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Original Articles

X-linked Agammaglobulinaemia in Hong Kong Chinese

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Abstract We reviewed retrospectively eleven Chinese children diagnosed with X-linked agammaglobulinaemia (XLA) and managed at the Department of Paediatrics & Adolescent Medicine of Queen Mary Hospital from 1987 to 2002. All of the eleven children had presenting signs and symptoms before fourteen months old, but diagnosis was delayed in most patients with the median age of diagnosis at 5.8 years (range 1.3-14.3 years). The respiratory tract was the most commonly affected site of infection (76%) before diagnosis. *Haemophilus influenzae* was the most commonly isolated microorganism before and after diagnosis. Intravenous immunoglobulin (IVIG) was given in all patients with a median dose of 700 mg/kg four weekly in order to achieve the pre-infusion IgG level within the normal reference range as well as control of clinical infections. The incidence of documented infections before IVIG replacement was 31 per 100 patient-months which decreased to 7.6 per 100 patient-months after IVIG replacement ($p<0.0001$). The height and weight centiles of the children also increased after IVIG replacement ($p<0.01$). Bronchiectasis was noted in three out of the eleven children who were diagnosed to have XLA late at 6, 12 and 14 years old. Adequate IVIG replacement could decrease the frequency of infections and normalize growth in children with XLA. It might prevent bronchiectasis if started early in life, which depends on early diagnosis of XLA.

Key words Agammaglobulinaemia; Bronchiectasis; Growth; Immunodeficiency

Introduction

X-linked agammaglobulinaemia (XLA) is an X-linked recessive B cell disorder which was first described by Dr. Bruton in the early 1950's and has remained as a prototype for primary immunodeficiency diseases (PID).[1] It is caused by a mutation of the Btk gene at the long arm (q 22) of X chromosome leading to the dysfunction of Bruton's tyrosine kinase (Btk), which interferes with the development and function of B cells and their progeny.[1-3] Major consequence of the defect appears to be an arrest at the stage of development of pre-B cells to B cells. Individuals affected have pre-B cells in their bone marrow but few to absent B cells in their blood and lymphoid tissue. The plasma cells, which are producers of serum immunoglobulins and derived from B cells, are also absent in the peripheral circulation and tissue. Individuals born with XLA are usually asymptomatic in their first six months of life, and as maternally acquired immunoglobulins disappear during the second six months of life, symptoms start to manifest. However, delayed manifestation is not uncommon with 20% of the patients having their first infection after their first birthday.[4] Intravenous

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immunoglobulin (IVIG) had replaced intramuscular injection of immunoglobulin as the standard form of treatment in the 1980's. In spite of IVIG replacement, complications though preventable have been observed to set in.[5] The objective of this study is to investigate the impact of IVIG replacement on the frequency of infections and growth in our patients with XLA.

Methods

Patients

The outpatient and inpatient records of eleven children diagnosed with XLA at the Department of Paediatrics & Adolescent Medicine of Queen Mary Hospital between 1987 and 2002 were reviewed. At the time of analysis all are alive with a median age of 14.9 years (range 6.8-24.1 years). The diagnosis of XLA was based on history, serum immunoglobulin levels by nephelometric studies and lymphocyte subset enumeration by flow cytometry. Identification of the Btk gene mutations was reported previously.[6] Patient outcome was documented by comparing height and weight percentile measurements before diagnosis and at their last follow up after a period of regular IVIG infusion. The dosage of the IVIG was adjusted in order to achieve the pre-infusion serum IgG level within the normal reference range as well as control of clinical infections. Oral prophylactic antibiotics were prescribed for varying periods of time for those who have adequate serum IgG levels but still with respiratory infections. Bronchiectasis, a well-known complication of XLA,[7] was documented by high-resolution computerized tomography (HRCT).

Infections and Prophylaxis

The clinical presentations of infections were reviewed retrospectively from the medical records. Each episode of infection identified was tabulated according to organ location and the causative organisms isolated. Documented infection was defined as all signs or symptoms experienced by the patients attributable to an infectious process necessitating symptomatic medical interventions. Severe infection was defined as an occurrence of an infectious process, that required hospitalization with intravenous antibiotic infusion, and with or without surgical or ancillary radiological interventions (e.g. X-ray, CT scan or MRI). The influence of long term IVIG was evaluated by comparing the incidence of infections before and after the start of IVIG replacement.

Statistical Analysis

Comparative analysis of incidences of infections and organ dysfunction before and after IVIG replacement were both calculated by Fisher Exact Test. The impact of IVIG replacement on the height and weight centiles was analyzed by Wilcoxon Rank Sum Test.

Results

Patients

All eleven patients are alive and had a total of 1017 months of follow up from 1987 to 2002 with a median follow up of 7 years (range 1.6-15 years). The median age at diagnosis was 5.8 years (range 1.3-14.3 years). On their last follow up the median age was 14.9 years (range 6.8-24.1 years).

Laboratory Examinations

All eleven patients' serum immunoglobulins (IgG, M, A) were found to be very low with virtually absent B cells in the peripheral blood (Table 1). Btk mutations in most of our patients were published previously.[6]

Infections

The median age of first infection was documented at 12 months (range 6-14 months). More than 76% of the documented infections was attributable to the respiratory tract, with 59.8% and 16.4% due to an upper and lower tract infection respectively (Table 2a). For the severe infections, lower respiratory infections (45%) were the most common followed by gastrointestinal infections (16%) (Table 2a). *Haemophilus influenzae* was the commonest bacteria isolated at 34% (3/9), followed by *Pseudomonas sp*. 22% (2/9).

Treatment, Effects and Complications

Our patients received a median dose of 700 mg/kg (range 500-1000 mg/kg) per infusion of intravenous immunoglobulin every 4 weeks. Some received intermittent oral septrin prophylaxis because of the frequency of their respiratory infectious episodes despite adequate IVIG replacement but none of them received long term antibiotic prophylaxis. There were 253 documented infections before starting IVIG and only 75 documented infections after regular IVIG replacement (Tables 2a & 2b). The reduction was significant from an incidence of 31 infections per 100 patient-months (PM) to 7.6 infections per 100 PM ($p < 0.0001$). The incidence of severe infections decreased

Table 1 Immunoglobulin levels and B-cell percentage in peripheral blood

Patients	Ig G mg/dl	Ig A mg/dl	Ig M mg/dl	B-cell percentage
(1)1	<200	<12	18	0.5%
(1)2	<70	<13	<7	0.0%
(1)3	<69	<12	12	0.1%
(2)4	<75	<13	<7	0.0%
(2)5	<75	<13	26	0.0%
6	<200	4.2	33	0.4%
7	<100	12	7	0.0%
8	<75	<13	<7	0.1%
9	<200	<16	15	0.0%
10	<200	50	34	0.2%
11	<73	20	42	0.0%

(1)1, (1)2 and (1)3 are maternal cousins

(2)4 and (2)5 are brothers

Table 2a Localization of documented infections and isolated organisms (before IVIG)

Location of infections	Documented infections		Severe infections		Isolated organisms
URI (tonsillitis, tonsillar abscess, stomatitis, parotitis, rhinitis)	160	59.8%	3	6.8%	
LRI (pneumonia, bronchitis, bronchiectasis, pleuritis, TB)	39	16.4%	18	41%	*Mycobacterium tuberculosis, Pseudomonas sp.*
GII					
Enteritis	9	6.7%	6	13.7%	*Salmonella sp.*
Intra abdominal abscess	1	0.7%	1	2.3%	
Conjunctivitis	1	0.7%			
Skin abscess and dermatitis	4	3.0%	3	6.8%	
Meningitis	1	0.7%	1	2.3%	*H. influenzae*
UTI	2	1.5%	1	2.3%	
Arthritis	4	3.0%	4	9.0%	*H. influenzae*
Septicemia	4	3.0%	4	9.0%	*B. fragiles, H. influenzae, Pseudomonas sp., Strep. pneumoniae*
Otitis media, externa	4	3.0%	2	4.5%	
Sinusitis	2	1.5%	1	2.3%	
TOTAL	**253**	**100.00%**	**44**	**100.00 %**	

URI: upper respiratory infection
LRI: lower respiratory infection
GII: gastrointestinal infection
UTI: urinary tract infection

Table 2b Localization of documented infections and isolated organisms (after IVIG)

Location of infections	Documented infections		Severe infections		Isolated organisms
URI (tonsillitis, tonsillar abscess, stomatitis, parotitis, rhinitis)	41	55%	1	5%	*H. influenzae*
LRI (pneumonia, bronchitis, bronchiectasis, pleuritis, TB)	7	9%	7	37%	*H. influenzae*
GII					
Enteritis	11	15%	8	42%	*Campylobacter j. (5), Salmonella sp. (2) Giardia lamblia*
Intra abdominal abscess	1	1%	1	5%	
Conjunctivitis	0	0	0	0	
Skin abscess and dermatitis	8	11%	0	0	
Meningitis	0	0	0	0	
UTI	0	0	0	0	
Arthritis	1	1%	0	0	
Septicemia	0	0	0	0	
Otitis media, externa	3	4%	2	11%	*H. influenzae (2), Pseudomonas sp.*
Sinusitis	3	4%	0	0	
TOTAL	**75**	**100.00%**	**19**	**100.00 %**	

URI: upper respiratory infection
LRI: lower respiratory infection
GII: gastrointestinal infection
UTI: urinary tract infection

from 5.4 infections per 100 PM before IVIG to 1.9 infections per 100 PM after IVIG replacement. The impact on height and weight centiles of children before and after IVIG replacement was also significant (Figures 1a & 1b, p=0.0078). Eight of eleven patients showed a gain of 25% or more in height percentile for age (Figure 1a) and eight of eleven patients showed a gain of 20% or more in weight percentile (Figure 1b) after IVIG replacement. Despite IVIG, three of the children had bronchiectasis documented by HRCT. These three children who developed bronchiectasis were diagnosed to have XLA at the age of 6, 12, and 14 years respectively, all above the median age of diagnosis of our patient cohort.

Discussion

All our patients with XLA experienced their first infection before 14 months of age. In one series of 96 patients with XLA, 20% experienced their initial clinical symptoms after their first year of life and 10% after 1½ years of age.[4] In another series of 44 XLA patients, 21% presented clinically as late as three to five years of age.[8] Despite repeated infections in our patient cohort, diagnosis was not made until 14.3 years in a patient, and the median age at diagnosis was 5.8 years overall. This may be related to a general lack of awareness of PID in Hong Kong. Diagnosis of patients with XLA depends on good history taking and vigilance in documenting the number and types of infections. These patients are prone to develop infections from organisms such as *Streptococcus pneumoniae*, *H. influenzae*, enterovirus and protozoa such as giardia.[4,7,8] In our series, there were 253 documented infections and 44 severe infections before IVIG treatment, *H. influenzae* was the most common organism isolated (Tables 2a & 2b).

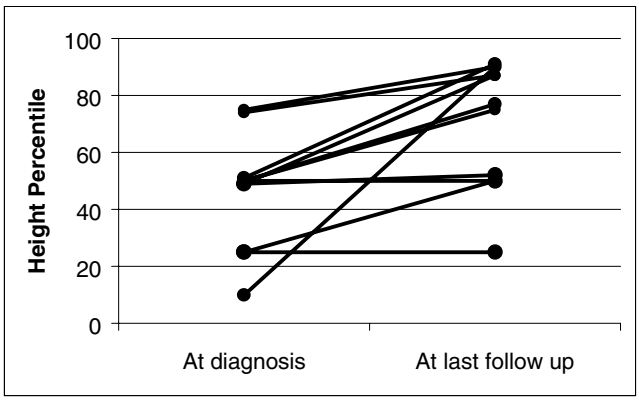

Figure 1a Height percentile of XLA patients pre and post infusion IVIG.

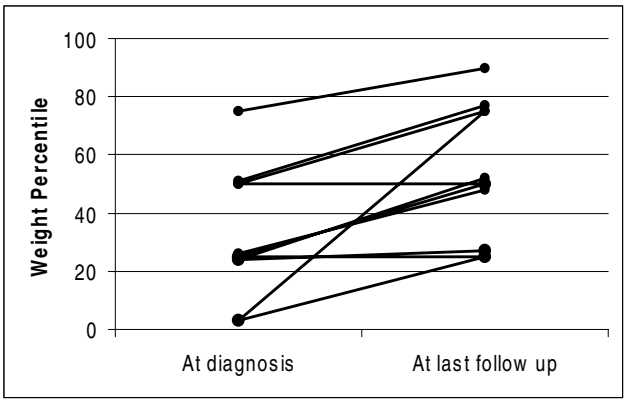

Figure 1b Weight percentile of XLA patients pre and post infusion IVIG.

Recurrent respiratory tract infection was the most common documented infection in our patient cohort. In a study done in Chile involving 208 children with recurrent respiratory infections "recurrent pneumonia was found to be a warning manifestation for suspecting primary immunodeficiency".[9] Septicemia was documented in four of our eleven patients with gram-negative bacteria isolated in three out of the four episodes (Table 2a). In France, pseudomonas septicemia with ecthyma gangrenosum led to the diagnosis of XLA in two previously healthy boys.[10] Two patients in our series had swelling of the large joints accompanied by a history of recurrent respiratory tract infection as a presenting manifestation. They were initially diagnosed as septic arthritis, though eventually investigation of their immunologic status led to the diagnosis of XLA.[11] Patients with rheumatologic diseases should have their serum immunoglobulins investigated as hypogammaglobulinaemia can present as rheumatologic disease. On examination of these patients, one will notice that despite the frequency of infections, peripheral lymphoid tissue is absent to hypoplastic (e.g. tonsils). Diagnosis of XLA depends on documenting the low to absent serum immunoglobulins with absence of B cells in the peripheral blood.[12] The T-cell mediated immunity assessment is normal. After diagnosis, monthly IVIG replacement is indicated with intermittent antibiotic prophylaxis for some patients with respiratory infective symptoms and signs despite adequate IVIG replacement. Early treatment of acute infections with antibiotics is essential to minimize complications.

The recurrent infections in XLA patients may adversely affect their weight and height. The impact on growth retardation was reflected by the mild to moderate wasting and stunting in some of our patients prior to their diagnosis of XLA and the significant improvement in growth subsequent to regular IVIG replacement. It is likely that the reduction in infectious episodes is one of the factors which led to improvement in growth of these children after IVIG replacement (Figures 1a & 1b).

In our patient cohort they had 31 infections per 100 PM before IVIG compared to 7.6 infections per 100 PM after IVIG replacement. The reduction was mainly in the respiratory infections and deep infections such as arthritis and septicaemia, while mucosal infections such as gastrointestinal infections remained similar before and after IVIG replacement. In a long-term follow-up study of 29 children in Germany, they received IVIG for 25 years and those receiving IVIG greater than 400 mg/kg every three weeks showed a significant decrease in the incidence of pneumonia and the number of days spent in the hospital compared to those receiving 300 mg/kg IVIG per infusion.[13] Another study at an even higher dose of 800 mg/kg in children every 4 weeks significantly reduced the number and duration of infections with the trough levels of serum IgG increasing significantly.[14]

Our patients were maintained on a median dose of 700 mg/kg IVIG at 4 weekly intervals. Despite this dosage of IVIG infusion with adequate pre-infusion IVIG levels within the reference range for age, bronchiectasis still developed in three of eleven patients. A series of 22 patients in Finland treated with IVIG showed that pulmonary abnormalities still developed in some patients, and the abnormalities were asymptomatic despite adequate levels of immunoglobulins being maintained.[15] So it seems

necessary to maintain trough IgG level near the upper normal limit for better treatment outcome. Whether an early diagnosis and prompt treatment may play a role in limiting the disease complications is still unclear, though all our three patients with bronchiectasis were diagnosed late. Despite bronchiectasis in the three patients, all are at present asymptomatic and can maintain a relatively normal activity level. Most of them enjoy normal school life and the eldest in our series is already working. However, it is noted that the two most common causes of death in XLA patients are chronic pulmonary disease with resultant cardiac failure and disseminated viral infections, e.g. enterovirus infections.[4]

In conclusion, XLA tends to be diagnosed late in Hong Kong and early diagnosis with IVIG replacement could put the child back to normal growth and decrease the frequency of infections. General paediatricians should send for quantitation of serum immunoglobulins if a patient has more than one severe infection, especially in a male with encapsulated bacterial infection. Whether early diagnosis followed by IVIG replacement will translate into long term benefit of minimizing bronchiectasis can only be confirmed by a large scale study in the future.

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