

## CLINICAL CASE

# Evolution of IgA deficiency to IgG subclass deficiency and common variable immunodeficiency

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### SUMMARY

First report: male child with repeated pulmonary infections from the age of 4 months. He was diagnosed as IgA deficiency (undetectable IgA levels) at the age of 3 years, when he presented repeated bouts of pneumonia and tonsillitis. Several immunologic evaluations were made between the ages of 4 months and 8 years. At 8 years and 9 months, the diagnosis of IgA deficiency was confirmed, and associated IgG2 and IgG4 deficiency (29.0 mg/dl y 0.01 mg/dl) with normal total IgG serum level was found. With the administration of intravenous gammaglobulin, the lung infections remitted and the subsequent clinical course has been uneventful up to now.

Second report: a boy with repeated infections since the age of 2 months. IgA deficiency was diagnosed at 1 year 7 months (undetectable serum IgA levels). At age 5½ years, his clinical course worsened and more serious infections appeared. A new immunologic study revealed IgA deficiency associated with CD4 cell deficiency (432 cells/mm<sup>3</sup>) and normal CD3, CD19, and CD8 levels. Despite intensive antibiotic treatment and care, the child died. The findings suggest an association of IgA deficiency and common variable immunodeficiency.

**Key words:** IgA deficiency. IgG2 and IgG4 subclass deficiency. Common variable immunodeficiency.

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### INTRODUCTION

IgA deficiency is the most common congenital immunodeficiency in humans. IgA serum levels under 5 mg/dl are diagnostic of IgA deficiency and levels under 20 mg/dl are diagnostic of partial deficiency (1).

The prevalence of IgA deficiency is estimated at 1:500 to 1:700 caucasian children (2). In the United States of America, the estimated prevalence in the general population ranges from 1:310 to 1:2171 (3). South American authors report a prevalence of IgA deficiency of 1:985 in blood donors and pregnant women (4).

IgA deficiency generally is considered a non-serious condition requiring only normal pediatric care.

### CASE REPORTS

PL, a 10-year-old male, had repeated episodes of diarrhea and upper respiratory infections since the age of 4 months, when total IgA deficiency (IgA under 5 mg/dl) was diagnosed. At the age of 3 years he had sporadic pneumonia and repeated bouts of tonsillitis. At 6 years, immunologic studies showed IgA deficiency with otherwise normal findings. From the age of 6 to 8 years, his lung condition worsened and total IgG decreased, although it remained within normal limits. At 8 years, IgG2 (29.0 mg/dl) and IgG4 (0.01 mg/dl) deficiency was diagnosed. From then on he received monthly intravenous gammaglobulin (400 mg/kg/dose). Laboratory results are shown in table I. The lung infections remitted and the clinical course has been favorable. Results suggest an association of total IgA and IgG subclass deficiencies.

**Table I**  
**Serum concentrations of immune globulins (mg/dl) and their isotypes (mg/dl)**

Date	IgG	IgM	IgA	IgG1	IgG2	IgG3	IgG4
July 94	1800	230	Undetectable				
February 98	395	157	6.6	291.0	29.0	270.0	0.01

A male child, BOT, had repeated infections since the age of 2 months. At 1 year 7 months, total IgA deficiency (undetectable total IgA) was diagnosed. At 5 years, he had repeated episodes of infectious diarrhea and serious lung infections. A new immunologic study revealed a persistent decrease in CD4 cells (36%, 432 cells/mm<sup>3</sup>). The main laboratory results are shown in table II. The child died despite intensive antibiotic treatment and care. The findings suggest an association of IgA and common variable immunodeficiency.

## DISCUSSION

Most children with IgA deficiency are asymptomatic, usually being diagnosed in the course of family studies of symptomatic carriers. One third of carriers are symptomatic (4). The main symptoms are repeated upper respiratory infections, such as tonsillitis, sinusitis and otitis, as well as diarrhea. These patients often have Giardia infestation as well as atopic condition like allergic rhinoconjunctivitis and asthma. Cow milk allergy is common.

IgA is the principal mucous membrane immune globulin. Its synthesis by circulating blood plasmocytes is enhanced in the presence of antigens on the mucous membranes. Under these conditions, bursa-equivalent (B) lymphocytes proliferate and mature, showing an accentuated increase in the reticuloplasmatic complex. The plasmocyte is the end-stage of maturation. At this point, plasmocytes synthesize monomeric IgA and the polypeptide chain J, which enter the epithelial cell where the secretory

component is produced. Two IgA monomers are joined by the J chain while surrounded by the secretory component, thus stabilizing IgA against enzymatic action. At this stage, dimeric IgA secretion by the mucous membranes occurs. This immune globulin defends the mucous membranes, blocking microorganism attachment to the mucous membrane through its action on bacterial pili, antigen agglutination, neutralization of toxins, and antiviral action against poliomyelitis virus. In the presence of IgA deficiency, mucosal infections and antigen passage occur; antigens may act as allergens and cause atopy.

Until recently, this immune deficiency was called "selective IgA deficiency" because its course was believed to be stable and benign. However, in recent years more aggressive cases have been observed and the entity now is called "IgA deficiency" (5). Our first patient experienced a progressive series of immune deficiencies. At first he had bouts of tonsillitis, otitis and diarrhea, and laboratory studies indicated IgA deficiency. However, at the age of 3 years, he began to present repeated bouts of pneumonia and a decrease in total IgG in relation to age. IgG2 and IgG4 subclass deficiency appeared.

IgG isotypes are responsible for coating encapsulated bacteria like *Streptococcus pneumoniae* and *Haemophilus influenzae*, thus enabling phagocytosis (6). These bacteria are the main causal organisms of pneumonia in childhood, which explains why this infection occurs so frequently in IgG subclass deficiency.

Our second patient had IgA deficiency but at first was almost symptom-free. However, his rapid

**Table II**  
**Serum levels of immune globulins (mg/dl) and CD4 and CD8 cells (% and cells/mm<sup>3</sup>). Neutrophil chemotaxis and phagocytosis**

Date	IgG	IgM	IgA	CD4	CD8	Chemotaxis	Phagocytosis
July 95	2715	133	Undetectable	—	—	—	—
January 97	2066	126	11	45%, 2157	20%, 959	Null	Null
August 97	2289	73	Undetectable	—	—	—	—
November 97	2650	123	Undetectable	36%, 432	19%, 756	Null	Null

evolution after the age of 5 years to repeated bouts of pneumonia indicate IgG subclass deficiency. Even more serious infections appeared eventually, together with a decrease in CD4-positive cells, suggesting a common variable immune deficiency of fatal outcome.

Congenital common variable immune deficiency may manifest mainly as a humoral IgG-component deficiency or as a cellular CD4-cell deficiency. Its estimated prevalence is 1:50.000 to 1:200.000 in the general population. It is usually a serious disease, which can be confused with acquired human immune deficiency syndrome because of its tendency to produce inversion of the CD4/CD8 ratio and the severity of intercurrent infections (5).

Reports of associated deficiencies in IgA and IgG2 and IgG4 subclasses are rare in the literature. The association of IgA and common variable immune deficiency is even less common. Until 1996 this association had been described in only 32 families. Since then, there have been few reports of this association and all reported cases have occurred in patients over 16 (9, 10). We conclude that IgA deficiency is not always consistent in terms of the type of immune deficiency present. It is important to follow-up of children with IgA deficiency in order to detect and treat other immune deficiencies that may appear. Pediatricians' unawareness of the possibility of fatal cases of IgA deficiency probably is responsible for their failure to follow-up on patients, limiting care to the treatment of intercurrent infections. However, it should be remembered that IgA deficiency is the most frequent congenital immunodeficiency.

## RESUMEN

Primer reporte: varón con repetidas infecciones pulmonares a partir de los cuatro meses de edad, diagnosticado con deficiencia de IgA (niveles indetectables) a la edad de tres años cuando el niño tiene repetidos ataques de neumonía y tonsilitis. Varias evaluaciones inmunológicas fueron realizadas entre la edad de los cuatro meses y ocho años. Con ocho años y nueve meses se confirmó el diagnóstico de deficiencia de IgA, encontrándose asociación con déficit de IgG2 (29,0 mg/dl) y IgG4 (0,01 mg/dl) con normal IgG (395 mg/dl). Fue administrada gammaglobulina intravenosa con desaparición de las infecciones pulmonares y subsecuente mejora clínica.

Segundo reporte: un niño con repetidas infecciones desde los dos meses de edad. Con un año y siete meses fue diagnosticado de deficiencia de IgA (niveles indetectables). A los cinco años y medio de edad, el rumbo clínico empeoró y aparecieron serias infecciones. La nueva investigación inmunológica reveló IgA deficiente asociada con células CD4 deficientes ( $432 \text{ cels/mm}^3$ ) y niveles normales de CD3, CD8 y CD19. A pesar de tratamiento antibiótico y cuidados intensivos, el niño falleció. Estos datos sugieren la asociación entre deficiencia IgA e inmunodeficiencia variable común.

**Palabras clave:** IgA deficiencia. Déficit de subclases de IgG2 e IgG4. Inmunodeficiencia variable común.

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