

demonstrated by TDI-induced reverse cross-species passive cutaneous anaphylaxis.

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X-linked agammaglobulinemia presenting as transient hypogammaglobulinemia of infancy

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X-linked agammaglobulinemia (XLA) is an X-linked recessive severe life-threatening disease characterized by the absence of B lymphocytes, total absence or severe deficiency of all immunoglobulin classes, and recurrent bacterial infections with pyogenic pathogens.¹ It has recently been associated with mutations and deletions in a gene encoding for a cytoplasmic tyrosine kinase (Bruton's tyrosine kinase [BTK]).² Typically, XLA can be differentiated from transient hypogammaglobulinemia of infancy (THI); the latter is characterized by low levels of immunoglobulin with intact antibody responses, normal lymph tissue and B-cell numbers, and milder infectious problems. It is often difficult to clinically differentiate XLA from common variable immunodeficiency disease (CVID), a heterogeneous group of disorders char-

Abbreviations used

BTK:	Bruton's tyrosine kinase
CVID:	Common variable immunodeficiency disease
THI:	Transient hypogammaglobulinemia of infancy
XLA:	X-linked agammaglobulinemia

acterized by variable mild, moderate, or severe deficiencies in IgG, IgA, and IgM and recurrent bacterial infections. In CVID, B-cell numbers are characteristically normal. Classification of XLA and CVID is based on major differences in the severity of the depression of immunoglobulin levels. In this report we present a patient with the phenotype of THI who was later thought to have CVID and was eventually found to have XLA on the basis of a mutation in the *BTK* gene. This patient thus represents an example of the extreme variation that can occur in XLA phenotype.

METHODS

Blood was obtained for immunologic and genetic analyses. Immunoglobulin levels were measured by ra-

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TABLE I. Immunologic parameters

	Initial presentation (1978-1979)	Reevaluation (1989-1990)
IgG	↓ 316 (553-971 mg/ml)	590 ↓ (750-2000 mg/ml)
IgA	↓ 15 (26-74 mg/ml)	94 (52-192 mg/ml)
IgM	↓ 13 (35-81 mg/ml)	18 ↓ (60-238 mg/ml)
IgE	ND	233 (3.6-437 mg/ml)
Tetanus Ab	0.078→2.8 (0.10 IU/ml)	0.05→0.05 (0.10 IU/ml)
Diphtheria Ab	0.0059→0.75 (0.1 IU/ml)	0.09→0.08 (0.01 IU/ml)
Pneumococcal Ab	ND	ND→1/12 (>200 ng/ml Ab)
<i>H. influenzae</i> Ab	ND	0.18→0.13 (>0.2 mg/ml)
Isoagglutinins*	Absent	anti A <1:2 (1:4-1:32) anti B <1:2 (1:4-1:32)
T lymphocyte	47%/6012 cells/m ³ † (46% to 70%)	85%‡ (63% to 85%)
B lymphocyte	10%/1279 cells/m ³ † (8.9% to 15.6%)	<1%‡ (7% to 19%)

Values in parentheses are normal levels; values in the Ab section are before to after (pre→post) vaccination.

Ab, Antibody; ND, not done.

*O⁺ blood type.

†E. rosette.

‡Monoclonal antibody.

dial immunodiffusion, IgE by radioimmunoassay and lymphocyte subsets by staining with monoclonal antibodies and analyses by means of flow cytometry.³ Specific antibody titers were performed by reference laboratories with conventional technology. Analysis of the gene encoding for *BTK* was performed as previously described.⁴

CASE REPORT

A 16-year-old boy had recurrent upper respiratory tract infections at 13 months of age and was diagnosed with THI at another institution on the basis of low immunoglobulin levels, normal diphtheria and tetanus antibody responses, normal anterior and posterior cervical nodes, normal tonsillar tissue, and normal numbers of B cells in the blood (Table I). IgA levels returned to normal at 15 months of age (42 mg/ml) and remained within normal limits over the next 12 months, and IgG and IgM levels remained relatively unchanged. The patient underwent adenoidectomy because of recurrent otitis media and evidence of adenoidal hypertrophy at the age of 5 years. At the time of surgery, his adenoids were recorded as being markedly enlarged. The patient continued to experience recurrent episodes of upper respiratory tract infections, sinusitis, and pneumonia, which were treated with oral antibiotics. At age 10 he was seen by an immunologist and began receiving intravenous gammaglobulin, which resulted in cessation of the infections. Details of this evaluation are not available. One year later, he was referred to our department. Intravenous gammaglobulin was discontinued for 4 months, and the patient was then reevaluated (Table I). He was found to have mildly depressed levels of IgG, normal IgA, and markedly diminished IgM. Vaccination responses to diphtheria, tetanus, pneumococcal, and

Haemophilus influenzae (polysaccharide) vaccines were absent; and peripheral B cells could not be demonstrated (Table I). Bone marrow samples revealed CD19 of 4%, CD20 of 4%, and CD21 of less than 1%. In light of his poor antibody responses, absence of B cells, clinical history, and previous evaluations, he was tentatively diagnosed with atypical common variable immunodeficiency and treated with intravenous gammaglobulin (600 mg/kg), which resulted in marked symptomatic improvement. Because of the persistent absence of peripheral B cells, the patient's RNA and DNA were analyzed for missense mutations (and deletions) in the *BTK* gene. Deletions of nucleotides corresponding to positions 1699-1763 of the *BTK* gene⁴ produced a splice junction defect, which resulted in the complete deletion of exon 16. A mutation-specific analysis with DNA from the patient's mother confirmed her carrier status.

DISCUSSION

In this report we present a patient with genetically documented XLA who phenotypically presented with THI at 13 months of age. Both his clinical and laboratory findings were consistent with THI.

The large dichotomy between the classic presentation of XLA and this patient's clinical and laboratory findings is extremely important. Patients with XLA usually have no circulating B cells, although in several cases, which were not genetically confirmed, normal numbers of B cells were exhibited.⁵ To our knowledge, no case of genetically documented XLA has been reported with

normal peripheral B-cell numbers associated with normal antibody responses. With the exception of low isoagglutinins, this patient's humoral immune system was intact initially and underwent a slow but progressive deterioration. It seems likely that different mutations in the *BTK* gene result in physicochemical differences in the enzyme, which account for variability in the time of onset, clinical severity, and different laboratory parameters⁴; however, with the exception of certain premature termination mutations, no consistent genotype-phenotype correlations can be identified. The variable expression of *BTK* deficiency reflects the complexities of development of the B-cell compartment and role of compensating mechanisms in humoral immunity. Bruton's original patient with XLA was noted to have adenoidal and tonsillar tissue similar to that of this patient, and Bruton's patient should be studied once again with definitive molecular methods, such as those used in this case, to determine whether that patient had CVID or XLA.

Patients with varying degrees of immunoglobulin deficiencies will require intensive investigation at the genetic level to distinguish accurately be-

tween clinical syndromes that, in the past, have been diagnosed on a phenotypic basis. In addition, investigations in this area will undoubtedly help to elucidate the complex interactions that are responsible for the development, maintenance, and function of the B-cell system.

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Elevated serum tryptase in exercise-induced anaphylaxis

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Exercise-induced anaphylaxis (EIA) is a unique medical emergency in that it derives from a physical allergy.¹⁻³ Sheffer et al.² believe EIA to be distinct from asthma, cholinergic urticaria, and angioedema, which can occur in some individuals who exercise. Several studies have suggested the role of mast cells in this disease^{3,4} as judged by biopsy and plasma histamine studies.

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Abbreviation used

EIA: Exercise-induced anaphylaxis

The opportunity to evaluate a young man with EIA in whom striking elevation of serum tryptase was demonstrated during an acute episode recently arose and is described below.

CASE REPORT

K.Z., an 18-year-old male high school football player was seen in consultation; he was complaining of acute skin rashes and hives associated with exercise. He also stated that he could at times experience wheezing and