Archives of Pediatrics
Melo KM, et al. Arch Pediatr 9: 316
www.doi.org/10.29011/2575-825X.100316
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Letter to Editor

Secondary Hypogammaglobulinemia in Children: Report of 20 Patients Under Immunoglobulin Therapy

Karina Mescouto de Melo[1*], Renata Portella Almeida Grattapaglia[2], Flaviane Rabelo Siqueira[1], Sheila Viviane Assunção Nóbrega[3], Cláudia França Cavalcante Valente[1], Fabíola Scancetti Tavares[4]

[1]Unit of Allergy and Immunology, Hospital da Criança de Brasília José Alencar, Brasília-Brazil

[2]School of health and medicine, Universidade Católica de Brasília, Brasília-Brazil

[3]Unit of pediatric nephrology, Hospital da Criança de Brasília José Alencar, Brasília-Brazil

[4]Unit of Allergy and Immunology, Hospital da Criança de Brasília José Alencar, Brasília-Brazil, Unit of child and adolescent, Hospital Universitário de Brasília (HUB), Brasília-Brazil

***Corresponding author:** Karina Mescouto de Melo, Unit of Allergy and Immunology, Hospital da Criança de Brasília José Alencar, AENW 3, Lote A - Brasília- Federal District / Brazil.

Citation: de Melo KM, Grattapaglia RPA, Siqueira FR, Nóbrega SVA, Valente CFC, et al. (2024) Secondary Hypogammaglobulinemia in Children: Report of 20 Patients Under Immunoglobulin Therapy. Arch Pediatr 9: 316. DOI: 10.29011/2575-825X.100316

Received Date: 11 July 2024; **Accepted Date:** 17 July2024; **Published Date:** 19 July 2024.

Keywords: Immunodeficiency; Hypogammaglobulinemia; Therapy; Immunoglobulin; Infection; Albumin.

To the Editor

Secondary hypogammaglobulinemia (SHG) represent an expanding field in clinical immunology, resulting from several conditions such as hematologic/oncologic diseases, autoimmune and neurologic diseases, as well as, use of immunosuppressive drugs (ISD), in particular B-cell–targeted therapy (BCTT) [1,2]. SHG may also result from renal or gastrointestinal immunoglobulin losses [3,4].

Immunoglobulin replacement therapy (IgRT) is the standard approach for primary immunodeficiencies, reducing infections, pulmonary sequelae and improving quality of life of patients [4,5]. On the other side, for SHG, efforts have been done to establish criteria for initiating IgRT, including clinical and laboratory parameters, such as serum immunoglobulin (Ig), response to vaccine antigens, prophylactic antibiotics and number of serious infections [2,6]. Most studies on SHG, include adult patients, with scarce data on pediatrics [7]. Here we describe data on number of infections, serum immunoglobulin (Ig) and albumin levels in children with SHG, pre and one-year-post IgRT. Concomitant use of ISD and continues antibiotics were also evaluated.

The study carried out enrolling children with SHG under regular IgRT, subcutaneous (SCIG) or intravenous (IVIG), over the period between 2014 and 2023 in a Brazilian children's hospital. The inclusion criteria were: (1) age from 1 month to 18 years at diagnosis; (2) baseline laboratory tests showing IgG levels below than 2 SDs for Brazilian age-reference values [8]; and (3) IgRT for at least 12 months. Patients with an underlying disease who presented with low IgG, due to a medication or non-primary immunodeficiency pathophysiology that causes low IgG production or increased IgG loss were defined as having SHG [2]. Pre-Ig was defined as the period between the first infection and IgRT initiation, and post-Ig assessment took place 12 months after initiation of IgG therapy. Patients were excluded if they lost the follow-up. The study was approved by the Institutional Ethics Committee and written consent was obtained from all legal caregivers. Data were collected from march-2022 to January-2023. Statistical analysis was performed using Graph Pad Prism v.10 ®. Shapiro-Wilk was used as normality test. Clinical and laboratory data pre versus post treatment were analyzed using Wilcoxon and McNemar-Bowker tests, respectively. For comparison between groups (prophylactic antibiotic, immunosuppressant and Ig route) the non-parametric Mann-Whitney U test was used. Statistical significance when p value < 0. 05.

The decision to initiate IgRT in the patients was based in previous guidelines approach for patients with antibody deficiencies [6,7]. In total 20 patients were evaluated and most of them were male (16; 80%). All patients had infection episodes previous to IgRT. SCIG route was predominant in the study group and, all patients received Ig in a hospital-day based regimen, once home-based SCIG infusion is not available for patients attended at health public institutions in our city (Table 1). Diagnosis of Nephrotic Syndrome (NS) (13; 65%) was predominant (Supplementary Table 1). Two patients had SHG related to ISD, rituximab to treat an autoimmune encephalitis, concomitant use of cyclophosphamide and corticosteroid because of ant neutrophil cytoplasmic antibody-positive pauci-immune glomerulonephritis (Table 1).

Epidemiological data	**N=20**
Male gender (n, %)	16 (80%)
Age at diagnosis of ID in months	48 (12-204)
Current age in years	6.5 (1-19)
Follow up in years	2 (1-5)
Diagnosis	
Nephrotic syndrome	13 (65%)
Acute Lymphocytic Leukemia	3 (15%)
Secondary to immunosuppression	2 (10%)
Intestinal lymphangiectasis	1 (5%)
Chronic kidney disease	1 (5%)
Immunoglobulin route	
Subcutaneous	16 (80%)
Intravenous	4 (20.0%)
Immunoglobulin dose mg/Kg/monthly	488 (210-666)
Patients taking Immunosuppressive medication	17 (85%)
Corticosteroids	13/17
Cyclosporine	10/17
Tacrolimus	4/17
Methotrexate	3/17
Cyclophosphamide	3 /17
Mycophenolate mophetil	2/17
Antibiotic prophylaxis	12 (60%)
IgG pre-IgRT (mg/dL)	64 (22-595)
IgG post-IgRT**** (mg/dL)	579 (53-1092)
Albumin pre-IgRT (g/dL)	2.3 (1.3-4.9)
Albumin post-IgRT** (g/dL)	4.0 (1.8-5.1)
CD19+ cells/μL at diagnosis	236 (0-3605)

Table 1: Clinical and laboratory data of children with secondary hypogammaglobulinemia under regular immunoglobulin therapy (n= 20); ID: Immunodeficiency. Values are expressed in median (range). Wilcoxon-test ** $p<0.01$, **** $p< 0.0001$.

Patients had significant improvement not only in serum IgG levels, but also in albumin after IgRT (Table 1; Figures 1A and 1B. One patient with NS did not have increment in IgG levels. In this particular case, frequent relapses in the study period was observed (IgG of 59.0 and 53.0 mg/dL pre and post IgRT, respectively). The annual number of infections/patients reduced from a median of 4.0 to 1.0, and from 2.4 to 1.0, for all infections and severe infections, respectively (p= 0.01; p= 0.02; Figures 1C and 1D). Patients with NS (n=13) were analyzed in a separate group and, although they presented with higher IgG and albumin levels post-IgRT, not differences were noted in the number of all infections (p=0.2) neither severe infections (p=0.4) (data not shown). Concomitant use of immunosuppressive medication and prophylactic antibiotic did not influence infection rate neither IgG or albumin levels in the study group (Figures 1A,1B and 1C, 1D)(Supplementary Table 2).

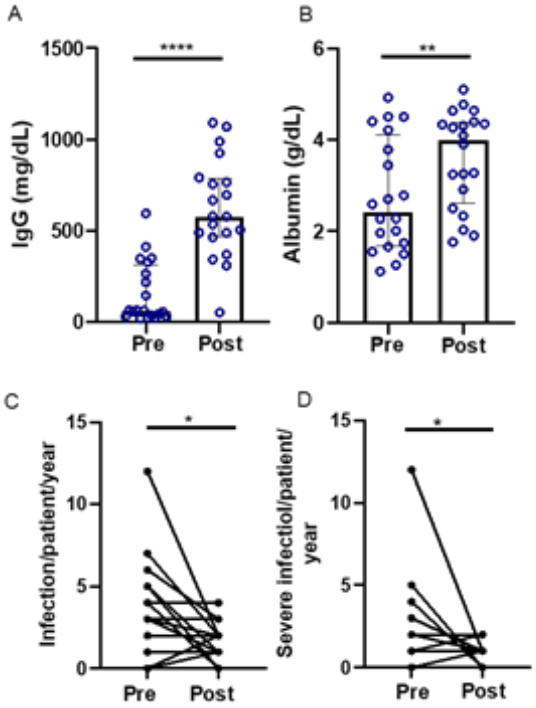

Figure 1: (1A) Serum IgG , (1B) serum albumin, (1C) and all infections, (1D) and severe infections, per patient per year before (pre-IgRT) and one year after initiation of immunoglobulin therapy (post-IGRT) in pediatric patients with secondary hypogammaglobulinemia (n=20). Wilcoxon-test. * p<0.05, ** p<0.01, **** p< 0.0001.

The increasing in serum IgG and albumin in the period post-IgRT, associated with reduction in frequencies of infections, show the benefits of therapy in the patients in a short period. It may lead to a better control of the underlying disease in a long-term treatment. In the present report more than half of patients had diagnosis of nephrotic syndrome (NS). It may represent a referral bias in our center, once hematological malignancies, neurological conditions, autoimmune diseases or immunosuppressive medications, such as rituximab (anti-CD20) are commonly described in other cohorts [2,8,9]. IgRT in patients with NS is still controversial [2]. Some recent works described that NS results from complex immune mechanism intrinsic, especially in cases of steroid-dependent/frequently relapsing nephrotic syndrome (SDNS/FRNS), as observed in our patients, once all of them were taking two or more ISD. Although there was an increase in IgG and albumin levels, we did not observe a reduction in the frequency of infection in the first year of IGRT in these patients. All children are still under follow-up at our institution and further studies, will give us more confident data about this specific group of patients.

The concomitant use of antibiotics and immunosuppressive medication observed in the majority of patients with SHG reflects the complexity of their diseases. The immune dysregulation at early age can lead to an organ-damage with a poor prognosis, and the overlapping between underlying secondary immune deficiency associated to immunosuppressive treatment, is currently a challenge for pediatric immunologists to decide the best therapeutic approach in each case [2]. It´s already known that Ig preparations are expensive

and, once prescribed, usually result in lifelong therapy. On the other hand, a delay in the beginning of IgRT may implicate a significant worsening of the prognostic outcome in some patients [10], especially children with comorbidities who are still in the immune maturing process.

The study has some limitations, including the small size of patients, lack data on lymphocyte subsets, as well as vaccine response. However, our data suggest benefit of IgRT in children with secondary HG, including patients with NS. Further studies with a larger number of patients would provide more reliable data.

Financial support

RPAG, Scientific Initiation Scholarship (January.2022 to January.2023) has been provided by Institute of Child Cancer and Specialized Pediatrics (ICIPE) /Hospital da Criança de Brasília José Alencar, Brazil.

Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

KMM: Analyzed the data, wrote and edited the manuscript; RPAG: Collected the data and wrote the manuscript; FRS, SVAN, CFCV: All the authors contributed to the conception of the work, attended the patients and revised critically the manuscript, FST: Conceived and supervised the study, revised the manuscript. All authors have read and agreed to the published version of the manuscript

Acknowledgments

The authors thank Prof. Dr. Beatriz Tavares Costa-Carvalho (in memoriam) for her contribution to clinical immunology studies in Brazil and Larissa Souza for statistical analysis support.

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Patient	Sex	Current age (years)	Age at onset IgRT (years)	Diagnosis	Ig route	IgRT dose (mg/Kg)	ATB	ISD	ISD	IgG-pre (mg/dL)	IgG-post (mg/dL)	Albumin pre (g/L)	Albumin post (g/L)
P1	F	13	11	post-RTX	IV	666	No	No		65	1070	3.78	4.64
P2	M	6	3	Leukemia	IV	662	Yes	Yes	MTX	348	989	4.4	4.64
P3	M	19	17	Leukemia	IV	472	Yes	Yes	MTX	595	1092	4.92	5.1
P4	M	6	3	NS	SC	210	No	Yes	CSA+CO	56	765	1.96	4.3
P5	M	14	10	NS	SC	400	No	Yes	TAC+CO	413	792	4.5	4,27
P6	M	4	1	NS	SC	319	Yes	Yes	CSA+CO	31	491	1.55	1.76
P7	M	7	5	Leukemia	SC	470	Yes	Yes	MTX	329	668	4.21	4.39
P8	M	2	1	NS	SC	210	Yes	Yes	CSA	46	490	2.01	2.5
P9	M	9	3	NS	IV	526	Yes	Yes	CTX+CO	147	697	4.5	4.33
P10	F	15	13	PIGN+ISD	SC	616	Yes	Yes	CTX+MMF	63	371	2.78	3.24
P11	M	17	12	IL	SC	643	Yes	No		265	506	2.27	2.03
P12	F	1	1	NS	SC	616	No	Yes	CSA+CO	24	578	1.74	3.9
P13	M	7	8	NS	SC	567	No	Yes	CSA+CO+ TAC+MMF	24	580	2.27	4.09
P14	M	2	2	CKD	SC	446	Yes	No		351	535	3.44	3.25
P15	M	5	4	NS	SC	470	No	Yes	CSA+CO+TAC	37	757	1.66	4.35
P16	M	5	4	NS	SC	476	No	Yes	CSA+CO	59	53	2.14	1.9
P17	M	4	3	NS	SC	522	Yes	Yes	CSA+CO	66	925	1.26	4.77
P18	F	9	8	NS	SC	617	Yes	Yes	CSA+CO+TAC	32	343	2.7	2.68
P19	M	5	4	NS	SC	500	No	Yes	CTX+CO	22	311	1.5	2.91
P20	M	7	6	NS	SC	408	Yes	Yes	CO	219	466	2.7	3.27

Supplementary Table 1: Clinical data of children with secondary hypogammaglobulinemia under regular subcutaneous immunoglobulin therapy (n=20); Ig: Immunoglobulin, IgRT: Immunoglobulin replacement therapy, RTX: Rituximab, NS: Nephrotic syndrome, PIGN: Pauci immune glomerunephritis, IL: Intestinal lymphagiectasy, CRD: chronic kidney disease, Ig: immunoglobulin, ATB: antibiotics, ISD: immunosuppressive drug, MTX: methotrexate, CSA: Cyclosporine A, CO: Corticosteroids, TAC: Tacrolimus, MMF: Mycophenolate mofetil, CTX: cyclophosphamide

Clinical parameters	**Prophylactic antibiotics**				
	No		Yes		
	Median	IQR	Median	IQR	*p**
IgG post (mg/dL)	668.5	478.7	520.5	396	0.79
Albumin (g/L)	4.2	1.2	3.3	2.0	0.70
Infections/patient	1.5	3.2	1.0	1.0	1.00
Severe infections/ patient	1.0	1.75	1.0	0.0	0.39
	Immunosuppressive medication				
	No		Yes		
	Median	IQR	Median	IQR	*p**
IgG (mg/dL)	535	564	580	407.5	0.69
Albumin (g/L)	3.3	1.2	4.1	1.6	0.77
Infections/patient	2.5	1.0	1.0	1.0	0.24
Severe infections/ patient	1.0	0.0	1.0	0.5	1.00

Supplementary Table 2: Association of clinical parameters and use of antibiotics or immunosuppressive medication in children with secondary hypogammaglobulinemia after one-year immunoglobulin replacement therapy (n=20); IgG: Immunoglobulin G, IQR: Interquartile range. Mann-Whitney test.