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Immune compromise in patients with Down syndrome. A case series

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ABSTRACT

Down syndrome, or trisomy 21, has a higher mortality than the general population, mainly due to respiratory tract infections. The objective of this study was to describe immune compromise in a series of cases of patients with Down syndrome referred to the Pediatric Immunology Section due to recurrent infections or pathological laboratory findings between 6/1/2016 and 5/31/2022.

Here we describe immune compromise in 24 patients. Twelve patients failed to develop a polysaccharide response and received antibiotic chemoprophylaxis, or gamma globulin replacement therapy. Three patients developed agammaglobulinemia with presence of B cells and gamma globulin replacement therapy was indicated. Nine patients had T-cell lymphopenia and 1 patient, combined immune compromise.

Keywords: *Down syndrome; trisomy 21; immune system diseases; recurrent infections; hypogammaglobulinemia.*

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INTRODUCTION

Down syndrome (DS) is related to trisomy of chromosome 21 and has an estimated prevalence of 1 in 1000 live births.[1] It is the most frequent viable chromosomal disorder among live newborns.[1,2] It is characterized by intellectual disability and particular phenotypic features. DS is associated with congenital heart disease, obesity, leukemia, autoimmune diseases (celiac disease, hypothyroidism, and type I diabetes mellitus), and Alzheimer's disease.[2] Life expectancy currently reaches 50–60 years of age.[3]

Morbidity and mortality are greatly increased due to respiratory tract infections. Non-immune causes include anatomical abnormalities of the airways, congenital alterations of the ear canal, gastroesophageal reflux, and nasopharyngeal aspiration.[4] The immune causes that increase such susceptibility include the following: hypogammaglobulinemia of isotypes A and M, of immunoglobulin G subclasses (IgG2, IgG4), decreased antibody response to vaccines, decreased proliferation of B cells, decreased number of total and memory B cells, decreased neutrophil chemotaxis, decreased absolute number of NK cells.[5–10] The factors that may contribute to immune dysregulation and the subsequent autoimmunity are impaired central tolerance, thymic abnormalities, and defects in thymocyte development, particularly in regulatory T cells.[11]

However, immunity is not always assessed in these patients.[12] The objective of this study was to assess immune compromise in patients with DS referred to the Department of Immunology of our hospital.

POPULATION AND METHODS

Here we describe a case series of all patients with DS and immune compromise seen at the Pediatric Immunology Section of Hospital Italiano de Buenos Aires between 6/1/2016 and 5/31/2022.

Clinical presentation, lab tests and blood count, immunoglobulin determination by nephelometry, antibody response by ELISA, and lymphocyte phenotype by flow cytometry were assessed. The patients were referred due to infections or the finding of a pathological lab result (hypogammaglobulinemia or mild leukopenia). The infections were recurrent, severe, long-term, or with poor response to standard treatments. They presented with complicated pneumonia requiring hospitalization or viral pneumonia or bronchiolitis, or suppurative otitis.

Compromised cellular immunity was established quantitatively based on the value of CD3, CD4 and CD8 T lymphocytes. Collected data were compared to the tables of normal values for age.[13]

Compromised humoral immunity was determined based on immunoglobulin values (IgG, IgA and IgM), and hypogammaglobulinemia was defined as values below 2 standard deviations for age. It was also determined qualitatively, evaluating the specific response to different protein antigens: antibodies against tetanus toxoid, hepatitis B (in children under 12 months of age who received more than 2 doses of vaccine), hepatitis A, measles, rubella, varicella (in children older than 12 months of age).

The response to polysaccharide antigens was assessed with global pneumococcal antibody titers pre- and post-immunization 6 weeks after administration of the unconjugated 23-valent pneumococcal vaccine. A value ≥ 113 mg/L was considered an adequate response.[14] Regarding the response to polysaccharide antigens, 2 groups were analyzed: patients between 2 and 4 years old and patients older than 4 years old. In the first group, a second dose of unconjugated vaccine was indicated after 4 years old and the response was reassessed. Definitive failed response to polysaccharides was defined as failure to respond only in patients older than 4 years. In both groups, failed response was defined both when they did not show an initial response with an appropriate level of pneumococcal antibodies and when such response was not maintained at 6 months.

Ethical considerations

This protocol was drafted and carried out in accordance with current national and international standards: the World Medical Association's Declaration of Helsinki, the Guidelines for Good Clinical Practice ICH E6, Resolution 1480/11 by the Argentine Ministry of Health, and Law 3301/09 by the City of Buenos Aires. Maximum patient protection was warranted. The protocol was submitted to and approved by the Committee of Evaluation for Research Projects of Hospital Italiano de Buenos Aires under no. 6218 PRIISA no. 5881.

RESULTS

A total of 30 patients with DS and suspected immune compromise were referred. Six patients with a normal immunological assessment

were excluded. A total of 24 patients were analyzed. Their median age at the time of the first consultation was 2 years and 3 months (2 months to 17 years). Seventeen patients were referred due to infections and 7, due to pathological laboratory findings, 1 of whom developed pneumonia during follow-up. In relation to the 17 patients who presented with infections, their median age at onset was 6 months (1 month to 9 years) and at the time of the first consultation, 2 years and 9 months. The median length of follow-up was 2 years and 5 months (minimum: 1 month and maximum: 6 years and 10 months).

T-cell lymphopenia was observed in 9 of 24 patients (37.5%, 95% confidence interval [CI]: 18.8–59.4) and CD4 lymphopenia, in 3 of 24 patients (12.5%, 95% CI: 2.7–32.4). Agammaglobulinemia with presence of B cells was observed in 3 of 24 patients (12.5%, 95% CI: 2.7–32.4). One patient (4.2%, 95% CI: 0.1–21.1) had reduced IgM and IgA values for age. B-cell lymphopenia was observed in 15 of 24 patients (62.5%, 95% CI: 40.6–81.2). Also, in 1 of 24 patients (4.2%, 95% CI: 0.1–21.1), combined immune compromise was detected: absolute T-cell lymphopenia and agammaglobulinemia of the 3 isotypes (*Table 1*). An adequate response to protein antigens was noted in the 24 patients assessed (95% CI: 85.8–100). Regarding the response to polysaccharide antigens, 2 groups were analyzed: patients between 2 and 4 years old and patients older than 4 years old. In the first group, 6 of 9 patients (66.7%, 95% CI: 30–92) had a failed response.

Table 1. Lab results

	Age (years)	TOTAL LYMPHOCYTES (/mm³)	CD3 N/mm³ (%)	CD4 N/mm³ (%)	CD8 N/mm³ (%)	CD19 N/mm³ (%)	IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)	Response to polysaccharide antigens
1	9	3648	3090 (84)	**659 (18)**	2311 (62)	**69 (1,9)**	1310	160	**40**	**FRP**
2	4	2548	2142 (84)	1224 (48)	841 (33)	239 (9)	851	**43**	**33**	**FRP**
3	0.5	3607	2240 (61)	1600 (44)	557 (15)	1039 (28)	792	22	34	**FRP**
4	1	**1248**	**831 (67)**	**522 (42)**	**217 (17)**	200 (16)	1130	58	66	**FRP**
6	17	4958	3294 (66)	1182 (24)	2091 (42)	**53 (1,4)**	2110	388	96	**FRP**
7	1	2508	**832 (33)**	**588 (23)**	**251 (10)**	925 (37)	1200	60	172	**FRP**
8	0.5	2880	2168 (73)	1448 (49)	700 (24)	709 (24)	**<200**	**9**	**14**	NP
9	1	2765	1554 (55)	**761 (27)**	724 (26)	454 (16)	814	195	121	**FRP**
10	8	**1440**	**1165 (75)**	**591 (38)**	**566 (36)**	140 (9)	1440	108	99	NP
11	0.16	NP	2903 (60)	1790 (37)	983 (20)	**290 (6)**	**<200**	**<6**	**<25**	NP
12	3.75	2984	2330 (78)	**538 (18)**	1734 (58)	**29 (1)**	752	143	99	**FRP**
13	4	2444	1397 (81)	NP	726 (42)	**205 (11)**	1100	86	47	**FRP**
16	2.5	2178	1906 (86)	856 (39)	843 (38)	**173 (7,8)**	635	53	28	**FRP**
17	1.5	**2327**	**1045 (45)**	**796 (34)**	**209 (9)**	825 (35)	628	52	58	**FRP**
18	0.16	**2250**	**1130 (49)**	**609 (26)**	**520 (22)**	683 (30)	**<200**	**9**	**26**	**FRP**
20	0.5	2644	**1849 (69)**	**1187 (44)**	602 (22)	**109 (4)**	347	32	118	NP
21	0.25	3510	2876 (75)	2244 (58)	652 (17)	**190 (5)**	**<200**	19	65	NP
24	1.5	**932**	**405 (44)**	**189 (20)**	**158 (17)**	**301 (32)**	619	44	64	NP
25	16	**658**	**546 (82)**	**308 (46)**	**227 (34)**	**38 (5)**	1190	243	71	NP
26	8	6908	6800 (91)	1933 (26)	4758 (64)	**22 (0,3)**	610	104	31	NP
27	2	2320	1533 (65)	523 (22)	961 (41)	**147 (6)**	556	35	55	Normal
28	2.75	2077	1808 (87)	1066 (51)	645 (31)	**65 (3)**	506	66	27	Normal
29	14	**1081**	**641 (60)**	**300 (28)**	**324 (30)**	**50 (5)**	1080	159	94	NP
30	3	1884	1383 (74)	**196 (11)**	1119 (60)	**189 (10)**	848	111	85	Normal

The table details lab test results of the first immunological assessment and the response to polysaccharide antigens (after the administration of the 23-valent pneumococcal polysaccharide vaccine). Values in red correspond to altered values for age. FRP: failed response to polysaccharides; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; NP: not performed.

Among children older than 4 years, such failed response to polysaccharides was observed in 6 of 6 patients (95% CI: 54–100).

The 12 patients with failed response to polysaccharides received gamma globulin, preventive, or antibiotic therapy; the recurrence of infections reduced sharply. In the 4 asymptomatic patients referred due to laboratory findings, cellular compromise was noted, which was managed with chemoprophylaxis. It is worth mentioning a patient who had presented chylothorax as a complication of her heart disease; lymphopenia and hypogammaglobulinemia were corrected when she overcame this condition. However, she developed failed response to polysaccharides 2 years later.

DISCUSSION

Susceptibility to respiratory tract infections is increased in patients with DS. In patients with normal immunoglobulin levels, functionality should be assessed. This is done by measuring specific antibody titers against the antigens contained in the vaccines, e.g., IgG against tetanus toxoid, hepatitis B, measles, varicella, etc. Most vaccines have a protein antigen; the humoral immune response against these antigens develops early in life and this is the reason why these vaccines can be indicated from the first day of life. In contrast, the antibody response to polysaccharide antigens is independent from T cells and develops later. It is assessed by the response to the unconjugated pneumococcal vaccine. The unconjugated pneumococcal vaccine may be administered as of 2 years old, but a failed response is defined only as of 4 years old. Between 2 and 4 years of age, there may be an absence of adequate response due to immaturity. Therefore, when the response is low, a second dose is indicated after 4 years of age to define such humoral immune deficiency. The chemoprophylaxis indicated for failed response to polysaccharides is a daily dose of trimethoprim-sulfamethoxazole 3–5 mg/kg/day; if it does not work, gamma globulin replacement therapy should be indicated.

Patients with isolated cellular compromise received chemoprophylaxis for *Pneumocystis jirovecii* with trimethoprim-sulfamethoxazole 3–5 mg/kg/dose 3 times per week.

To conclude, our study describes humoral, cellular, or combined immune compromise in 24 patients with DS. Preventive treatment was indicated in 17 patients; a significant decrease in morbidity was observed, without hospitalization requirement after this intervention, which significantly improved the quality of life of these children and their families. Therefore, we reinforce the indication that patients with DS and recurrent infections or pathological laboratory findings should be referred to an immunologist, who will assess their immune compromise and eventually indicate a treatment in order to prevent infections. ■

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