X-linked Agammaglobulinemia of incidental finding

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Abstract

X-linked agammagobulinemia (XLA) is a primary immunodeficiency disorder caused by a mutation in the Bruton Tyrosine Kinase (BTK). Usually, patients present severe infections before the age of 2, and require immunoglobulin replacement therapy during all their life. We present the case of a 16-years-old male for whom the diagnosis was incidental. He did not present any infection since childhood. At the age of 4, immunoglobulin assay was performed because he had recurrent fever episodes. A panhypogammaglobulinemia was identified, but the boy became asymptomatic and explorations were stopped. At the age of 16, the patient's parents suggested a control of the deficit which was confirmed. Genetic testing revealed a novel mutation on BTK, located in the pleckstrin homology domain [c.70A>C, p.(Asn24His)]. Initially, he received immunoglobulin substitution at the rate of one subcutaneous injection per week but stopped it after 2 years of treatment by immunoglobulin and continued to present no symptom. We thereafter report the case of an asymptomatic patient presenting a novel missense mutation of BTK. The patient doesn't have circulant B cell. He doesn't receive immunoglobulin substitution and doesn't present infectious diseases.

Introduction

Bruton's disease, also known as X-Linked Agammaglobulinemia (XLA) is a primary immunodeficiency disorder characterized by a blockade in the B-cell ontogenesis, first described in 1952 [1]. This disorder is linked to a mutation in the gene encoding the Bruton's Tyrosine Kinase (*BTK*). BTK is necessary to intramedullary B-cell lymphocytes' maturation. The result is the significant reduction in the concentration immunoglobulin serum [2].

The patients have increased sensibility to bacterial infections and also some parasitic (Giardia sp) and viral (enterovirus, astrovirus) infections. Initially, patients are protected by the maternal IgG immunoglobulin but more than 50% present severe infections before 2 years of age [3]. Recurrent otitis are the most common infectious site but 60% of patients are diagnosed following one severe infection such as pneumopathy, meningitis or arthritis. The most common germs are *Streptococcus pneumoniae* and *Haemophilus influenzae*.

In the literature, only few cases of late diagnosis of the disease were reported [4–8]. This article presents a case of an adolescent patient who presented no severe infection.

Case presentation

A 16-year-old man, from parents of French origin and not consanguineous, was presented in paediatric immunology consultation to control a hypogammaglobulinemia diagnosed during childhood. The immunoglobulin dosage was made because he presented recurrent and resistant warts at the age of 4 and recurrence at

the age of 15. This family history did not early death histories and these parents and this sister did not find severe infectin during their life.

Before the age of 4, he presented, few otitis (<5). These infections were not severe and only oral antibiotherapy was necessary for treatment. At the age of 4, the child had recurrent febrile syndrome without recovered etiology and an immunoglobulin dosage was made. The dosage found a global deficit of immunoglobulin, predominantly on IgM (Table 1).

Between 4 and 15 years old, the patient had only one ethmoiditis at the age of 5. The ethmoiditis was no complicated and healed with oral antiobiotherapy and without sequelae. He had a good height-to-weight and he did not present with severe infection. At the age of 15, he had a recurrence of warts on the feet. Before laser treatment, the patrician prescribed a new immune assessment. The immunoglobulin dosage found an immunoglobulin deficit predominantly on the IgM, with a moderate decrease of IgG and a normal rate of IgA (Table 2).

This family history did not find severe infection or early death histories. The lymphocyte population found normal lymphocyte T population (naive and memory) but absence of B cells (<1%) (Table2). Post-vaccination serologies were performed and were negative for *Streptococcus pneumoniae*(<3.33 mg/L) and *Haemophilus influenza type b*(<0.11mg/L) and positive but weak for tetanus (2.46 UI/mL, positive > 0.1 mg/L) and diphteria (1.12 UI/mL, positive > 0.1 UI/mL), antibody against *Hepatitis B* was weak. A cervico-thoraco-abdomino-pelvic scanner was then performed and did not find deep infectious focus or no pulmonary lymph nodes.

Diagnosis of XLA was confirmed by the *BTK* gene analysis that found a c.70A>C (p.Asn24His), which was considered as a novel mutation, with a deleterious effect on the protein.

Initially, the immunoglobulin substitution was introduced, sub-cutaneously. The IgG serum level was restored (Table 2). The treatment was well tolerated by the patient. After 23 months of immunoglobulin substitution, the patient decided to stop the treatment because he did not present any severe infectious and he would not continue the treatment because the patient did not consider himself sick. Actually, he doesn't receive any immunoglobulin substitution or prophylactic antibiotic therapy, and he did not present with any infectious disease. He conserved an absence of B cells (<1%) and a deficit of immunoglobulin, predominantly on IgM (Table 2)

Discussion

We present one original case of XLA which is diagnosed late in life and with a poor infectious story. The patient did not present any severe infections since the age of 6. He presented only with resistant warts, one non complicated ethmoiditis at the age of 4 and recurrent otitis during early childhood. The first immunoglobulin serum level revealed a global deficit. The patient presented also with recurrent fever episodes which lead to search for the possible diagnosis of Marshall syndrome. But the patient did not present the criteria of Marshall Syndrome.

The diagnosis of XLA was incidentally made. The patient came in the immunology consultation not because he presented signs of infection but because his parents asked for a control of the immunoglobulin serum level. The control showed a persistent deficit on IgG and IgM, but the IgA level was normal. The clinical presentation and the immunology test evoked XLA. The genetic test revealed a novel missens mutation on the*BTK* gene (c.70A>C), [p.(Asn24His)]. This mutation in on the pleckstrin homology (PH) domain, located near the N-terminus, and implicated in phospholipids' membrane interactions. The bioinformatics analysis software SIFT (deleterious, score: 0) and Polyphen-2 (probably damaging, score: 0.999) suggested a deleterious effect, by comparing with the reference sequence (NM_000061.2). This mutation probably generates a deleterious effect on the protein and can cause XLA. The patient was thus diagnosed with Bruton's disease in accordance with the diagnostic criteria of the European Society of Immunodeficiency Disease [9]. The genetic research was performed both to his mother and sister, both being conductive. This diagnosis caused his' mother anxiety and guilt while the patient remains asymptomatic.

The patient conserved a persistent IgA serum level. Other XLA patients with normal IgA serum level were described in the literature[10,11]. A recent study analysed 5 adults with delayed onset XLA [12] and compared these patients with a Mexican cohort of XLA's patients. The authors suggested that missense mutations in PH domain and Src homology 2 (SH2) domain are correlated with a late XLA phenotype. Many studies would establish a correlation between genotype and phenotype on XLA, but it is not explicit. In 2010, a study on 62 Chinese patients showed a correlation between genotype and disease onset and occurrence of severe infections [13]. Another study on 110 American studies showed that the mutation in Btk influences the severity of XLA. In fact, patients with amino acid substitution or substitution on high conserved consensus site are more likely to have a later diagnosis, more plasma IgM and higher percentages of B cells [14]. But the mutation in Btk is not enough to explain the variability of XLA. One study on 54 Spanish patients proved the correlation between the mutation in Btk and the age at diagnosis, the levels of IgG and IgA and the number of hospitalisations, but the severity of mutation did not explain the starting age of the disease [15]. Another study on 174 Chinese patients showed the correlation between the genotype and the age of onset but no with the severity of infections [16]. The severity of XLA could be explain by the severity of mutation in Btk but the heterogeneity of phenotype could be explain by another genetic or epigenetic factor.

In summary, we present an exceptional case of XLA of incidental finding. Actually, the patient doesn't present any infectious disease though having no circulating B-cells and a deficit both on IgG and IgM. The patient is not treated by immunoglobulin substitution anymore. He has a novel missense mutation on the PH domain that has not been previously described. We conclude that diagnosis of XLA can still be made after childhood with some patients remaining asymptomatic.

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Table 1 – Immunoglobulin serum levels according to the patient's age

	Before immunoglobulin replacement therapy	Before immunoglobulin replacement therapy	Before immunogl
	29/05/2002 (4 years old)	28/08/2014 (16 years old)	03/03/2015 (17 y
IgG (g/L)	4.47 (N: 4.8-9.0)	5.55 (N: 6.6-12.8)	5.40 (N: 6.6-12.8
IgM (g/L)	<0.14 (N: 0.41-1.41)	<0.07 (N:0.7-3.4)	<0.05 (N:0.7-3.4
IgA (g/L)	0.40 (N: 0.54-1.53)	1.15 (N: 0.5-2.1)	1.08 (N: 0.5-2.1)

Table 2 – Lymphocyte counts and dosage of sub-class immunoglobulin

	At diagnosis (17 year-old)	At 20 year-old	1 year from the end of treatment	Reference range
Lymphocyte Population	% (G/L)	% (G/L)	% (G/L)	Reference range (%)[18,19]
Total lymphocytes	44.4 (3.91)	43.7 (4.651)	39.4 (5.049)	5-15
Lymphocytes T				
CD3 +	93 (3.77)	94.3 (4.38)	94.0 (4.746)	56-84
CD3+ CD4+	43.5 (1.58)	45.8 (2.13)	44.6 (2.251)	31-52
CD3+ CD8+	42 (1.525)	41.4 (1.92)	38.5 (1.942)	18-35
Index CD4/CD8	1.04	1.11	1.16	0.6-3.9
Lymphocytes B				
CD19+	0.24 (0.009)	0.49 (0.023)	0.24 (0.012)	6.5-24.0
CD20+	0.33 (0.012)			
CD19+ CD27+	0.08 (0.003)	0.19 (0.009)	0.12 (0.006)	7.0-29.0
CD19+ CD5+	0.04 (0.001)	0.05 (0.002)	0.02 (0.001)	
Lymphocytes Natural Killer				
CD3- CD16+ CD56+	5.8 (0.211)	4..85 (0.2 3)	3.92 (0.198)	3-22

	At diagnosis (17 year-old)	At 20 year-old	1 year from the end of treatment	Reference range
Immunoglobulin	g/L	g/L	g/L	Reference range (g/L)[20]
IgG	4.93	6.10	7.07	6.6-12.8
IgA	1.05	1.51	2.52	0.5-2.1
IgM	0.04	0.18	<0.17	0.7-3.4
Sub-class Immunoglobulin				
IgG1	2.54	2.81	3.56	3.7-9.1
IgG2	1.71	2.20	2.52	1.1-4.85
IgG3	0.55	0.70	0.93	0.24-1.16
IgG4	0.57	0.56	0.069	0.052-1.961

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