Rev Inst Nal Enf Resp Mex
Volumen 21 - número 4
Octubre-Diciembre 2008
Páginas: 288-291

Caso Clínico

A teenager with recurrent respiratory infections and difficult-to-treat allergies

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Trabajo recibido: 22-IX-2008; aceptado: 16-XII-2008
Conflicto de intereses: Ninguno

ABSTRACT

This journal section begins with a case vignette highlighting a clinical immunology problem, from patients seen at the National Institute of Respiratory Diseases. A discussion of the disease and its management then follows. This time we present the case of a male teenager with a long history of respiratory allergies and recurrent respiratory infections, and the development of bronchiectases. As it turned out, the patient had an IgG subclass deficiency, which could explain both his recurrent complicated respiratory infections and a failure to respond to sublingual immunotherapy for his allergies.

Key words: Primary immunodeficiencies, IgG subclass deficiency, immunoglobulins.
Palabras clave: Inmunodeficiencia primaria, deficiencia de subclases de IgG, inmunoglobulinas.

RESUMEN

Esta sección de la Revista comienza con una viñeta que destaca un problema inmunológico clínico de pacientes vistos en el Instituto Nacional de Enfermedades Respiratorias. Le sigue una discusión de la enfermedad y su manejo. Esta vez presentamos el caso de un adolescente varón con una historia larga de alergias respiratorias e infecciones respiratorias recurrentes, con el desarrollo de bronquiectasias. Se detectó una deficiencia de subclases de IgG, lo que podría explicar, tanto las infecciones respiratorias complicadas y recurrentes de este paciente, como su incapacidad para responder a la inmunoterapia sublingual que se administró para sus alergias.

THE PATIENT

A 12-year-old boy was referred to our center with bronchiectases and a serum IgE level greater than 2,000 UI/mL, to complete an evaluation for allergic rhinitis, asthma refractory to treatment, and frequent respiratory infections.

His family history was noncontributory. He had an elder brother in apparent good health. Immunizations were up to date.

When he was 5 years old he started suffering from persistent sneezing, itchy watery eyes and throat, and a runny nose, as well as cough spells with dyspnea and audible wheezing. He also had frequent upper and lower respiratory tract infections. At that time, a skin prick test was positive for house dust mite, and he was treated as an outpatient with a long-acting bronchodilator, and nasal and inhaled steroids. A trial of sublingual immunotherapy was given for 1.5 years, with no response.

His allergy symptoms showed partial improvement, but he continued having recurrent respiratory infections and a chronic cough.

THE WORKUP

When he was twelve, he was referred to the Clinical Immunology department, and was found

Table I. Report of patient's immunoglobulin serum levels (major isotypes).

IgG	1,040 mg/dL
IgA	143 mg/dL
IgM	93 mg/dL
IgE	2,000 UI/mL

Table II. Report of patient's total IgG and subclasses.

IgG	1,150 mg/dL
IgG1	655 mg/dL
IgG2	287 mg/dL
IgG3	90 mg/dL
IgG4	< 1 mg/dL

to have a serum IgE level of greater than 2,000 UI/mL. A chest CT scan showed overdistended lungs with small, isolated, bilateral, cylindrical bronchiectases.

On physical examination, he had Dennie-Morgan creases in both lower eyelids, with normal conjunctivae; a wet, pale and boggy nasal mucous membrane, and bilateral hypertrophic occlusive turbinates; transparent rhinorrea, a retronasal drip, and no auscultatory findings in his chest.

A skin prick test was performed, with a positive reaction to house dust mite and cat epithelium allergens. Serum IgM antibodies to *Aspergillus* were mildly positive (1:4). A complete blood count showed mild leukocytosis with neutrophilia. His serum IgG levels were normal, and so were IgA and IgM (Table I). Serum complement levels were also within normal range. IgG subclasses were requested, which reported undetectable IgG4 (Tables II and III).

THE DIAGNOSIS

IgG subclass deficiency (isolated IgG4 deficiency)

Immunodeficiency diseases are commonly classified into disorders that affect one or more of the four mayor limbs of the immune system: humoral immunity, cell mediated immunity, phagocytes and complement.

B cell (humoral) immunity is mediated by immunoglobulins, and they consist of five major classes or isotypes: IgG, IgA, IgM, IgE and IgD. The most abundant immunoglobulin class is IgG.

IgG is further subdivided into four subclasses: IgG1, IgG2, IgG3 and IgG4, which differ in the structure of their heavy chains and in their roles. IgG1 through 4 respectively constitute 65, 25, 7, and 3% of the total serum IgG.

IgG deficiencies may occur as isolated deficiencies or in association with deficiencies of other immunoglobulin types; IgG subclass deficiencies may be observed even when the total IgG concentration is normal.

IgG plays an important role in host defense against infection, protecting tissues from bacteria, viruses and toxins. Different subclasses of IgG neutralize bacterial toxins, activate complement and enhance phagocytosis by opsonization.

Only IgG1 and IgG3 effectively fix complement, and they generally provide the response to protein antigens (T-cell dependent) from bacteria, viruses, vaccines and food. IgG2 antibodies are directed predominantly against carbohydrate antigens (T-cell independent), and are thus important in protection against encapsulated organisms. The role of IgG4 is controversial. It is produced in re-

Table III. IgG subclasses (1 through 4) normal serum levels.

Age (years)	IgG1 (mg/dL)	IgG2 (mg/dL)	IgG3 (mg/dL)	IgG4 (mg/dL)
0–1	190–620	30–140	9–62	8–63
1–2	230–710	30–170	11–98	4–43
2–3	280–830	40–240	6–130	3–120
3–6	350–810	50–310	9–160	5–180
> 6	270–1,740	30–630	13-320	11–620

sponse to repeated antigenic stimulation, and it has been suggested to act as a blocking antibody in parasitic and allergic diseases.

IgG1 deficiencies often result in a decreased level of total IgG, it is often associated with recurrent infections, and might occur in combination with deficiencies of other IgG subclasses.

In about half of all IgG subclass deficiencies, the IgG2 concentrations are decreased. An isolated IgG2 deficiency is associated with a decreased response to infections with encapsulated bacteria; these patients present with recurrent respiratory tract infections caused by pneumococci or *Hemophilus influenza* type B. IgG2 deficiency is often associated with otitis media and sinusitis; an association with ataxia-telangiectasia (AT) and systemic lupus erythematosus (SLE) has also been reported. Low concentrations of IgG2 often occur in association with a deficiency in IgG4 and IgA.

IgG3 deficiency has been linked with a history of recurrent respiratory infections, leading to chronic lung disease. Decreased IgG3 levels are frequently associated with IgG1 deficiency.

Several studies have shown that a large number of patients with recurrent respiratory tract infections have low IgG4 concentrations, although low IgG4 is also detected in a substantial percentage of healthy children.

In allergy to many different allergens, some allergen-specific IgG antibodies are of the IgG4 subclass, and their levels increase during desensitization therapy. The use of IgG4 antibody assays to monitor immunotherapy is thus justifiable; if no IgG4 antibody is induced by conventional immunotherapy, the therapy is likely to have been ineffective. An immunotherapy may be considered effective if a substantial increase (10 to 100 fold) in allergen-specific IgG4 is induced.

Patients with recurrent infections by encapsulated bacteria often show decreased levels of IgG2 and IgG4. Recurrent respiratory infections with bronchiectases are often associated with decreased levels of IgG3 and IgG4.

In which patients should we measure IgG subclasses levels?

- Several specific infections, such as meningitis caused by pneumococci, *Hemophilus influenzae* and meningococci, as well as osteomyelitis and severe pneumonia.
- Recurrent purulent infections of the upper and lower respiratory tract.
- Bronchiectases and/or purulent infections of unclear etiology.
- IgA deficiency associated with infectious disease.

Table IV. Summary for IgG subclass isolated deficiency.

Category:	Humoral primary immunodeficiency
Prevalence:	Unknown, probably common (1:500) and under-recognized. 3:1 male predominance in children, IgG2 deficiency most common; reversed after puberty for a predominance of females with IgG3 deficiency. Often associated with IgA deficiency.
Key features:	Frequent respiratory infections (otitis media, sinusitis, and bronchopulmonary). Lack of response to immunotherapy for allergies. May also be asymptomatic (detected in healthy blood donors).
Defect:	Defective isotype switch, presumably due to a regulatory defect of immunoglobulin gene expression in B-cells, and/or abnormal interaction with T-cells.
Heritability:	Autosomal dominant pattern, unconfirmed. May be transient in children.
Invading pathogens:	Viruses, bacteria and parasites. Encapsulated bacteria.
Treatment:	Monthly endovenous or subcutaneous gammaglobulin to prevent infection recurrence. Antibiotics to treat acute infections. Conjugated vaccines to enhance protection against encapsulated bacteria.

Treatment of such patients will generally consist of antimicrobial therapy, immunoglobulin replacement and vaccines (Table IV).

CONCLUDING REMARKS

Deficiencies of individual subclasses of IgG were first described more than 40 years ago, but their exact prevalence and clinical significance are still unclear. The quality of an immunoglobulin is probably as important as its quantity, and thus functional antibody assays may constitute a better assessment of immunocompetence.

In daily clinical practice, the detection of IgG subclasses is an expensive test, and is rarely of any help to change a diagnosis or decide a treatment, so that most authors do not recommend it as a routine screening aid. Here we show a case from a tertiary center, in which an IgG4 isolated deficiency seems to be the only explanation for a long history of respiratory infections, and a lack of response to sublingual immunotherapy. The patient was started on monthly endovenous immunoglobulin replacement, after which the number and intensity of infections have decreased, without further complications or any adverse effect.

FURTHER READINGS

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In memoriam
Dr. Eduardo Jeresel Rivera Montuy
(1956-2008)

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*Editor

El pasado diciembre de 2008 falleció el Dr. Eduardo Jeresel Rivera Montuy, quien fuera miembro del Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas desde 1988. El Dr. Rivera Montuy hizo la carrera de Medicina Interna en la Unidad de Medicina Interna del IMSS. En nuestro Instituto desempeñó su especialidad, tanto como consultor en los diferentes servicios clínicos como en la consulta externa.

Su principal contribución a la Medicina, sin duda, la seguiremos observando en las aportaciones que hizo en la docencia y en sus aportaciones clínicas en el área respiratoria de nuestro Instituto.