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DECLINE OF ANTIBODIES IN XLA INFANT: WHEN TO START IVIG

I. U. Okocha, C. G. Hanson, J. Chinen, and W. T. Shearer*

*Baylor College of Medicine and Texas Children's Hospital, Department of Pediatrics, Allergy and Immunology Section, Houston, TX, USA

Summary Statement

Maternal antibody levels in XLA neonates may predict when to start replacement IgG.

Keywords

IVIG; Loss of maternal antibodies in neonates; X-linked agammaglobulinemia

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Patients with X-linked agammaglobulinemia (XLA) are protected for the first few months of life by maternal antibody, which is actively transported across the placenta during the last months of pregnancy¹. Patients do not typically present clinically with infection until after 6 months of age, when the infant's maternally-derived antibody level approaches zero². After diagnosis, treatment includes replacement intravenous immunoglobulin (IVIG), which significantly reduces the risk of infection³.

The rate of decline for specific maternal antibody loss has not been well studied in XLA patients that are followed from birth, even in patients with a positive family history. Information on the decline of specific maternal antibodies may be important in deciding when to start immunoglobulin replacement in these cases, apart from just knowing the serum IgG level.

We had the unusual opportunity to study specific maternal antibody decay in a full term (39 week gestation) male infant with a BTK mutation (161delG) diagnosed prenatally with a frameshift with amino acid changes in codons 54 and 55 and a termination codon in position 56. The baby's serum IgG level was within normal limits for age at birth: 890 mg/dL (Table1). When the child was brought to Texas Children's Hospital at 2 months of age, his IgG level had dropped to 393 mg/dL (normal), and his IgA and IgM levels were detectable. As measured at 2 months of life, the patient had serological evidence of transplacental specific maternal antibody with wide diversity to diphtheria toxoid: 0.57 IU/mL (>0.1 IU/mL protective), tetanus toxoid: 2.15 IU/mL (>0.1 IU/mL protective), *Haemophilus influenzae* type b: 1.3 µg/mL (>1.0 µg/mL protective), and 1/4 positive serotypes of pneumococcus tested in the mother two months post-partum (serotype 7F:4.21 µg/mL, >1.3 µg/mL protective (Table 1). Values of optimal protective levels of these antibodies were assumed from information given by the testing laboratories and clinical experience.

Corresponding Author William T. Shearer, M.D., Ph.D. Allergy and Immunology, Texas Children's Hospital, 1102 Bates Avenue, Suite 330, Houston, TX 77030-2399, Telephone: 011 (832) 824-1274, Fax: 011 (832) 825-7131, wtshearer@texaschildrens.org.

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Lymphocyte phenotyping performed at 2 months of age confirmed the expected results: absent B cells (0.2% CD20+ cells, 6 CD20+cells/ μ L (as compared to normal ranges 6-28%, 256-1579 cells/ μ L). Lymphocyte proliferation studies with mitogens and antigens were normal (data not shown).

At 3 months of age, the baby's serum IgG level dropped to 254 mg/dL (normal) and his specific antibody levels decreased: diphtheria toxoid titer to 0.2 IU/mL (protective), tetanus toxoid titer to 0.4 IU/mL (protective), and *H influenzae* type b to 0.43 μ g/mL (not protective (Table 1)). One pneumococcal serotype antibody level remained protective. IVIG replacement therapy (400 mg/kg) was begun after blood for antibody titers had been obtained and was given monthly thereafter. The child responded to the IVIG infusion with progressive increases in total IgG and many of his specific antibodies showed progressive increases in titer.

This opportunity to study serum IgG and specific antibody decline in an infant with known XLA has been instructive. That is, although serum IgG levels may be used as a surrogate marker for the infant's protection, measurements of specific antibody levels appear more sensitive. A case in point is the fall in this patient's anti-*H. Influenzae* type b antibody level to a less than protective level at 3 months of age, a time in which the serum IgG level was normal. These observations are in agreement with those of other investigators who studied vertical transmission rate of several of the same antibodies in non-immunized/non-relevant antigen-immunized controls at birth and their persistence at 2 months of age of the infant^{5, 6}.

Thus, in addition to serum IgG levels in XLA infants, measurement of specific antibody levels may prove helpful in deciding when to begin IgG replacement in XLA infants.

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Abbreviations

BTK	Bruton's tyrosine kinase
IgG	Immunoglobulin G
IVIG	intravenous immunoglobulin
XLA	X-linked agammaglobulinemia

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