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Immunological Profile of Patients Presenting Down Syndrome and Alopecia Areata

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Abstract

Aim: This study was undertaken to contribute to knowledge of the immunological profile of Down syndrome and alopecia areata patients.

Material and Methods: Observational, case series study, with comparison group. The following data were computed: gender, age, karyotype, previous disease and immunological profile: complete blood count, Blood Sedimentation Rate (BSR), cellular and humoral immunity and autoimmunity. Frequency, central trends and dispersion measurements for descriptive analysis. The nonparametric χ^2 test and Fisher Exact test for exploratory analyses; significance level for p value < 0.05.

Results: Eighty-three Down Syndrome (DS) patients were evaluated: 21 with Alopecia Areata (AA) and 62 without it. The average age of patients with AA was 13.3 years (SD ± 5.0) and of DS without AA was 12.2 (SD ± 5.3); 94.7% presented free trisomy. The predominant previous illness was hypothyroidism, which occurred only in DS patients with AA (3/21). Hemogram was normal in 40.9% and the most frequent alteration was an increase of hematocrit (22.9%). The BSR was elevated in 71.1%. About cellular immunity, the principal abnormality was the decrease in CD4. Immunoglobulin electrophoresis was normal in 100.0%; DS patients showed normal levels of IgA in 100.0% of cases, of IgM in 98.8% and IgG, in 85.5%. Complement C4 and C3 were decreased in 67.4% and in 9.6% of the patients, respectively. The majority of studied antibodies were non reagent, but the presence of antiperoxidase antibody was significant in DS patients with AA.

Conclusion: There was no significant difference between the groups, related to their immunological profile, except for the presence of antiperoxidase antibody that maybe associated with the presence of hypothyroidism in DS patients with AA. Perhaps some of the findings are justified by the small sample; the authors suggest further studies with a larger sample and with HLA testing in order to understand the mechanism of AA in DS.

Keywords: Down's Syndrome; Alopecia areata; Immunology

Introduction

Down Syndrome (DS), trisomy 21, is the most frequent chromosomal anomaly [1]. The prevalence of DS is approximately 1:770 births, with a slight preponderance in the male gender [2]. DS individuals present an abnormal immune system, which leads to susceptibility to infections, with abnormal lymphocytes function, such as a decrease in the immune-dependent T-cell response and IgG deficiency [3-6]. Anatomic evidence suggests that the immune defect in DS individuals is primarily due to disarrangement of the thymus, in consequence of lymphocyte depletion, reduction of the cortex, loss of corticomedullary delimitation and enlargement of Hassall's corpuscles in the thymic medulla. Consequently, there is an abnormal thymic maturation, resulting in phenotypic and functional abnormalities in the circulating T-lymphocytes [4]. DS individuals present an increased incidence of autoimmune disorders [7]. Several studies report an increase in Alopecia Areata (AA) frequency in DS, varies from 1.3% to 11.0% [8-14].

AA is described as asymptomatic, well-circumscribed, circular area of hair loss ranging from 2 to 5 cm in diameter and in extensive cases coalescence of the lesions and/or involvement of other hairy surfaces is observed [15,16]. Immune and autoimmune dysfunction have previously been described in DS and AA patients, and frequently present an increase of the auto-antibodies related to thyroid gland [13].

The purpose of this study was to describe the immunological profile of a cohort of DS patients.

Material and Methods

This was a case-series study of DS and AA individuals attended at the Medical Genetics Service of Martagão Gesteira Pediatric Institute

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(IPPMG) – Federal University of Rio de Janeiro (UFRJ). Eighty-three patients with DS: 21 with AA (14 male and 7 female patients) and 62 without AA, included as a comparison group, paired by gender and age. All individuals were diagnosed clinically, most by cytogenetic analysis, and presented a documented medical history of AA or presented alopecia at the time of a consultation at the Medical Genetics Services. AA was considered to be hair loss leading to a "flaw" on any hairy body surface.

The following data were computed: 1-gender and age, 2- cytogenetic exam (karyotype), 3- occurrence of previous disease, 4- immunological profile: group of tests to assess the immunological profile, grouped by the authors as: a) nonspecific (complete blood count, blood sedimentation rate, total and fractional proteins), b) cellular immunity (CD2, CD3, CD4, CD8 and CD19), c) humoral immunity (IgA, IgG, IgM, electrophoresis of immunoglobulins and complements C3 and C4), and d) autoimmunity (anticoagulant lupus, antiperoxidase antibody, antithyroglobulin, anti-gastric parietal cell antibody and anticardiolipin IgG and IgM). These tests were performed as a courtesy by Laboratório Célula.

All the participants of the study were submitted to anamnesis and clinical exams to confirm DS and AA diagnosis. Exclusion criteria included: trichotillomania, clinical picture of concomitant infection, treatment with immunosuppressive drugs, zinc deficiency and presence of polycystic ovaries (evaluated by pelvic ultrasound in post-menarche female DS patients).

The clinical research protocol was approved by the Ethical Research Committee (IRB) of the IPPMG. The patients that participated in this study were all included in the database and platform that we have been developing named DataGenno [17].

Frequency, central trends and dispersion measurements were used for descriptive analysis. The nonparametric χ^2test and Fisher Exact test were used for exploratory analyses and significance level was considered for p value < 0.05.

Results

At The Medical Genetics Service of IPPMG/UFRJ, Brazil, 345 DS patients were attended from January 2000 to June of 2003; 151 females and 194 males. In relation to the total number, AA frequency was 4.3% (15/345). Of the 15 patients identified with AA, two did not respond to the invitation to participate in the study. Four children with DS and AA were sent to our service, two being from Fernandes Figueira Institute – FIOCRUZ, and two from Gafreé Guinle Hospital – UNIRIO, through the authors invitation.

Until the end of data collection, four additional cases of children with DS and AA attended at the IPPMG were incorporated to the study. Thus, the study was concluded with 21 children with DS and AA. For the comparison group, 62 patients with DS and without AA were selected.

Of the 84 DS patients selected for the study:

- One for the comparison group was excluded, due to clinical picture of flu at the time of laboratory collection. As such, the sample size for the laboratory exams was 83 DS patients
- No cases of trichotillomania, polycystic ovary, zinc deficiency or clinical picture of infection were identified during the collection of biological material.
- None of patients was under concomitant treatment with immunosuppressive drugs.

Gender distribution of 83 patients with DS: 55 (66.3%) males and 28 (33.7%) females. Twenty one patients presented or had presented AA (25.3%); 14 male and 7 female; 62 DS patients without AA (41 male and 21 female), paired by gender and age. The average age of DS patients with AA was 13.3 years (SD ± 5.0) and of DS without AA was 12.2 (SD ± 5.3). In relation to cytogenetics exam: 94.7% (54/57) of the patients presented free trisomy; there were three cases of mosaicism, all in DS patients without AA. The predominant previous illness was hypothyroidism, which occurred only in DS patients with AA (3/21).

	With AA (n=21)				Without AA (n=62)				P value
	Present		Absent		Present		Absent		
	N	%	N	%	N	%	N	%	
Increased hematocrit	4	19.0	17	81.0	15	24.2	47	75.8	NS
Leucopenia	3	14.2	18	85.8	15	24.2	47	75.8	NS
Anemia	5	23.8	16	76.2	8	12.9	54	87.1	NS
Monocytosis	2	9.5	19	90.5	2	3.2	60	96.8	NS
Anisocytosis	1	4.7	20	95.3	2	3.2	60	96.8	NS
Leucocytosis	0	0.0	21	100.0	3	4.8	59	95.2	_
Lymphocytosis	0	0.0	21	100.0	2	3.2	60	96.8	_
Neutropenia	0	0.0	21	100.0	2	3.2	60	96.8	_
Atypical lymphocytes	0	0.0	21	100.0	1	1.6	61	98.4	_
Eosinophilia	0	0.0	21	100.0	1	1.6	61	98.4	_
Lymphopenia	1	4.7	20	95.3	0	0.0	62	100.0	_
Macrocytosis	0	0.0	21	100.0	1	1.6	61	98.4	_

Table 1: Distribution of the frequency of abnormalities of hemogram in DS patients.

	With AA				Without AA				P value
	Normal		Abnormal		Normal		Abnormal		
	n (N)	%	n (N)	%	n (N)	%	(N)	%	
CD3	12 (18)	66.6	6 (18)	33.4	39 (60)	65.0	21 (60)	35.0	NS
CD4	10 (18)	55.5	8 (18)	44.5	38 (60)	63.3	22 (60)	36.7	NS
CD8	12 (18)	66.6	6 (18)	33.4	46 (60)	76.6	14 (60)	23.4	NS
CD19	10 (16)	55.5	6 (16)	44.5	43 (57)	75.4	14 (57)	24.6	NS

Table 2: Distribution of the "Cluster of differentiation" according to presence of AA in DS patients.

		With AA (n=21)			Without AA (n=62)				P value
	Reagent		Non Reagent		Reagent		Non Reagent		
	n	%	n	%	N	%	n	%	
Antithyroglobulin	4	19.0	17	81.0	8	12.9	54	87.1	NS
Antiperoxidase	13	61.9	8	38.1	9	14.5	53	85.5	**<0.0001**
Anticardiolipin IgM	0	0.0	21	100.0	0	0.0	62	100.0	_
Anticardiolipin IgG	1	4.7	20	95.3	12	19.3	50	80.7	NS
Anti-gastric parietal cells	0	0.0	21	100.0	0	0.0	61	100.0	_
Lupus anticoagulant	0	0.0	20	100.0	0	0.0	62	100.0	_

Table 3: Distribution of the frequency of auto-antibodies in DS patients.

One DS patient without AA presented vitiligo.

The hemogram was normal in 40.9% of the patients. The abnormalities are shown in (Table 1). The most frequent abnormality was an increase of hematocrit (22.9%) followed by leucopenia (21.6%), anemia (15.6%), monocytosis (4.8%) and anisocytosis and leucocytosis (3.6% each). Other abnormalities were: lymphocytosis, neutropenia, atypical lymphocytes, eosinophily, lymphopenia and macrocytosis. (Table 1) also shows that there was no statistical difference between the two groups. The blood sedimentation rate (BSR) was shown to be elevated in 71.1% (59/83) of the total patients studied with an average of 21.6 (SD ± 16.7), 24.1 (SD ± 20.9) for DS with AA and 20.8 (SD ± 15.0) for DS without AA. There was no significant difference between the two groups.

In relation to cellular immunity, there was no significant difference between the two groups (Table 2) and the principal abnormality was the CD4 decreased in 44.5% (8/18) patients with DS and AA and in 36.7% (22/60) patients with SD without AA.

About the humoral immunity of all DS patients, the immunoglobulin electrophoresis was normal in 100.0%. DS patients showed normal levels of IgA in 100.0% of cases, of IgM in 98.8% (82/83) and of IgG, in 85.5% (71/83). IgG was increased in four patients with AA and in eight without AA. Complement C4 and C3 were decreased in 67.4% (56/83) and in 9.6% (8/83) of patients, respectively. There was no significant difference between the two groups.

Table 3 shows the frequency of auto antibodies distributed in the two groups. The presence of antiperoxidase antibody was significant in DS patients with AA.

Discussion

Our study is the first one which compares the immunological profile of DS patients, with and without AA in a sample of the Brazilian population. Carter and Jegasothy (1976) and Barakin and Guenter (2003) found a larger prevalence of AA in DS patients, mainly in females, which differs from our findings. In another study, in patients without DS, Muller and Winkelmann (1963) reported a greater prevalence of AA in females. We probably found a predominance of AA in males in our study due to the total of patients attended at the service, there was a predominance of males; or perhaps on account of the small sample studied. In relation to age, the average age of the patients with AA was 13.3. Muller and Winkelmann (1963) reported an elevated frequency of AA among patients younger than 16 years old. In our study DS patients with AA under this age, represented 75% of individuals with AA.

DS patients may present a variety of hematopoietic abnormalities [17]. In our study the hemogram was altered in 59.1% and the most frequent abnormality was an increase of hematocrit. Roizen and Amarose compared the hematologic parameters of 18 DS children with 18 healthy non-DS controls and observed that children with DS had hematocrit increased significantly compared to controls and decreased White Blood Cells (WBC) compared to controls. Although hematocrits were within normal limits for age for all DS and non-DS subjects, the DS patients had significantly higher hematocrits ($P < 0.014$). Furthermore they concluded that macrocytosis and leucopenia are common in children with DS [18].

No patient was found with leukemia or megaloblastic anemia [19]. Found leucopenia in 13.6% of children with DS and our study found 21.6%, during routine hemograms. We observed macrocytosis in only one patient in our sample. Three individuals with DS but without AA presented abnormalities of the granulocytes (neutropenia and eosinophilia). Different result was found in another study that evaluated the hematological profile of eighty-three children with DS, in which the most relevant results were macrocytosis and normal leucocytes [20].

Anemia was the third present abnormality in our study (15.6%) [21]. Conducted a study with 149 children with DS 8.1% had presented anemia. Among the 38 children who had iron studies, 50.0% had iron deficiency. They concluded that children with DS are at risk for anemia and iron deficiency similar to the general population and should be monitored for anemia and iron deficiency with early intervention [21].

The blood sedimentation rate (BSR) reflects the increase in plasma concentration of acute phase proteins, especially fibrinogen [22]. The BSR was shown to be elevated in 71.1% of patients studied, with average of 21.6. BSR elevation could be indicative of many disorders, including: infection, diabetes mellitus, chronic renal disease, hypothyroidism, autoimmune diseases, rheumatic diseases, low hematocrit, macrocytosis and hypercholesterolemia [22]. On the other hand, some factors may decrease it, as hypofibrino genemia, hypogamma globulinemia, polycythemia, microcytosis, hemolytic anemia and hemoglobinopathies [23]. Our sample presented factors that could decrease or increase the BSR, and it is important to call attention that the individuals had no infectious process at the moment of evaluation. As far as we know, there is no data related to BSR in DS patients with no comorbidities.

In relation to cellular immunity, there was no significant difference between the two groups (Table 2) and the principal abnormality was the CD4 decreased in 44.5% (8/18) patients with DS and AA and in 36.7% (22/60) patients with SD without AA. As described in literature; there is a decrease of total leukocytes, lymphocytes and CD4 + subpopulations in DS [24].

Regarding to the investigation of humoral immunity, found values within the normal limits only in DS patients, as in our study [13]. There are few studies of complement system in DS individuals, in which are observed both normality and increase in C3 and C4 [25,26].

Individuals with DS have a variety of changes of the immune system,

making them more susceptible to recurrent infections. The mannose binding lectin is a protein which is involved in first-line host defense against different pathogens. A study conducted by Nisihara concluded that children and adolescents with DS have lower concentrations of this protein than people without DS. He also noted that the deficiency was associated with the presence of recurrent infections, especially pneumonia, in children and adolescents with DS, with a three times increased risk [27].

Anti-thyroperoxidase antibodies are found in thyroid gland disorders (Hashimoto disease, primary myxedema disease and thyrotoxicosis), iron deficiency anemia, diabetes mellitus and idiopathic Addison disease [1]. In our study, the DS patients presented positive antibodies in a range of 15.6 to 26.5%. We found a significant predominance of positive antiperoxidase antibodies in DS patients with AA, maybe as a consequence of the presence of hypothyroidism in this group, as follow: hypothyroidism, sub-clinical hypothyroidism and congenital hypothyroidism, all in DS patients with AA. This data suggests that DS patients with AA should be investigated for thyroid abnormalities.

This study presented some limitations, the convenience reduced sample, which could have led to results that may not have been found in a larger sample. However, due to the relative lack of information in this area, we understand that it is important to report the initial differences between the groups.

Conclusion

There was no significant difference between DS patients with and without AA, related to their immunological profile, except for the presence of antiperoxidase antibody that maybe associated with the presence of hypothyroidism in DS patients with AA. Perhaps some of the findings are justified by the small sample; the authors suggest further studies with a larger sample and with HLA testing in order to understand the mechanism of AA in DS.

References

1. Gelehrter T D, Collins FS (1992) Citogenética. In: Fundamentos de Genética Médica. Guanabara Koogan: 135-160.
2. Fryns JP (1990) Chromosome 21, trisomy 21. In: Buyse ML, Birth Defects Encyclopedia, Blackwell Scientific Publications:391-393.
3. Bertotto A, Crupi S, Fabietti GM, Troiani S, Parente C, et al. (1999) CD3+/CD30+ circulating T lymphocytes are markedly increased in older subjects with Down's syndrome (Trisomy 21), Pathobiology 67:108-110.
4. Bertotto A, Gerli R, Spinozzi F (1994) CD26 surface antigen expression on peripheral blood T lymphocytes from children with Down's syndrome (Trisomy 21). Scandinavian Journal of Immunology 39:633-637.
5. Estefan JL, Queiroz M, Costa F, Coutinho M, Higino K, et al. (2013) Clinical Characteristics of Alopecia Areata in Down Syndrome, Acta Dermatovenerol Croat 21:253-258
6. Miller M E, Mellman WJ, Kohn G, Dietz WH (1970) Qualitative and quantitative deficiencies of immunoglobulin G (IgG) in newborns with Down syndrome, Annals of the New York Academy Sciences 171:512-516.
7. Scotson J (1989) A patient with Down's syndrome, mild hypothyroidism and alopecia, The Practioner, 233:121.
8. Du Vivier A, Munro D D (1975) Alopecia Areata, autoimmunity and Down's syndrome, British Medical Journal 1:191-192.
9. Carter D M, Jegasothy BV (1976) Alopecia Areata and Down syndrome, Archives of Dermatology 112:1397-1399.
10. Roselino A M F, Almeida A M, Hippolito MA, Cerqueira B C S, Maffei C M L, et al. (1996) Clinical-epidemiological study of Alopecia Areata, International Journal of Dermatology 35:181-184.
11. Wunderlich C, Braun-Falco O (1965) Mongolismus and Alopecia Areata, Die Medizinische Welt 10:477-481.
12. Daneshpazhoo M, Nazemi T M, Bigdeloo L, Yoosefi M (2007) Mucocutaneous findings in 100 children with Down syndrome, Pediatric Dermatology 24:317-320.
13. Dourmishev A, Miteva L, Mitev V, Pramatarov K, Schwartz R.A (2000) Cutaneos Aspects of Down syndrome, Pediatric Dermatology 66:420-424.
14. Garg S, Messenger A G (2009) Alopecia Areata: Evidence-Based Treatments, Seminars in Cutaneous Medicine and Surgery 28:15-18.
15. Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J (2010) Alopecia areata update. Part I. Clinical picture, histopathology, and pathogenesis, Journal of the American Academy Dermatology 62:177-188.
16. Wasserman D, Guzman-Sanchez D A, Scott K, McMichael A (2007) Alopecia areata. International Journal of Dermatology 46:121–131.
17. Costa FF, Foly LS, Coutinho M P (2011) DataGenno: building a new tool to bridge molecular and clinical genetics The Application of Clinical Genetics 4:45-54.
18. Roizen NJ, Amarose AP (1993) Hematologic abnormalities in children with Down syndrome, American Journal of Medical Genetics 46:510-2.
19. Boy R, Neto JGB, Vargas FR, Fontana C, Almeida JCC, Llerena J (1995) Síndrome de Down: análise clínica, citogenética e epidmiológicaem 165 casos, Jornal de Pediatria 71:88-92.
20. Ibarra B, Rivas F, Medina C, Franco ME, Romero-García F, et al. (1990) Hematological and biochemical studies in children with Down syndrome, Annales de Génétique 33:84-87.
21. Tenenbaum A, Malkiel S, Wexler ID, Levy-Khademi F, Revel-Vilk S, et al. (2011) Anemia in Children with Down Syndrome, International Journal of Pediatrics 2011: 1-5.
22. Rosa Neto NS, Carvalho JF (2009) O uso de provas de atividade inflamatória em reumatologia, Revista Brasileira de Reumatologia 49: 413-430.
23. Collares G B, Vidigal PG (2004) Recomendações para o uso da velocidade de hemossedimentação, Revista Médica de Minas Gerais 14:52-57.
24. Murphy M, Epstein LB (1992) Down syndrome peripheral blood contains phenotypicaly mature CD3 TCR alpha and beta cells but abnormal proportions of TCR gama delta, TCR alpha beta and CD 4+ 45 RA cells: Evidence for an inefficient release of mature T cells by DS thymus, Clinical Immunology Immunopathology 62:245-251.
25. Ribeiro L M, Jacob C M, Pastorino AC, Kim CA, Fomin AB, Castro AP (2003) Avaliação dos fatores associados a infecções recorrentes e/ou graves em pacientes com síndrome de Down, Jornal de Pediatria 79:141-148.
26. Trincado MVR, Toledano FL, Ramos MMM, Cortina AR, Villalobos VS (1984) Evaluation of the immune system in Down's syndrome patients, Allergologia et Immunopathologia 12:45-54.
27. Nisihara R M (2009) Concentrações séricas da lectina ligante da manose na síndrome de Down: associação com infecções recorrentes e doenças auto-imunes. Tese de doutorado - Curso de Pós-Graduação em Medicina Interna, Setor de Ciências da Saúde, Universidade Federal do Paraná: 1-85.

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