

Received Date : 18-Sep-2015

Revised Date : 07-Jan-2016

Accepted Date : 01-Feb-2016

Article type : Letter to the Editor

Clues to management of neonatally-diagnosed BTK deficiency

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To the Editor:

We present a full term male infant born at 39 weeks of gestation (birth weight 3.230 Kg) who was neonatally diagnosed as X-linked agammaglobulinemia (XLA) on the basis of familial history (an 11-year-old brother and his healthy mother carrying the truncating p.K18fsX23 mutation in the *BTK* gene) and a positive *BTK* genetic analysis performed during the first week of life.

No incidents were reported during pregnancy or labour. The first immunological examinations carried out on the 2nd day of life revealed normal lymphocyte count (3200 lymphocytes/mm³; normal range 3000-7600 lymphocytes/mm³) and absence of circulating B lymphocytes (0% lymphocytes in patient, normal range 700-1000 B lymphocytes/mm³). The immunoglobulin levels are presented in Table 1. From birth the breastfed patient was closely followed up and remained asymptomatic until the present. The evolution of different immunological parameters was monitored from

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12549

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birth, including serum immunoglobulin levels (immunoturbidimetry, ABBOT laboratories) and several specific antibodies: diphtheria toxoid (Diphtheria IgG ELISA; Sekisui VIROTECH, protective values ≥ 0.1 IU/mL), tetanus toxoid (Tetanus IgG testkit ELISA; VIROTECH; protective values ≥ 0.1 IU/mL), varicella (ELFA, Sistema vidas, BioMérieux; Cut-off > 0.9) and pneumococcus (ELIZEN, Pneumococcus IgG Immunopotency level; ZEN TECH, protective values >250 U/L). At the age of two months, serum IgG level remained within the normal range for age, while specific antibodies against varicella, diphtheria and *S. pneumoniae* were no longer protective. The patient then started immunoglobulin replacement therapy (IRT) (dose 500 mg/kg q4w), showing good tolerance. The evolution of total IgG serum level and specific antibodies under IRT confirmed correct protection. The evolution of total and specific patient immunoglobulins as well as that of the mother at the time of birth is summarized in **Table 1**.

Major efforts are currently underway to develop effective methods for neonatal detection of the most severe primary immunodeficiencies (PID), since their early diagnosis and treatment are essential to improve the prognosis and patient quality of life [1]. In this sense, newborn screening programs for PID using Guthrie blood samples are being carried out for severe T and B lymphopenias by quantifying T-cell receptor excision circles (TRECs) and *kappa*-deleting recombination excision circles (KRECs), respectively [1,2]. Nevertheless, currently no consensus exists regarding the optimal screening technique (TRECs/KRECs/ACTB multiplex-PCR or tandem mass spectrometry), the advantages/drawbacks of including KREC determinations and the best cut-offs for TRECs/KRECs for each technique [2]. It is expected that in the near

future neonatal diagnosis of severe PID, including XLA, will be more common. In the meantime, guidelines concerning its management are needed.

Patients with XLA are theoretically protected during the first few months of life by maternal IgG antibodies, which are actively transported across the placenta during the third trimester of pregnancy; they do not present life threatening-infections until the age of 6 months or older, when their maternally-derived IgG levels approach zero [3]. The results shown here, which have been pooled with the only previously reported neonatally-diagnosed XLA patient in whom the level of immunoglobulins was monitored during the first months of life [3] (**Figure 1**), may shed light on the clinical management of these patients. One of the main questions to address is determining when IRT should be started. As is shown in **Figure 1**, the IgG serum level of the two neonatally-diagnosed XLA patients does not show the theoretically expected decline for an IgG half-life of 23 days [4]. This finding is not surprising given that marked differences between the expected and the real decline of antibody titers in healthy newborns have previously been described. The observed variability of postnatal decline of maternal antibodies has been attributed to different factors, including the catabolism of antibodies and the expansion of the volume occupied by the plasma and extravascular proteins during the growth of infants, which would vary considerably from child to child [5]. In our patient, as well as in the XLA patient reported by Okocha et al. [3], the level of total IgG remained in the normal range for two months of age, although the level of specific antibodies of some preventable diseases dropped below protective levels, with the consequent risk of infection for the patient. The protective antibody concentrations are well established for a number of vaccine-preventable diseases, including tetanus, diphtheria and pneumococcus [6]. Considering these results, the decision to start IRT should take into

account the patient's level of specific maternal antibodies as well as measurement of total IgG serum level. The evolution of specific antibody titers observed in both our case and the previously reported case lends weight to the suggestion to start IRT in patients with XLA at the age of two months.

The previous observations regarding the natural evolution of maternally-derived specific antibodies in patients with XLA raise the question of the role of maternal immunization status. In the patient here described, at the time of delivery his mother had no protective serum levels of antibodies against *St. pneumoniae*, a potentially serious infection in newborn infants. If this information had been available beforehand, it might have been decided to vaccinate the mother during pregnancy to increase the active transplacental transfer of specific antibodies and consequently improve the baby's protection. The effectiveness of maternal antibodies (natural or after vaccination) in protecting neonates and infants against some infectious diseases has been demonstrated, with some of the most impressive examples being the protection of children from the influenza virus [7] and respiratory syncytial virus (RSV) [8]. In fact, vaccination of pregnant women for vaccine-preventable diseases carries a potential benefit for both mothers and newborns [9], and the World Health Organization (WHO) recommends tetanus and influenza vaccination during pregnancy. Nevertheless, it must also be considered that the level of specific antibodies and the duration of the protection they offer is not consistent and may differ depending on the disease in question, as shown in studies of Parainfluenza type 3 virus [5], Hepatitis A virus and Varicella Zoster Virus [10]. Taking this into account, the decision to start immunoglobulin replacement based only on the specific antibody levels could be controversial since starting early treatment would offer better protection to the newborn. In the particular scenario of

families with PID, there are currently no specific recommendations regarding the advisability of vaccination of pregnant women when there is suspicion that the future baby might be affected with a PID.

In conclusion, we present the case of a neonatally-diagnosed XLA patient in whom total and specific IgG levels were monitored to improve knowledge of the condition's natural course. The results obtained are similar to the only previously reported neonatally-diagnosed XLA patient with IgG monitoring. These results should contribute to the decisions to be taken with regards to the treatment and management of future patients with XLA diagnosed at birth through the implementation of newborn screening programs for B-cell deficiencies.

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Financial support:

This study was supported by Fondo de Investigacion Sanitaria (FIS, project number PI12/01990 and PI15/01094 to LA).

Disclosure Statement: LA received a research grant from CSL Behring to perform the specific antibody responses pre- and post-Privigen 10% immunoglobulin replacement therapy.

Conflict of Interest Statement: All authors have no conflict of interest relevant to this article to disclose.

Table

Table 1. Evolution of levels of total IgG and specific antibodies.

Age at sample collection	Mother	Patient					
	38 yrs	2 days	10 days	1.5 mo	2 mo	3 mo*	5 mo*
Total IgG (mg/L)	1056	974	756	495	387	555	906
Anti-VZV antibody	pos		pos	neg	neg	pos	pos
Anti-tetanus toxoid antibody (IU/mL)	0.69			0.27	0.24	0.39	2.1
Anti-diphtheria toxoid antibody (IU/mL)	0.49			0.13	neg	0.57	0.64
Anti-pneumococcal antibody (U/L)	232			160	26	310	> 1100

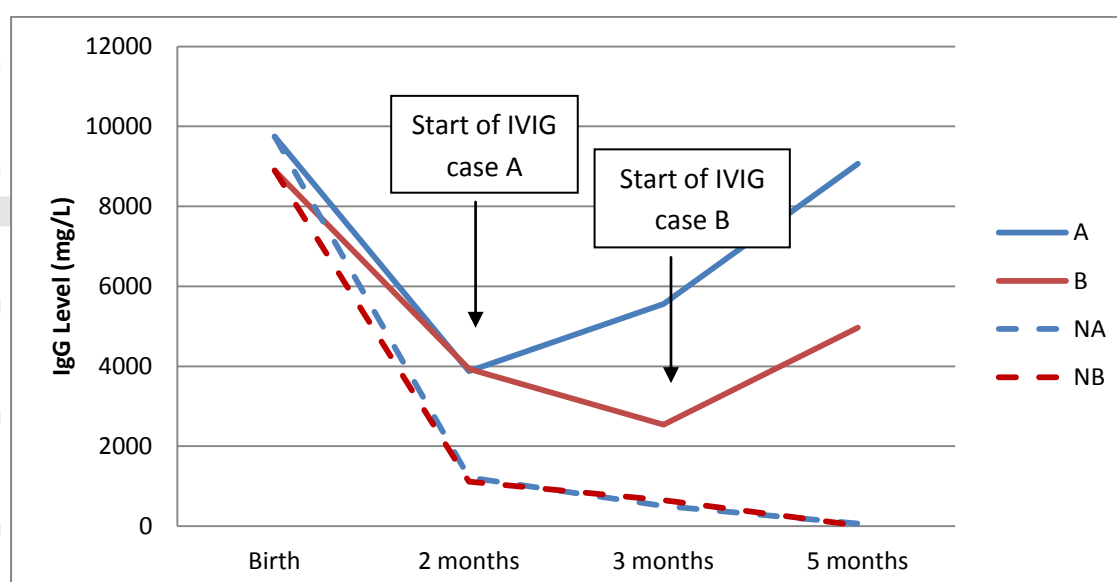
*Start of intravenous immunoglobulin

Abbreviations: pos: positive; neg: negative; VZV: Varicella Zoster Virus; yrs: years; mo: months old.

Specific Antibody Protective levels: anti-tetanus toxoid antibody: ≥ 0.1 IU/mL; anti-diphtheria toxoid antibody: ≥ 0.1 IU/mL; anti-pneumococcal antibody >250 U/L.

Figure

Figure 1. Evolution of newborn IgG levels (our case (A) and case of Okocha et al. (B)) compared with normal expected decline (half-life of 23 days).



A: Our case. B: Okocha et al. case; NA: normal expected decline in index case; NB: normal expected decline in Okocha et al. case. IVIG: intravenous immunoglobulin.