EAR, NOSE AND THROAT MANIFESTATIONS IN PATIENTS WITH PRIMARY ANTIBODY DEFICIENCIES

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Abstract - Recurrent ear, nose, and throat (ENT) infections are common presenting symptoms in patients with primary antibody deficiencies, but sometimes they remain undiagnosed for many years and are subjected to different antibiotics because of a lack of experience in immunodeficiencies. In order to determin the frequency of ENT symptoms among the patients with antibody deficiencies, 83 antibody deficient patients were studied from 1980 during a 20-year period, and their ENT symptoms were registered.

This historical cohort study comprised of 83 patients including 25 X-link agammaglubulinemia, (XLA) 40 common variable immunodeficiency (CVID), 14 IgA deficiency (IgA-D); 50 male, 33 female. The average length of time between onset and diagnosis was 40 months in our patients. Seventy two of our patients (86.7%), had recurrent ENT symptoms (sinusitis, otitis and/or mastoidits) during the course of their disease. Each XLA patient had experienced 3.6 episodes of otitis per year, but after diagnosis it decreased to 0.7 episode per year. This decrease was about 5.8 folds in CVID (3.8 to 0.65) and 1.4 folds in IgA (2.2 to 1.6). These results show that a significant number of antibody deficient patients can be present with ENT symptoms (48% in this study). Diagnostic delay was not much different from other reports. Early diagnosis and treatment of immunodeficiencies significantly prevents recurrent infections hence preventing long time complications.

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INTRODUCTION

Antibody immunodeficiency disorders comprise a spectrum of diseases characterized by decreased immunoglobulin levels ranging from a complete absence of all classes to selective deficiency of a single class or subclass. Following Bruton's first description of agammaglobulinemia in 1952, a large number of patients have been reported so far (1,2,3).

Patients with primary antibody deficiency are susceptible to infections with capsulated organisms like H. Influenza and S. Pneumonie in different organs, especially in upper and lower respiratory tract (4,5,6,7).

Many patients with antibody deficiency present with recurrent infections in the ear, nose and throat (e.g. otitis media and sinusitis) and therefore are frequently referred to clinicians with little experience in immunodeficiency and sometimes they remain undiagnosed for many years receiving different antibiotics.

A survey in the north west region of England showed that average delay in immunodeficiency diagnosis was 2.5 years in children and 5.5 years in adults (8). Also in a study done by Cunningham-Rundles in the United States, the diagnostic delay in 248 studied CVID patients was 4-6 years (5).

This shows a remarkable delay in diagnosis of these two important primary antibody deficiencies and this delay can cause many severe complications. Although most patients with sinus and ear infections are not immunodeficient, a significant proportion of patient with chronic and recurrent infections unresponsive to medical and/or surgical therapy may have an immunodeficiency.

It has been shown that immunologic defects have an important role in recurrent ear and sinus infections and some studies have shown that recurrent otitis media or recurrent sinusitis can be the only symptom in patients with primary antibody deficiency (7,9,10).

In order to increase the awareness of physician about otolaryngological manifestations of patients with antibody deficiencies, we carried out a retrospective analysis of otolaryngological manifestations in 83 patients with antibody deficiencies who were investigated in Children's Medical Center, Tehran University of Medical Sciences.

MATERIALS AND METHODS

Patients

The immunodeficiency clinic at Children's Medical Center serves as a referral center for patients with known or suspected immune deficiency diseases. Patients with antibody deficiency referred to or diagnosed at this center since 1980 over a 21-year period were evaluated for inclusion in the study, this report is restricted to patients with antibody deficiency seen between 1980 and 2000.

The diagnosis of antibody deficiences was made by standard criteria for each specific antibody deficiency (1). In this study 83 patients with primary hypogammaglobulinemia including 25 with X-link agammaglobulinemia (XLA), 40 with CVID, 14 with IgA deficiency (IgA-D) and 4 with IgG subclass deficiency (IgG-SCD) were studied.

Collection of data

A two-page questionnaire was developed to contain all the patiens' demographic and medical history information, including diagnosis, age at onset, age at diagnosis, first clinical presentation, and type number, severity and time of each relevant infection in the course of illness. Data were collected using patients' records and direct interviews.

The course of the illness was divided into two periods, 1-since the onset of the disease until the time of diagnosis (before treatment), 2-since the time of diagnosis until the time of study (after treatment). Therefore, infectious episodes were also divided into two above categories regarding their time. Only infections requiring treatment or hospitalization were included in the analysis.

RESULTS

In this historical cohort study, 83 patients with primary hypogammaglobulinemia (25 with XLA, 40 with CVID, 14 with IgA-D and 4 with IgG-SCD were studied. The age and sex distribution of patients and their laboratory findings have been summarized in table 1 and 2 respectively.

Of these patients 50 were male and 33 were female with the median age of 10 years (range: 1-28 y). The mean duration between onset and diagnosis (delay in diagnosis) was 31 months for XLA, 45 months for CVID, 33 months for IgA-D and 75 months for IgG-SCD; and the average length of time between onset and diagnosis was 40 months in our patients (table 3).

Seventy two of our patients (86.7%), had recurrent ENT symptoms (sinusitis, otitis and/or mastoidits) during the course of their disease. This frequency was 82.5% (33 of 40) for CVID, 92% (23 of 25) for XLA, 93% (13 of 14) for IgA-D and 75% (3 of 4) for IgG-SCD. At the time of diagnosis 40 of our patients (48.1%) presented with an ENT symptom; and this was 50% (20 of 40) for CVID, 48% (12 of 25) for XLA, 42% (6 of 14) for IgA-D and 50% (2 of 4) for IgG-SCD (table 4).

We recovered 112 presenting symptoms for all 83 patients (because of considering more than one symptom for some cases): 43 (38%) of which were ENT symptoms including otitis media, sinusitis and

Table 1. Age and Sex distribution of patients (n = 38).

	number of	Sex		Age
Disease	patients	male	female	Median (range)
XLA	25	25	0	10 (2-28)
CVID	40	19	21	11 (1.5-24)
IgA-D	14	4	10	8 (1-17)
IgG SCD	4	2	2	11 (6-12)
total	83	50	33	10 (1-28)

XLA : X-linked agammaglobulinemia
CVID: Common Variable Immunodeficiency
IgA-D : IgA Deficiency
IgG SCD : IgG Subclass Deficiency

Table 2. Laboratory data in 83 patients with primary antibody deficiencies

	XLA		CVID		IgA-D		IgG-SCD	
Disease	mean	range	mean	range	mean	range	mean	range
WBC	7704	1075-18000	7663	4900-14400	7932	3050-15100	5504	5700-10240
Lymph. (%)	37.2	11-74	37.3	11-64	35.5	11.2-61	32.8	20-72
IgG	126.3	0-370	236	0-450	587.3	250-2000	969.4	690-1500
IgA	15.2	0-150	46.5	0-380	7.8	0-40	108.4	40-380
IgM	31	0-322	87.7	0-400	132	71-339	507	18-240
CD3 (%)	85.15	61-95	87.3	12-99	65.43	13-89.7	69.9	59.3-85
CD4 (No.)	1147.2		855.9	220-3425	1221	34-2355	609.3	407-1095
CD8 (No.)	1008.8	921-2116	1138	256-3900	14.59	17-3001	673.8	658-1490
CD19 (No.)	15.4	1-30	332.4	16-1718	844	41-2174	330.3	260-415

mastoiditis, and 69 (62%) non-ENT infectious symptoms. Recurrent otitis media was the presenting symptom in 9 of XLA patients (36%), 16 of CVID patietns (40%), 1 of IgA-D patietns (7.1%) and 1 of IgG-SCD (25%). Recurrent sinusitis was seen in 5 of XLA patients (20%), 4 of CVID patietns (10%), 3 of IgA-D patietns (21.5%) and 1 of IgG-SCD patients (25%) at presentation. Mastoiditis was not as common as two other ENT symptoms in our patients; two of our CVID patients (5%) and one of our XLA patients (4%) presented with mastoiditis (table 5).

Table 3. Mean duration of delay in diagnosis and follow up in each patient group

Disease	Mean duration of delay in diagnosis (months)	Mean duration of follow up (months)
XLA	31	62
CVID	45	51
IgA-D	33	36
IgG SCD	75	48
total	40	51

XLA : X-linked agammaglobulinemia
CVID: Common Variable Immunodeficiency
IgA-D : IgA Deficiency
IgG SCD : IgG Subclass Deficiency

it decreased to 0.7 episode/year per patient, which shows a 5.1 folds decrease. This decrease was about 5.8 folds in CVID (3.8 to 0.65) and 1.3 folds in IgA-D (2.2 to 1.6); similar results were obtained for frequency of sinusitis episodes, which are shown in table 6.

Table 4. Overal ENT symptom frequencies in patient groups

Disease	Number	as presenting symptom		during the course of disesae	
		No.	%	No.	%
CVID	40	20	50	33	82.5
XLA	25	12	48	23	92
IgA-D	14	6	42	13	93
IgG-SCD	4	2	50	3	75
Total	83	40	48.1	72	86.7

DISCUSSION

According to our results, recurrent ENT infections are common presenting symptoms in our patients with primary antibody deficiencies. ENT symptoms comprise about 38% of presenting symptoms in our patients.

Among the three ENT symptoms observed in our patients, otitis media had the most frequency (32% of patients), and sinusitis and mastoiditis were less frequent (15.7% and 3.6% respectively) (table 4). Otitis

Table 5. Frequency of ENT symptoms in patients at presentation

Symptoms	XLA		CVID		IgA-D		IgG-SCD		Total	
	n = 25		n = 40		n = 14		n = 4		n = 83	
	No.	%	No.	%	No.	%	No.	%	No.	%
Otitis Media	9	36	16	40	1	7.1	1	25	27	32.5
Sinusitis	5	20	4	10	3	21.5	1	25	13	15.7
Mastoiditis	1	4	2	5	0	0	0	0	3	3.6

Table 6. The values of episode / year of Otitis and Sinisitis of patients in each group

symptom	episode / year							
	XLA		CVID		IgA-D		IgG-SCD	
Duration	Be.	Af.	Be.	Af.	Be.	Af.		
Otitis	3.6	0.7	3.8	0.65	2.2	1.6	1.1	0.63
Sinusitis	1.2	0.1	1.8	0.1	2.4	1.9	1.2	0.42

Be : Before diagnosis
Af : After diagnosis
XLA : X-linked Agammaglobulinemia
CVID: Common Variable Immunodeficiency
IgA-D: IgA Deficiency

The mean number of episodes of otitis and sinusitis for each patient in all groups before and after diagnosis and then the number of "episodes per year per patient" for each symptom in each patient group were calculated. Each XLA patient has had 3.6 episodes of otitis per year before the diagnosis, but after diagnosis

was also the most frequent symptom in all groups except for IgA-D in which recurrent sinusitis was more frequent (table 5); and sinusitis was the most frequent in IgG-SCD patients.

Shapiro and co-workers studied 61 patients with recurrent sinusitis and showed that 34 of these patients

had immunodeficiency with decreased IgG3 level and deficient reaction to pneumococcal antigens (Shapiro).

Howevere, The apparent association of IgG3 subclass deficiency and atopy raises the possibility that the high incidence of sinus disease in this group relates more to underlying allergic status than to a humoral immunologic defect (11).

Although we cannot make a scientific comparison between the frequencies, it seems that deficiency in IgG production has a stronger effect on susceptibility to otitis media; and IgA levels play a more important role in preventing sinus infections.

Our results indicated that 48.1 percent of our antibody deficient patients had had an ENT symptom, especially otitis media, at presentation. There are also some other studies, which show that resistant sinus infections can frequently be the first presenting symptom in immune deficiencies, especially antibody deficiencies (7,9,10,12).

It notifies the general practitioner, ENT specialist and family doctor, that ENT infections can be an alarm and should not be neglected specially in those with recurrent episodes or unresponsiveness to routine treatments.

The scarcity of clinical immunology services in the past has resulted in many patients being managed in centers where only a few patients with antibody deficiencies are seen. As a result of lack of experience, the diagnosis of immunodeficiencies has been delayed as long as many years in some instances.

Early diagnosis is desirable and immunoglobulin replacement therapy is essential, though recent reports suggest that after a late diagnosis, immunoglobulin replacement therapy does not eradicate ENT infections possibly because of the structural damage occured in the mucociliary system.

As is shown in table 3, the mean delay in diagnosis has been nearly 40 months in our patients. It shows that many patients have remained undiagnosed, receiving different antibiotics for their infections without any knowledge of the underlying cause of their recurrent infections. We can also see that after diagnosis of the underlying disease (i.e. antibody deficiency) and receiving antibody replacement therapy, number of episodes of recurrent infections per year falls dramatically (table 6).

In a previous report of 50 CVID cases in 1976, the average length of time for diagnosis was 10 years (13). But in a study on 103 CVID patients , the difference between average age at diagnosis and average age at onset was 3 years (5). Possibly the increased awareness of immunodeficiency diseases and a good referral system over time between those two studies permitted earlier diagnosis.

We conclude that clinical history is the most important aspect of suspecting a diagnosis of primary antibody deficiencies. All patients with a history of recurrent ENT infections should have a full assessment of immune system including measurements of immunoglobulin levels, IgG subclasses and also antibody responses to protein and carbohydrate antigens. Diagnostic delay and failure to provide adequate therapy results in organ damage and cause complications. With early diagnosis and effective treatment, many people with primary immunodeficiency are able to have active lives.

REFERENCES

1. WHO Scientific Committee: Primary immunodeficiency diseases. Report of an IUIS Scientific committee, International Union of immunological Societies. Clin Exp Immunol, 118 (suppl. 1): 1-28; 1999.

2. Ochs HD, Immunologic disorders in infants and children of Stiehm, 4th ed., Philadelphia, WB Saunders, 1996.

3. Hermaszewski RA, Webster ABD. Primary hypogammaglobulinemia: a survey of clinical manifestations and complications Q J Med. 86: 31-42; 1993.

4. Cunningham-Rundles C. Clinical and immunologic analysis of 103 patients with common variable immunodeficiency. J Clin Immunol 9:22-33, 1989.

5. Cunningham-Rundles C.et al; common variable immunodeficiency, clinical and immunological features of 248 patients; Clinical Immunology. 92(1): 34-48; 1999.

6. Herrod HG: Immunologic Considerations in the child with recurrent or persistent sinusitis. Allergy asthma proc. May-Jun: 18(3): 145-8; 1997.

7. Sethi DS, Winkelstein JA, Lederman H, Lovry MC, Immunologic defects in patients with chronic recurrent sinusitis: Diagnosis and management. Otolaryngol Head & Neck Surgery Feb; 112(2) 242-7; 1995.

8. Nlore J, Haeney M: Primary antibody deficiency and diagnostic delay. BMJ. 298: 516-7, 19.

9. Armenaka M, Grzzanti J, Rosenstriech DL: Serum immunoglbulins and IgG Subclass level in adults with chronic Sinusitis: evidence for decreased IgG3 levels. Ann Allergy. Jun; 72(6): 507-14; 1994.

10. Shapiro CG, Virant FS, Furukawa CT, and Pierson WE: Immonologic defects in patients with refractory sinusitis. Pediatrics. Mar; 87(3): 311-6; 1991.

11. Sperber K, Levine S. Reiter M, Cunningham-Rundles C. Potential association of IgG3 subclass deficiency with atopy. I Allergy Clin Immunol. 83:204; 1989.

12. 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 Qtolaryngologol. 256 (9): 445-9; 1999.

13. Webster ADB,' Shiner M, Slavin G, Levi AJ, Loewi G, Asherson GL: Nodular Lymphoid hyperplasia of the bowel in primary hypogammaglobulinemia. GUT. 18:364-372, 1977.