

## IgG2 IMMUNODEFICIENCY

### ASSOCIATION TO PEDIATRIC PATIENTS WITH BACTERIAL MENINGOENCEPHALITIS

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**ABSTRACT-** An IgG subclass deficiency is often associated with bacterial infections. We studied four pediatric patients suffering from meningoencephalitis, two of them due to *Streptococcus pneumoniae* and two due to *Haemophilus influenzae* type b. Simultaneous diagnostic serum and cerebrospinal fluid samples were taken during income. The four subclasses of IgG and albumin were quantified in both biologic fluids by radial immunodiffusion. Very low levels of seric IgG2 with non detectable cerebrospinal fluid IgG2 were found in the patients. No intrathecal IgG subclass synthesis was found in two patients. One patient with *S. pneumoniae* had IgG3 intrathecal synthesis. Intrathecal IgG1, IgG3 and IgG4 synthesis was found in one patient suffering from *H. influenzae* according with reibergrams. Substitutive therapy with intravenous gammaglobulin was given to the patients as part of the treatment.

**KEY WORDS:** IgG subclass, IgG2 deficiency, albumin, cerebrospinal fluid, serum, meningitis.

#### **Inmunodeficiencia de IgG2: asociación en pacientes pediátricos con meningoencefalitis bacterianas**

**RESUMEN** – Las deficiencias por subclases de IgG se asocian frecuentemente con infecciones de origen bacteriano. Se estudian cuatro pacientes en edad pediátrica con meningoencefalitis, dos de ellos a *Streptococcus pneumoniae* y dos a *Haemophilus influenzae* tipo b. Se toman muestras simultáneas diagnósticas de suero y líquido cefalorraquídeo en el momento del ingreso. Se cuantificaron las cuatro subclases de IgG y albúmina en ambos líquidos biológicos por inmunodifusión radial. Se encontró que los pacientes presentaban cifras muy disminuidas de IgG2 sérico y ningún exhibía IgG2 en el líquido cefalorraquídeo. Dos pacientes no sintetizaron ninguna subclase de IgG intratecalmente. Un paciente con *S. pneumoniae* sintetizó IgG3 intratecal. Uno de los pacientes con meningoencefalitis a *H. influenzae* sintetizó IgG1, IgG3 e IgG4 intratecalmente de acuerdo com el reibergrama. Estos pacientes recibieron terapia substitutiva com gammaglobulina intravenosa como parte de la medicación.

**PALABRAS-CLAVE:** IgG subclase, IgG2 deficiencia, albúmina, líquido cefalorraquídeo, suero, meningoencefalitis.

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An IgG subclass deficiency is frequently associated with bacterial infections. The most common identified selective antibody deficiency is an impaired response to polysaccharide antigens such as those present in capsule of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b<sup>1,2</sup>. Since IgG2 is the predominant antibody produced in response to some polysaccharide antigens it is possible that patients with decreased IgG2 levels may have an impaired response to infections with encapsulated bacteria<sup>3,4</sup>.

Herein we present data from two pediatric patients suffering from meningoencephalitis due to *Streptococcus pneumoniae* and two from meningoencephalitis due to *Haemophilus influenzae* type b with IgG2 deficiency.

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## PATIENTS

Case 1. Patient aged 31 days had vomiting, irritability, fever, anorexia and bulging fontanelle with several hours from the beginning of these clinical manifestations at admission. The diagnostic lumbar puncture indicated a purulent cerebrospinal fluid (CSF) with granulocyte predominance. CSF microbiological culture demonstrated *Streptococcus pneumoniae*. As part of the treatment, knowing the IgG2 deficit, intravenous gammaglobulin was used.

Case 2. Patient 3 months old with fever, irritability, anorexia and bulging fontanelle at admission. Signs of meningeal inflammation began several hours before his income. CSF demonstrated high cell content, granulocytes predominantly. Once IgG2 deficit was detected, intravenous gammaglobulin was employed with the antibiotic treatment. A *Streptococcus pneumoniae* was isolated from the diagnostic CSF sample by culture.

Case 3. Patient aged 1 year old with fever, photophobia, confusion, vomiting, and seizures difficult to control. The diagnostic lumbar puncture revealed a purulent CSF with granulocytes predominance. He had a previous history of otitis media and recurrent pneumonia. The lumbar puncture was performed within the first two hours from the beginning of the seizures. Intravenous gammaglobulin therapy was used jointly with antibiotics and other drugs employed. An *Haemophilus influenzae* strain was isolated from CSF culture.

Case 4. Patient 3 years old with clinical manifestations like fever, headache and nuchal rigidity. The patient had a previous history of mastoiditis, pneumonia and other infectious disorders. The lumbar puncture was performed several hours before the installation of the first clinical manifestations. The causative agent was *Haemophilus influenzae* according to CSF culture. Intravenous gammaglobulin therapy was employed with antibiotic therapy.

The isolation and characterization of bacteria was performed in the Microbiology Department of the Hospital Pediátrico San Miguel and confirmed in the Hygiene and Epidemiology Division's Provincial Microbiology Laboratory.

## METHOD

Simultaneous diagnostic CSF and serum samples were obtained from the patients during their income under standard conditions. CSF samples had no blood contamination.

Albumin was quantified in serum by NOR Partigen immunoplates and CSF albumin by LC Partigen immunoplates (Dade Behring, Marburg, Germany).

IgG subclasses levels in serum were performed by BINARID LL-radial immunodiffusion plates and in CSF with NANORID radial immunodiffusion plates (The Binding Site, Birmingham, USA).

The analysis of the results was performed by the Neuroimmunolab program<sup>5</sup>.

Immunoglobulin G subclasses intrathecal synthesis was calculated by the improved hyperbolic function<sup>6</sup>. For graphical representation the reibergrams were applied<sup>7</sup>.

## RESULTS

Individual values of IgG subclasses and albumin in serum and CSF of each patient suffering from meningoencephalitis (Table 1) demonstrate very low levels of IgG2 in these patients.

Figure 1 presents reibergrams for each IgG subclass. The hyperbolic line (heaviest) represent the limit between IgG subclass blood-derived from local synthesis in CSF. The point above it shows the IgG1+3+4 intrathecal synthesis of one patient with Hemophilus influenzae meningoencephalitis. The other cases do not exhibit IgG subclasses intrathecal synthesis. Notice that IgG2 reibergrams are not plotted because there is no detectable IgG2 in CSF's patients and  $Q \text{ IgG2} = \text{CSF IgG2} / \text{serum IgG2} = 0$ .

All patients showed CSF-blood dysfunction with  $Q_{alb} > 5 \times 10^{-3}$ .

Table 1. Individual values of albumin and IgG subclasses in CSF and serum (g/L), and ratio quotients (Q).

Patient	Albumin	IgG1	IgG2	IgG3	IgG4
CSF					
1	0.88	0.011	0	0.01	0.0025
2	0.264	0.007	0	0.0048	0.0011
3	0.226	0.016	0	0.0308	0.00172
4	0.227	0.0101	0	0.00031	0.0001
Serum					
1	77.18	2.5	0.00050	1.06	0.09
2	37.10	2.26	0.00053	1.07	0.58
3	42.46	1.16	0.00064	0.32	0.4
4	26.0	3.9	0.00075	0.134	0.031
Ratio quotients					
	Q Alb	Q IgG1	Q IgG2	Q IgG3	Q IgG4
1	11.40	4.4	0	9.34	4.32
2	7.11	3.09	0	4.48	1.91
3	5.32	13.79	0	96.25	4.32
4	8.73	2.58	0	2.31	3.22

## DISCUSSION

It is well known that the finding of a decreased level of one of the IgG subclasses can never provide a definitive diagnosis but should rather be considered as an indication of a disturb of the immune system, requiring further diagnostic investigations. These patients had a previous history with chronic and recurrent infections like sinusitis and otitis. This seems to be a signal to take into account when patients have an actual meningoencephalitis with normal total IgG in serum<sup>8</sup>

Our patients had a selective deficiency of IgG2 with normal or high levels of the other IgG subclasses. Only the Patient 1 had a slight decrease of IgG1 level. To quantify IgG2 in serum it was necessary to employ the special plate used to perform CSF IgG subclass determination.

An isolated IgG2 deficiency is associated like in our cases with decreased response to infection with encapsulated bacteria<sup>3,9</sup>. In humans, IgG2 antibodies have been found to play a key role in immunity against infections with encapsulated bacteria. This defense does not only depend upon complement activation since IgG2 has a poor complement-activating activity. It has been shown that phagocytosis by neutrophil granulocytes is the major underlying mechanism.

The CSF/serum concentration quotient of albumin (Qalb) represents the best variable to characterize the individual blood-CSF barrier function and to detect a blood-CSF barrier dysfunction. The high specificity and sensitivity of the albumin quotient, Qalb, for the blood-CSF function reflects the origin of CSF albumin exclusively from blood and the fact that the CSF albumin / serum albumin quotient value is independent of the individual variations of the albumin concentration in blood. To be taken into account, however, are the age-related variations of the reference range. The evaluation of Qalb should replace total protein for characterization of the blood/CSF barrier function, because variations of total protein are greater than albumin in all concentration ranges<sup>6</sup>.

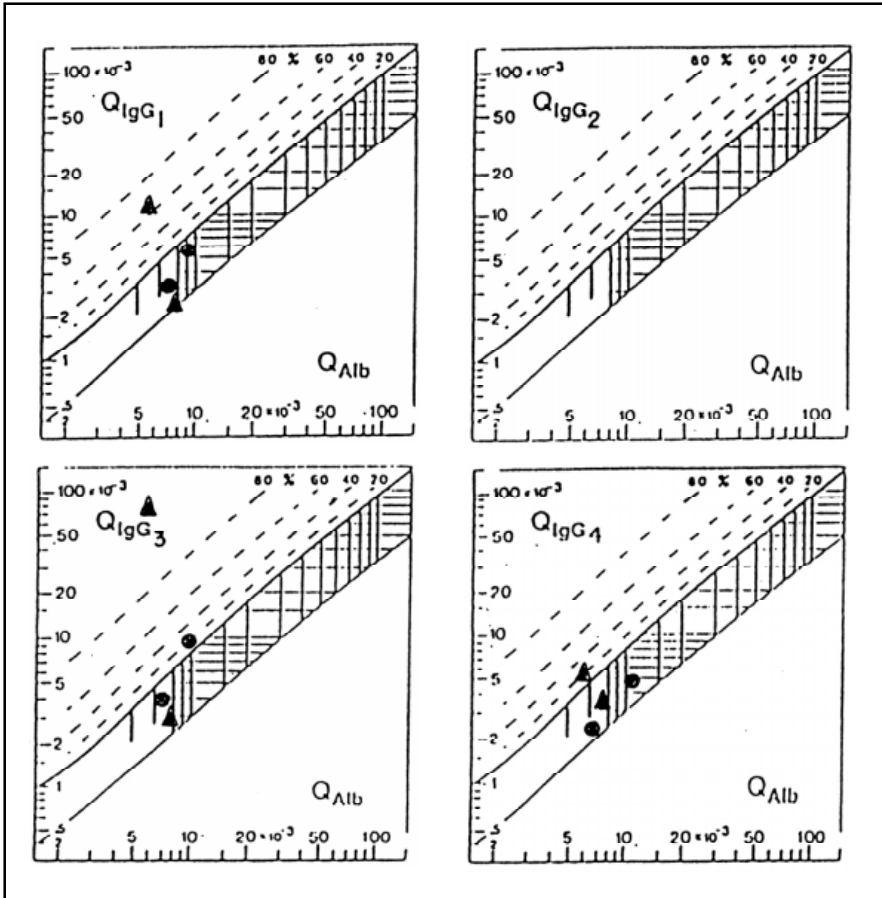


Fig 1. IgG subclass reibergrams. The upper hyperbolic curves (thick lines) represent the discrimination lines between brain-derived and blood-derived IgG subclass fractions. Values above these upper discrimination lines represent intrathecal IgG subclass synthesis. The dashes lines indicate the extent of intrathecal synthesis as intrathecal fractions in percent of total CSF concentration of the immunoglobulin. The limit of the reference range for  $Q_{Alb}$  between normal and increased CSF protein concentration (blood-CSF barrier dysfunction) is indicated by the age-dependent vertical lines at  $Q_{Alb}=5 \times 10^{-3}$  (up to 15 years); at  $Q_{Alb}=6.5 \times 10^{-3}$  (up to 40 years); at  $Q_{Alb}=8 \times 10^{-3}$  (up to 60 years). The black points represent the data from the patients suffering from *S. pneumoniae* infection and the black triangles the data from the ones with *H. influenzae*. Notice that Patient 3 has IgG 1+3+4 intrathecal synthesis.

The main signs in CSF of an acute, active disease in central nervous system are the increased CSF cell count and an increased  $Q_{Alb}$ , i.e. reduced CSF turnover. The increased  $Q_{Alb}$  is typical of bacterial meningoencephalitis. Each increased, age-related,  $Q_{Alb}$  value resembling mechanical and inflammatory restrictions of CSF-turnover, as well as hemorrhage. All our patients had dysfunction of the blood-CSF barrier ( $Q_{Alb} > 5 \times 10^{-3}$ ) according with age. The reibergrams or CSF/serum quotient diagrams with hyperbolic lines according to Reiber<sup>6,7</sup> allow to recognize the situation of blood-CSF barrier and the IgG subclass synthesis (or immunoglobulins synthesis) at the same time. It is the best way to analyse both clinical information, and it is widely recognized as a helpful tool for differential diagnosis of neurological diseases. The IgG subclass response is shown together with the blood-CSF barrier function in the reibergram. Representative patterns of humoral immune responses are

really quite typical for some diseases. The reliability of such patterns is generally best for the first diagnostic puncture. It is clear, however, that representative patterns are not found in all of patients with a given disease, even at a given stage of the disease.

Our patients have a common characteristic: they have an absence of IgG2 in CSF and a very low quantity in serum. The older patients have a previous history of recurrent bacterial infections typically found in such immunodeficiencies.

Looking at the synthesis of IgG subclasses in an early diagnostic lumbar puncture is quite often to observe that there is IgG synthesis in bacterial meningitis<sup>10</sup>. CSF IgG2 was not possible to measure with this technique. Perhaps with an ELISA according with its sensitivity it would be possible to find IgG2 but anyway the intrathecal synthesis would be very unusual in our patients with this clinical picture and their background.

Other major immunoglobulins like IgA and IgM could be quantified in serum and CSF and their patterns of intrathecal synthesis may help in the diagnosis. For instance, the intrathecal IgA response at time of first diagnostic puncture typically indicates a bacterial origin of the disease<sup>11</sup>.

Herein we only present the results of the first diagnostic lumbar puncture that was performed few hours after clinical manifestations.

A patient with *H. influenzae* infection had IgG1+3+4 intrathecal synthesis during the first diagnostic lumbar puncture and a patient with *S. pneumoniae* had IgG3 intrathecal synthesis. It would be possible to think that the lumbar puncture was performed with delay or, like these ones, in dependence of the biological agent and age, an early IgG subclass synthesis in children would be produced<sup>12,13</sup>.

Substitutive therapy with intravenous gammaglobulin were received by the patients as part of the treatment. In patients with primary specific immunodeficiency who have significantly diminished serum IgG levels, intravenous immunoglobulins replacement therapy is currently most frequent used, since administration of immunoglobulins may reduce the incidence of bacterial and viral infections and patients with selective IgG subclass deficiency may benefit from IgG replacement<sup>14</sup>.

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