospital is the referral centre for primary immunodeficiency in Iran. Among those patients who were diagnosed and treated during a 24-year period (1980–2004) 109 patients with primary antibody deficiency who had fully detailed and completed medical history records were selected as the subjects of this study.

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The diagnosis of patients was based on standard criteria introduced by the European Society for Immunodeficiencies and Pan-American Group for Immunodeficiency.[12] ENT problems had been diagnosed and confirmed by ENT specialists.

Demographic data and medical histories of ENT infections were collected for each patient mainly by reviewing the past documented medical history before diagnosis of primary antibody deficiency and registry record after diagnosis, and also by direct interviews with patients. Acute rhinosinusitis was defined as a sinus infection in which clinical symptoms are completely resolved within 12 weeks.[13,14] Diagnosis of sinusitis was made according to clinical signs and symptoms including chronic nasal obstruction, mucopurulent rhinorrhoea, post-nasal discharge and cough.[13] Recurrent acute rhinosinusitis consists of multiple acute episodes with complete resolution of disease between episodes. Chronic rhinosinusitis was diagnosed when sinus infection accompanied by low-grade signs and symptoms persisted for more than 12 weeks and its diagnosis was confirmed by a computed tomography scan.[15–18] The diagnosis of otitis media was made according to the presence of mild to moderate otalgia, fever and hearing loss.

The course of the disease for each patient was divided into two periods of time; before diagnosis and after initiation of treatment, once the diagnosis was made. In addition to analyzing the number of ENT infections, the episodes of ENT infections per patient per year were compared between these two periods to evaluate the probable effect of treatment. It should be mentioned that only documented infections requiring treatment, were included in the analysis.

Diagnosis delay is defined as a period of time between age at onset and age at diagnosis. Also, the follow-up period is considered as the period of time between diagnosis age and current age. Data analysis was performed using SPSS statistical software package (version 11.0). The comparison of ENT infections before and after treatment was performed, using the Wilcoxon signed ranks test. *P* values less than 0.05 were considered as significant.

Results

Characteristics of patients

In this study, 109 patients (76 males and 33 females) aged 2–56 years with primary antibody deficiency including 64 with common variable immunodeficiency, 36 with X-linked agammaglobulinaemia and nine with Hyper IgM syndrome were studied. The median age at onset of symptoms was one and a half years of age (range: 1 month to 46 years) and the median age at diagnosis was 5.3 years (range: 6 months to 54 years). The median diagnosis delay of these patients was three years (range: 0–485 months). The patients were followed up after diagnosis for a median period of four years (range: 1–288 months) (Table I).

At the time of this study, 68 patients were alive, 21 were dead and the remaining 20 have not been referred to our clinic during the past three years. Among the patients who died prior to this study, 15 patients had common variable immunodeficiency, four had X-linked agammaglobulinaemia and two had Hyper IgM syndrome.

Laboratory findings

The patients' median values of immunoglobulin levels at the time of diagnosis were 150 (range: 0–600 mg/dl) for IgG, 16 (range: 0–1240 mg/dl) for IgM and 5 (range: 0–29 mg/dl) for IgA (Table II).

ENT presenting illnesses

Fifty-two (47.7 per cent) out of 109 patients presented with ENT infections, mainly sinusitis (27 patients), followed by otitis media (24 patients). One of the patients with a history of otitis media presented with mastoiditis. In the common variable immunodeficiency group, 13 patients (20.3 per cent) presented with otitis media and 17 patients (26.5) with sinusitis. These frequencies were nine (25 per cent) with otitis media and eight (22.2 per cent) with sinusitis for X-linked agammaglobulinaemia, and two (22 per cent) with otitis media and two (22 per cent) with sinusitis for Hyper IgM syndrome patients.

ENT infections during the course of disease

Eighty-two (75.2 per cent) of 109 patients developed ENT infections (sinusitis, otitis and/or mastoiditis) either as the presenting symptom or during the course of the disease. Among the patients who encountered otitis media during the course of their disease; 55 (50.5 per cent) and 47 (43.1 per cent) patients experienced this problem before and after treatment, respectively. The total number of patients manifested with sinusitis, was 75 (68.8 per cent) during the course of the disease in which the

TABLE I

AGE AND SEX DISTRIBUTION OF PATIENTS WITH PRIMARY ANTIBODY DEFICIENCIES

Disease	No. of patients	Sex		Onset age/median (range) years	Diagnosis age/ median (range) years	Current age/ median (range) years	Diagnosis delay/ median (range) years	Follow up/ median (range) years
		Male	Female					
XLA	36	36	0	1 (< 0.1–6.8)	3.75 (0.5–14)	11 (1.5–34)	2 (0–13)	8 (0.5–24)
CVID	64	33	31	2 (0.5–46)	8.25 (2–54)	12.5 (2.3–56)	3.25 (0.5–39)	3 (<0.1–18)
HIGM	9	7	2	1.5 (0.5–7)	4.6 (2–24.5)	10 (4–30)	1.75 (<0.1–17.5)	4.5 (1–13)
Total	109	76	33	1.5 (<0.1–46)	5.3 (0.5–54)	12 (1.5–56)	3 (0–39)	4 (<0.1–24)

XLA = X-linked agammaglobulinaemia; CVID = Common variable immunodeficiency; HIGM = Hyper IgM syndrome

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TABLE II

LABORATORY DATA OF PATIENTS WITH PRIMARY ANTIBODY DEFICIENCIES

	CVID		XLA		HIGM	
	Median	Range	Median	Range	Median	Range
IgG (mg/dl)	170	0–1150	105	0–700	85	0–555
IgA (mg/dl)	5	0–220	4	0–322	5	0–70
IgM (mg/dl)	22	0–204	3	0–220	480	228–1260
CD3 + T cells (%)	76	34–99	91	61–97	74	43–99
CD4 + T cells (%)	31	4.5–68.3	44	6.5–68	33	18–60
CD8 + T cells (%)	37	17–73	40.5	17–93	35	12–52
CD19 + B cells (%)	8.1	0.5–70.2	0.5	0.1–0.9	8.9	2–19

XLA = X-linked agammaglobulinaemia; CVID = Common variable immunodeficiency; HIGM = Hyper IgM syndrome

number of those before treatment was 62 (56.9 per cent) and those after treatment was 68 (62.4 per cent). The status of nine patients (8.3 per cent) was complicated with mastoiditis (five before making diagnosis and four after treatment).

Efficacy of immunoglobulin replacement therapy

All patients received intravenous (IV) immunoglobulin replacement therapy (400–500 mg/kg every three to four weeks). The mean IgG level in the total patient group increased from 178.4 ± 167.9 mg/dl before treatment to 545.9 ± 345.1 after treatment (p value < 0.001).

Although there was an increase of IgG serum level in all groups of patients (common variable immunodeficiency: from 195.1 to 552.2 mg/dl, $p < 0.001$; X-linked agammaglobulinaemia: from 164.2 to 512.9 mg/dl, $p < 0.001$; Hyper IgM syndrome: from 112 to 669 mg/dl, $p = 0.089$), there were no significant differences between serum levels of IgA and IgM before and after treatment.

All patients were followed up during a total of 581.9 patient years. The median number of episodes of otitis media and sinusitis for each patient in all groups before and after diagnosis and then the number of 'episodes per patient per year' for each manifestation in each patient group were calculated. Among all patients, the median number of episodes of otitis media was three (range: 0–29) before treatment and one (range: 0–10) after treatment. In patients who suffered from sinusitis, the median number of episodes was four (range: 0–25) before treatment and two (range: 0–12) after treatment.

The median number for otitis media was 0.86 (range: 0–36) per patient per year before treatment and 0.14 (range: 0–4) per patient per year after treatment. The frequencies of sinusitis (per patient per year) were 1.0 (range: 0–36) before and 0.47 (range: 0–6) after treatment. After treatment with IV immunoglobulin the incidence of otitis media and sinusitis significantly decreased (p value < 0.001) (Table III).

Discussion

Primary antibody deficiency is a heterogeneous group of rare disorders characterised by decreased levels of serum immunoglobulin isotypes and increased susceptibility to infections in different organs, especially in the respiratory tract.[1,2,6,7] It has been shown that the majority of patients with antibody deficiency have a history of recurrent ENT infections.

In our study, three quarters of all patients were affected by ENT complications during the course of the disease. In a cohort study on 248 common variable immunodeficiency patients, 243 (98 per cent) cases had recurrent sinusitis, otitis or bronchitis during the course of their disease.[7] Another study on primary antibody immunodeficient patients showed that chronic rhinosinusitis was observed in 49 (86 per cent) of 57 cases with agammaglobulinaemia, and it was also high (76 per cent) in common variable immunodeficiency.[19] Moreover, two other studies showed that 68.5 per cent and 75 per cent of patients with X-linked agammaglobulinaemia encountered upper respiratory tract infections during the course of the disease.[9] Another study revealed that infections of the upper respiratory tract occur several years before the appearance of lower respiratory tract infections.[20] All these studies show that immunological defects have an important role in recurrent ear and sinus infections.

ENT infections, especially sinusitis and otitis media, were the most common presenting manifestations in our studied population. This was in agreement with previous studies, which showed that resistant sinus infections could frequently be the first presenting symptom in immunodeficiencies, especially antibody deficiencies.[8,21,22]

As we observed in our study, half of our patients presented with ENT infections. In some instances the patients are frequently seen by ENT specialists and treated with different courses of antibiotics without attention being paid to the underlying disease. As a result of the lack of knowledge about primary antibody deficiencies among physicians the diagnosis might be delayed for many years in some instances.[11] It should be noted that the approach to the treatment of ENT infections in patients with primary antibody deficiency is not the same as that for non-immunodeficient patients and requires appropriate therapy directed at the underlying immunological abnormality.

By calculating the episodes of ENT infections per patient per year for each symptom in each patient group, we have shown that all groups had a high incidence of infections before diagnosis and still high but fewer incidents after diagnosis. Sinusitis and otitis media continue to be important problems in patients

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TABLE III

THE MEDIAN VALUES AND RANGE OF EPISODES OF OTITIS MEDIA AND SINUSITIS PER PATIENT, PER YEAR IN EACH GROUP OF DISORDER

	Otitis media			Sinusitis		
	Before	After	*p* value*	Before	After	*p* value*
CVID	0.73 (0–10)	0.12 (0–4)	0.004	1.0 (0–30)	0.67 (0–6)	0.018
XLA	1.0 (0–6.7)	0.12 (0–2)	0.002	1.0 (0–6)	0.27 (0–4)	0.012
HIGM	2.2 (0.86–5)	0.81 (0.2–1)	0.043	1.1 (0–6.7)	0.75 (0.2–1)	0.075
Total	0.86 (0–36)	0.14 (0–4)	<0.001	1.0 (0–36)	0.47 (0–6)	<0.001

*Wilcoxon signed ranks test; XLA = X-linked agammaglobulinaemia; CVID = Common variable immunodeficiency; HIGM = Hyper IgM syndrome

with primary antibody deficiency. It seems that immunoglobulin replacement therapy does not eradicate ENT infections late after diagnosis, possibly because of the structural damage that strikes the mucociliary system.[23]

- **Otolaryngological infections are common medical problems in primary antibody deficiency patients. Persistent and recurrent infections should be suspected as originating from a possible underlying immunodeficiency**
- **In this study 109 patients with primary antibody deficiencies were selected in order to determine the frequency of ear, nose and throat complications**
- **Eighty-two of 109 patients (75.2 per cent) experienced ENT infections during the course of the disease**
- **Sinusitis and otitis media are the most frequent ENT presentations of patients with primary immune deficiency**

As we noticed in our patients after initiation of IV immunoglobulin the incidence of otitis media and sinusitis significantly decreased. Our finding is in contrast to the study that suggested non-respiratory and upper respiratory infectious events may not be prevented by IV immunoglobulin alone, even at standard doses, and the patients may need parallel surgical or pharmacological approaches to be optimally cured.[23] The management of sinusitis in patients with primary antibody deficiency is controversial. An objective assessment of the extent of sinus disease, a standardised therapeutic approach and a careful follow up are very important. In patients without underlying immune defects, sinusitis can be effectively treated with a combination of broad spectrum antimicrobials, anti-inflammatory agents, and saline nasal washes.[22] We suggest the administration of prophylactic antibiotics in patients who suffer from recurrent ENT infections in spite of receiving regular IV immunoglobulin and with an adequate desired serum level (500–600 mg/dl).

Moreover, it is suggested that regular use of IV immunoglobulin associated with prophylactic antibiotics could effectively prevent ENT infections. Herein, it is concluded that persistent and recurrent ENT infections, refractory to treatment, should be suspected as originating from a possible underlying immunodeficiency. Clinical history is the most important aspect of being suspicious to the diagnosis of primary antibody deficiencies. All patients with a history of recurrent ENT infections should have a full assessment of their immune system including measurements of immunoglobulin levels, IgG subclasses and also antibody responses to protein and polysaccharide antigens. Diagnostic delay and failure to provide adequate therapy result in organ damage and permanent complications.

Early diagnosis and effective treatment increase the quality of life of patients with primary antibody deficiency while delay in diagnosis results in permanent organ damage such as bronchiectasis. It should be emphasised that recurrent and chronic ENT infections should alert the general practitioner and ENT specialist to the need to perform immunological investigations.

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References

1 Notarangelo L, Casanova JL, Conley ME, Chapel H, Fischer A, Puck J *et al*. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005. *J Allergy Clin Immunol* 2006;**117**:883–96
2 Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K *et al*. Primary immunodeficiency in Iran: First report of the national registry of PID in children and adults. *J Clin Immunol* 2002;**22**:375–80
3 Tsukada S, Saffran DC, Rawlings DJ, Parolini O, Allen RC, Klisak I *et al*. Deficient expression of a B cell cytoplasmic

https://doi.org/10.1017/S0022215107008626 Published online by Cambridge University Press

tyrosine kinase in human X-linked agammaglobulinemia. *Cell* 1993;**72**:279–90
4 Aghamohammadi A, Fiorini M, Moin M, Parvaneh N, Teimourian S, Yeganeh M *et al*. Clinical, immunological and molecular characteristics of 37 Iranian patients with X-Linked agammaglobulinemia. *Int Arch Allergy Immunol* 2006;**141**:408–14
5 Ballow M. Primary immunodeficiency disorders: antibody deficiency. *J Allergy Clin Immunol* 2002;**109**:581–91
6 Hermaszewski RA, Webster AD. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. *Q J Med* 1993;**86**:31–42
7 Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999;**92**:34–48
8 Pettit SJ, Bourne H, Spickett GP. Survey of infection in patients receiving antibody replacement treatment for immune deficiency. *J Clin Pathol* 2002;**55**:577–80
9 Plebani A, Soresina A, Rondelli R, Amato GM, Azzari C, Cardinale F *et al*. Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: An Italian Multicenter Study. *Clin Immunol* 2002;**104**:221–30
10 Galicia G, Betancourt MA, Canales LE, Cristerna L. Ear, nose, and throat manifestations in patients with primary immunodeficiencies [in Spanish]. *Rev Alerg Mex* 1999;**46**:108–19
11 Blore J, Haeney MR. Primary antibody deficiency and diagnostic delay. *BMJ* 1989;**298**:516–17
12 Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. *Clin Immunol* 1999;**93**:190–7
13 Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, Kennedy DW *et al*. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg* 2003;**129**:S1–32
14 Pichichero ME, Casey JR. Otitis media. *Expert Opin Pharmacother* 2002;**3**:1073–90
15 Morris PS. Management of otitis media in a high risk population. *Aust Fam Physician* 1998;**27**:1021–9
16 Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 1997;**117**:S1–7
17 Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA *et al*. Rhinosinusitis: establishing definitions for clinical research and patient care. *J Allergy Clin Immunol* 2004;**114**:155–212
18 Roland PS. Chronic suppurative otitis media: a clinical overview. *Ear Nose Throat J* 2002;**81**:8–10
19 Bernatowska E, Mikoluc B, Krzeski A, Piatosa B, Gromek I. Chronic rhinosinusitis in primary antibody immunodeficient patients. *Int J Pediatr Otorhinolaryngol* 2006;**70**:1587–92
20 Karlsson G, Petruson B, Bjorkander J, Hanson LA. Infections of the nose and paranasal sinuses in adult patients with immunodeficiency. *Arch Otolaryngol* 1985;**111**:290–3
21 Cooney TR, Huissoon AP, Powell RJ, Jones NS. Investigation for immunodeficiency in patients with recurrent ENT infections. *Clin Otolaryngol Allied Sci* 2001;**26**:184–8
22 Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. *Pediatrics* 1991;**87**:311–16
23 Favre O, Leimgruber A, Nicole A, Spertini F. Intravenous immunoglobulin replacement prevents severe and lower respiratory tract infections, but not upper respiratory tract and non-respiratory infections in common variable immune deficiency. *Allergy* 2005;**60**:385–90

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