ORIGINAL ARTICLE

Delineating the immunological profile of Algerian children with Down syndrome: A case series

Caractérisation du profile immunologique des patients algériens atteints d'une trisomie 21

Linda Mokrane[1#], Azzeddine Tahiat[1#], Samira Aggoune[2], Souad Touri[3], Hayet Belhadj[4], Chafa Bendahmane[5], Ouardia Ibsaine[5], Lila Kedji[3], Réda Belbouab[6], Rachida Boukari[6], Kamel Djenouhat[1]

1. Algiers University of Health Sciences, Rouiba Hospital, Department of Medical Biology, 16000, Algiers, Algeria.
2. Algiers University of Health Sciences, El-Harrach Hospital, Department of Pediatrics, 16000, Algiers, Algeria.
3. University of Blida, Blida University Hospital, Department of Pediatrics, 09000, Blida, Algeria.
4. Algiers University of Health Sciences, Army Mother and Child Hospital, Department of Pediatrics, 16000, Algiers, Algeria.
5. Algiers University of Health Sciences, Ain Taya Hospital, Department of Pediatrics, 16000, Algiers, Algeria.
6. Algiers University of Health Sciences, Mustapha University Hospital, Department of Pediatrics, 16000, Algiers, Algeria.
#: equal contribution

Abstract

Purpose: This study aimed to characterize the immunological profile of Algerian children with Down Syndrome (DS).
Methods: Serum immunoglobulin (Ig) levels were measured using nephelometry, and lymphocyte subpopulations were analyzed by flow cytometry (FACSLyric™, BD Biosciences, US). The lymphocyte phenotype in DS patients was compared to that of patients with combined immunodeficiency (CID).
Results: Our cohort included 33 patients with DS (20 males), and 40 patients with CID (24 males). All patients had a clinical history of recurrent or severe infections, including upper and lower respiratory tract infections in 25 patients (76%). Serum Ig were measured in 29 patients, with normal levels of IgG, IgA, and IgM in 83%, 73%, and 80% of patients, respectively. Elevated IgG, IgA, and IgM levels were found in 14%, 17%, and 3% of patients, while reduced levels were seen in 3%, 10%, and 17% of patients, respectively. Lymphocyte phenotype analysis revealed CD4 lymphopenia in 24 (73%) patients, CD8 lymphopenia in 19 (58%) patients, B-cell lymphopenia in 16 (48%) patients, and reduced NK cells in 7 (21%) patients. Naïve CD4+ and CD8+ T cells were analyzed in nine patients, with low percentages observed in three. Patients with DS exhibited significantly milder CD3 and CD4 lymphopenia compared to those with CID.
Conclusion: Children with DS typically present with T- and B-cell lymphopenia, while maintaining generally normal Ig levels. T-cell lymphopenia in DS is less pronounced than in CID, and the increased susceptibility to infections stems from both immunological and non-immunological factors linked to trisomy 21.

Keywords: Down Syndrome, recurrent infections, lymphocyte phenotype, T-cell lymphopenia, Combined immunodeficiency, serum immunoglobulins.

Résumé

Objectif: établir un profil immunologique caractéristique des patients algériens atteints de trisomie 21 (T21).
Méthodes: le dosage pondéral des immunoglobulines sériques a été réalisé par néphélémétrie. Les sous-populations lymphocytaires ont été analysées par cytométrie en flux (FACSLyric™, BD Biosciences, US). Les résultats du phénotypage lymphocytaire des patients trisomiques ont été comparés à ceux des patients atteints de déficit immunitaire combiné (DIC).
Résultats: l'étude a inclus 33 patients trisomiques et 40 patients atteints de DIC, tous présentant des antécédents d'infections sévères ou récurrentes, notamment des infections respiratoires chez 25 patients. Le dosage des immunoglobulines, réalisé chez 29 patients, a révélé des taux normaux d'IgG, IgA et IgM chez respectivement 83%, 73% et 80% des patients, des taux augmentés chez 14%, 17% et 3%, et des taux diminués chez 3%, 10% et 17%. Le phénotypage lymphocytaire a mis en évidence une lymphopénie TCD4+ chez 24 patients (73%), une lymphopénie TCD8+ chez 19 patients (58%), une lymphopénie B chez 16 patients (48%) et NK chez 7 patients (21%). L'analyse des lymphocytes T naïfs, réalisée chez 9 patients, a montré des pourcentages diminués chez trois. Les patients trisomiques avaient des taux significativement plus élevés de lymphocytes TCD3+ et TCD4+ que ceux observés chez les patients DIC.
Conclusion: les patients trisomiques présentent des lymphopénies T et B, avec des taux d'immunoglobulines globalement dans les normes. La lymphopénie observée chez les patients trisomiques est moins prononcée que celle observée au cours des DIC. La susceptibilité accrue aux infections semble résulter de facteurs immunologiques et non immunologiques associés à la T21.

Mots clés: Syndrome de Down, infections récurrentes, phénotypage lymphocytaire, lymphopénie T, déficit immunitaire combiné, immunoglobulines sériques.

Correspondance
Azzeddine Tahiat
Department of Medical Biology, Rouiba Hospital, Algiers Faculty of Medicine, University of Algiers 1, Algiers, Algeria
Email: azzedinetahiat@gmail.com

LA TUNISIE MEDICALE-2025; Vol 103 (11): 1605-1611 DOI: 10.62438/tunismed.v103i11.5770

What is known?

- T-cell and B-cell lymphopenia are frequently observed in patients with Down syndrome.
- Immunoglobulin levels are generally within the normal range in DS patients.

What this article adds

- This is the first study to explore the immunological profile of DS patients originating from the Maghreb.
- This study seeks to establish an immunological profile for Algerian DS patients, aiding in the differential diagnosis between DS and CID, particularly in cases of recurrent infections.
- T-cell lymphopenia is less pronounced in DS patients compared to those with combined immunodeficiency.
- T CD8+ lymphopenia is also a frequent finding in Algerian patients with DS, suggesting that disrupted T-cell development and homeostasis is a global phenomenon affecting both $CD4^+$ and $CD8^+$ subsets.

Introduction

Down syndrome (DS) is a genetic disorder caused by a complete or partial trisomy of chromosome 21 (1). It is the most prevalent chromosomal abnormality among liveborn infants (2). Chromosome 21 contains approximately 200 protein-coding genes, including those that encode key components of the immune system, such as type I and II interferon receptors (IFNAR1, IFNAR2, and IFNGR2) (3,4).

Interestingly, the presence of an additional copy of chromosome 21 does not always lead to increased expression of all its genes. Some genes on chromosome 21 may exhibit reduced expression, while dysregulation can also extend to genes located on other chromosomes (5–7). As a consequence, DS is associated with a broad spectrum of clinical manifestations. Common features include characteristic dysmorphic traits, cognitive impairment, musculoskeletal anomalies, neurodevelopmental disorders, and respiratory, gastrointestinal, and cardiovascular conditions. Additionally, individuals with DS have a higher prevalence of certain less common conditions, such as hematologic disorders, Hashimoto's thyroiditis, celiac disease, type 1 diabetes, various endocrine dysfunctions, Alzheimer's disease, and autism (8).

Recurrent respiratory infections represent one of the leading causes of mortality in children and adults with DS. Pneumonia has been identified as a major cause of death in several studies on DS patients across all age groups (9–12). It is also known that autoimmune diseases such as celiac disease, and type 1 diabetes, and hematological disorders, in particular, acute lymphocytic leukemia (ALL), and acute myeloid leukemia (AML), are more prevalent in DS individuals compared to healthy subjects (7,13,14). DS is also associated with immunological impairments of both innate and adaptative immune system, with a constant presence of abnormalities affecting T and B cells (15). These variations partially mirror the phenotype of combined immunodeficiencies (CIDs), a group of monogenic T-cell disorders affecting both cellular and humoral immunity (16). Thus, establishing a baseline immunological profile in patients with DS is essential for accurate differential diagnosis, particularly in the clinical context of recurrent infections.

Several cohort studies from countries worldwide, including the United States, France, Italy, Turkey, and Egypt, have investigated both T-cell and B-cell immunity in children and adults with DS (17–21).

The findings revealed significant variability, particularly in T-cell counts, with some studies reporting T-cell lymphopenia, while others observed normal or even elevated T-cell levels (18,20–25). Another challenge in establishing an immunologic profile in individuals with DS is the demographic heterogeneity observed across published studies, which include pediatric and adult patients, those with and without recurrent infections, and hospitalized and non-hospitalized DS individuals (18,24–27).

While most studies have compared DS patients to healthy controls, to our knowledge, no research has specifically examined the differences between DS and bona fide CIDs. Therefore, the aim of the present study was to establish a characteristic immunological profile of a cohort of Algerian children with DS, and to compare it with a group of patients diagnosed with CID.

Methods

Study design and patient enrollment

The study was conducted at the Medical Biology Laboratory of Rouiba University Hospital on a series of DS patients with a medical history of severe or recurrent infections, referred to us from various pediatric departments in Algiers. Serum immunoglobulin (Ig) levels and lymphocyte phenotype were evaluated, and clinical data were collected for each patient. To identify immunological differences between DS and CIDs, we compared the lymphocyte counts of DS patients with those of CID patients previously diagnosed at our center. Patients with severe combined immunodeficiency and Omenn syndrome were excluded due to their distinct clinical and immunological phenotypes. The study was approved by the local ethics committee, in accordance with the Declaration of Helsinki.

Immunological assessment

A complete blood count (CBC) was performed on EDTA-anticoagulated peripheral blood samples using a Coulter counter (ADVIA® 360, Siemens, Germany) to calculate absolute leukocyte and lymphocyte counts. Serum Ig levels (i.e., IgG, IgA, and IgM) were measured by laser nephelometry, using a BN ProSpec System (Siemens, Germany). Lymphocyte phenotype analysis was performed using flow cytometry (FCM) with a lyse-wash protocol, applying direct immunofluorescence staining

to the following lymphocyte markers: CD3 for total T cells, CD4 and CD8 for T cell subpopulations, CD19 for B cells, and CD56/CD16 for NK cells. Data acquisition was conducted on an eight-color FACSLyric™ cytometer (BD Biosciences, US). Lymphocyte subpopulation percentages were determined, and absolute values were calculated based on the CBC. An extended T cell phenotyping was performed in DS patients exhibiting a profound CD4+ and/or CD8+ T cell lymphopenia, as well as in all CID patients. This analysis used the following markers: CD3, CD4, CD8, CD45RA, CD45RO, and CCR7 (CD197) to determine the distribution of naïve (CD45RA+CCR7+) and memory (CD45RO+) CD4+ and CD8+ T cells.

Statistical analysis

The Mann-Whitney U test was used to compare median lymphocyte counts between DS and CID populations. The threshold for statistical significance was set to a P value of less than 0.05. The statistical analysis was performed using SPSS version 25.0 (software package (IBM), Chicago, IL, USA).

Results

Baseline characteristics

A total of 33 patients with DS and 40 patients with CID were included in this study, comprising 20 males (61%) and 13 females (39%) with DS, and 24 males and 16 females with CID. The median age of DS patients at the time of the study was 54 months (range: 1–156 months), and the median age at diagnosis for CID patients was 36 months (range: 2–552 months). Only two DS patients (6%) were born from consanguineous parents, and one had a family history of recurrent infections. All patients had a clinical history of recurrent or severe infections, including upper and lower respiratory tract infections in 25 (76%) patients, recurrent diarrhea in 8 (24%) patients, oral candidiasis in 8 (24%) patients, urinary tract infections in 4 (12%) patients, and skin abscesses in 1 (3%) patient. Additionally, 9 (27%) patients were born with congenital heart disease, 4 (12%) patients exhibited failure to thrive, and 5 (15%) patients had immune dysregulation conditions, including asthma in 3 (9%) patients, as well as type 1 diabetes, inflammatory bowel disease, and autoimmune hemolytic anemia in 3 distinct patients.

Immunological profile in DS patients

Serum Immunoglobulins

Serum Ig levels were measured in 29 patients; 4 were under 4 months of age and were not tested. IgG levels were normal in 24 patients (83%), elevated in 4 patients (14%), and reduced in one patient (3%). IgA levels were within normal ranges in 21 patients (73%), increased in 5 patients (17%), and decreased in 3 patients (10%). IgM levels were normal in 23 patients (80%), high in one patient (3%) and low in 5 patients (17%). Overall, 15 patients (52%) exhibited normal IgG, IgA, and IgM levels, concomitantly (Table 1).

Table 1. Immunological findings in Down syndrome patients

	Median	Findings		
		Decreased *n (%)*	Normal *n (%)*	Increased *n (%)*
Serum Ig levels (n=29)	**(g/l)**			
IgG	7.94	1 (3%)	24 (83%)	4 (14%)
IgA	0.83	3 (10%)	21 (73%)	5 (17%)
IgM	0.57	5 (17%)	23 (80%)	1 (3%)
Lymphocyte phenotype (n=33)	**(Cells/mL)**			
Lymphocytes	2639	20 (61%)	11 (33%)	2 (6%)
T cells	1614	21 (64%)	9 (27%)	3 (9%)
CD4+ T cells	964	24 (73%)	9 (27%)	0 (0%)
CD8+ T cells	491	19 (58%)	9 (27%)	5 (15%)
CD4/CD8 ratio	1.74	8 (24%)	22 (67%)	3 (9%)
B cells	428	16 (48%)	17 (52%)	0 (0%)
NK cells	411	7 (21%)	22 (67%)	4 (12%)
Extended T-cell phenotyping (n=9)	**(%)**			
Naïve CD4+ T cells (CD4+CD45RA+CCR7+)	70%	3 (33%)	6 (67%)	0%
Memory CD4+ T cells (CD4+CD45RO+)	27%	0 (0%)	6 (67%)	3 (33%)
Naïve CD8+ T cells (CD8+CD45RA+CCR7+)	46%	3 (33%)	6 (67%)	0%
Memory CD8+ T cells (CD8+CD45RO+)	15%	0 (0%)	6 (67%)	3 (33%)

Ig, Immunoglobulin

Lymphocyte phenotype

Immunophenotypic abnormalities were observed in 32 DS patients (97%). Moderate CD3 lymphopenia was noted in 18 patients (55%), while severe T-cell lymphopenia (<500 cells/mm³) was observed in only 3 patients (9%). The most common variation in circulating lymphocytes was CD4 lymphopenia (24 patients; 73%), followed by CD8 lymphopenia (19 patients; 58%). B- and NK-cell lymphopenia were seen in 16 (48%) and 7 (21%) patients, respectively. The CD4/CD8 ratio was decreased in 8 patients (24%). Lymphocytosis primarily involved CD8 T cells (15%) and NK cells (12%). Additionally, naïve and memory T cells were analyzed in 9 patients. The percentages of naïve CD4+ T cells and naïve CD8+ T cells were moderately reduced in 3 patients (1/3). Elevated frequency of memory T cells was observed in 3 patients (1/3) (Table 1).

Comparative analysis of the lymphocyte phenotype in DS and CID patients

The comparison of lymphocyte subpopulations between DS and CID patients revealed significantly lower counts of total lymphocytes, CD3+ T, CD4+ T, and NK cells in CID patients compared to DS patients. However, no

statistically significant differences were observed in CD8+ T cells and B cells between the two groups (Table 2) (Figure 1).

Table 2. Lymphocyte subpopulation counts in Down syndrome and combined immunodeficiency patients.

T-B-NK enumeration	DS group Median (Cells/mL)	CID group Median (Cells/mL)	*P*
Lymphocytes	2639	1829	**0.008**
T cells	1614	1118	**0.024**
CD4+ T cells	964	432	**0.000**
CD8+ T cells	491	454	0.335
B cells	428	251	0.056
NK cells	411	228	**0.023**

CID, Combined Immunodeficiency; DS, Down Syndrome.

Discussion

The present study aimed to define the immunological characteristics of Algerian children with DS. While similar studies have been published, this is the first report from the Maghreb region. Analysis of the demographic data revealed that only a small percentage (6%) of DS patients were born to consanguineous parents or had a positive family history of recurrent infections, which contrasts with findings in patients with CID and other inborn errors of immunity at our center (data not shown) (28).

This suggests that the immunological abnormalities observed in our patients are more likely linked to DS itself.

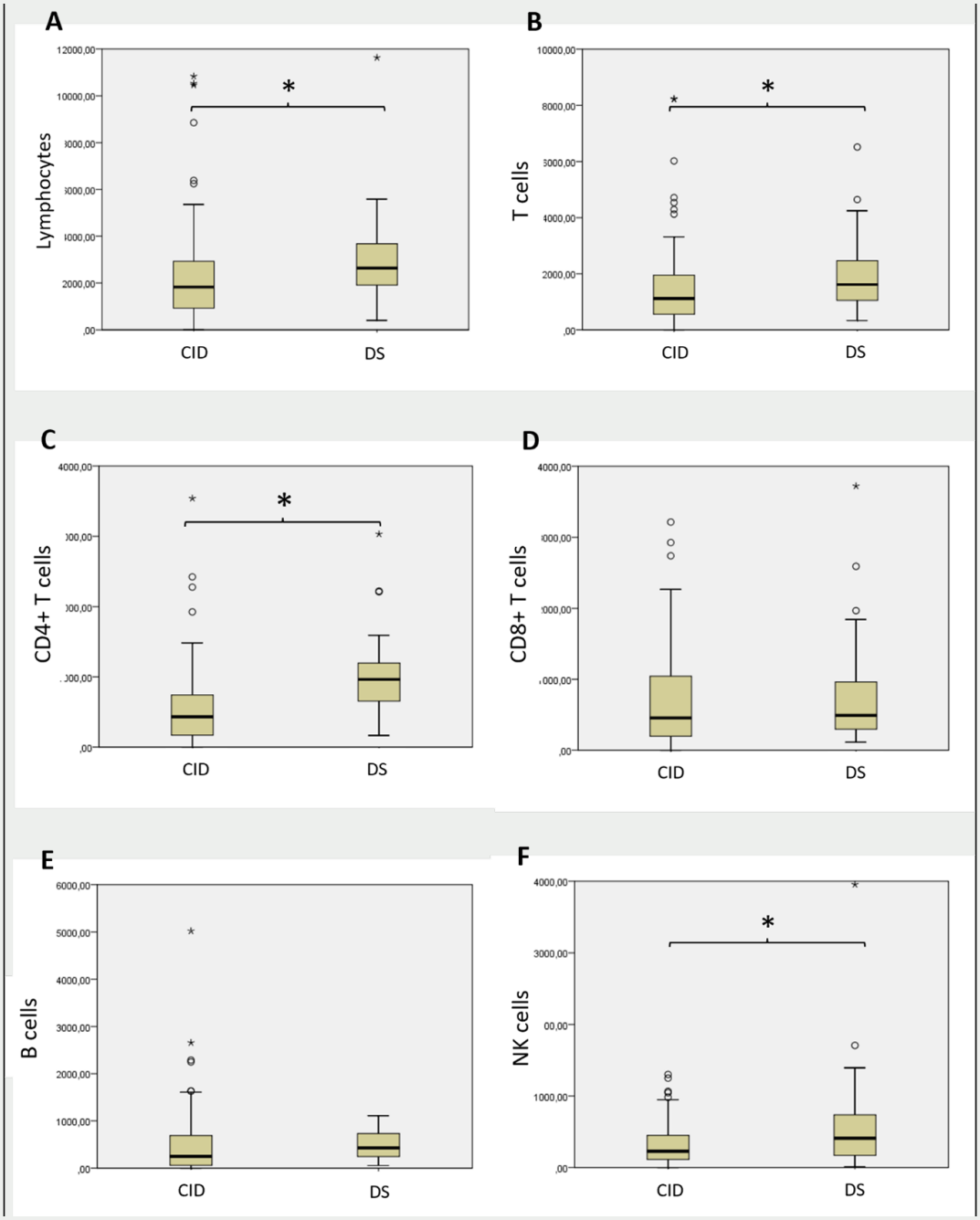

Figure 1. Comparison of lymphocyte (A), T-cell (B), CD4 T-cell (C), CD8 T-cell (D), B-cell (E) and NK-cell (F) counts between DS and CID patients.

*: statistically significant.

CID, Combined immunodeficiency; DS, Down syndrome.

Serum IgG levels were within normal ranges in most patients (83%), elevated in 4 patients, and reduced in one. While some studies have found IgG levels in DS patients comparable to those of healthy controls (18,19,24), others have reported higher IgG levels in DS patients (17,25). Serum IgA levels were normal in 73% of DS patients and elevated in 17%. Many studies have documented normal IgA levels (17–19,24), although a few have noted elevated IgA in DS patients (25,29). Serum IgM levels were within normal ranges in 80% of patients, increased in 3%, and reduced in 17%. These findings align with an Argentinian study in which 21% of DS patients had reduced IgM levels (23).

Additionally, several studies have reported lower IgM levels in DS patients compared to healthy controls (29–32). Overall, although findings across studies show variability, Ig levels in DS patients remain within the normal range, with hypogammaglobulinemia being a rare occurrence.

Furthermore, altered antigen-specific antibody responses, as reported in several studies, raise concerns about the functional efficacy of the antibody response in DS (15,30,32).

Nearly half of DS patients exhibited reduced B-cell count. B lymphocytopenia is a consistent finding in almost all studies reported to date (17,18,20–26,33,34). These B-cell abnormalities are similar to those found in common variable immunodeficiency (CVID), including a reduction in memory B cells and impaired B-cell proliferation. However, DS patients differ from CVID in that their serum Ig levels remain generally normal, whereas Ig levels are typically low in CVID (35). Significant T cell abnormalities were observed in our DS cohort, CD4 lymphopenia was present in 24 (73%) patients, whereas CD8 lymphopenia was present in 19 (58%). CD4 lymphopenia is a common finding in most reported studies (17,20–23,25,26,33,34). In contrast, CD8 lymphopenia has been documented in only a few studies (21,26), with the majority reporting normal to elevated CD8+ T-cell counts, which contrasts with our findings (17,18,20,24,34). Analysis of the naïve and memory T-cell subsets revealed a moderate decrease in the frequency of naïve CD4+ and CD8+ T cells in one third of patients, consistent with findings from both American and Polish studies [17, 33]. Comparison of T-cell counts between DS and CID patients showed that T-cell lymphopenia is less pronounced in DS, highlighting distinct immunological profiles between the two groups (Table 2). NK cell lymphopenia appears to be less common in DS compared to T and B cell abnormalities. Most studies report normal or slightly elevated NK cell numbers, although functional impairments have been documented (15,36,37). This relative preservation of NK cell counts may be attributed to their thymus-independent development and distinct homeostatic regulation, in contrast to the T and B cell lineages, which are more affected in DS (36,37).

Several hypotheses have been proposed to explain the T-cell and B-cell impairments observed in DS.

Histological analyses of thymic tissue from children with DS reveal a blockage in early T lymphocyte development, suggesting a defect in thymic output (38). However, other factors appear to contribute to T lymphopenia as well. Notably, the deficiency of trace elements, such as zinc, which is commonly found in DS patients, may also play a role (27,39,40). An Italian study, for instance, demonstrated that oral zinc supplementation not only reduced recurrent infections but also increased circulating T lymphocyte numbers, although it had no effect on circulating B cell counts (41). Increased apoptosis is another prominent theory. Elsayed et al. observed elevated levels of early apoptotic cells, particularly T cells, in children with DS compared to healthy controls, suggesting that accelerated aging may be one of the mechanisms underlying immune system impairments in DS (42). Another hypothesis involves the over-expression of genes on chromosome 21, which encodes interferon receptor genes, including IFNAR1, IFNAR2, and IFNGR2. Xiao-Fei Kong et al. reported elevated IFN-R expression on monocytes, along with increased levels of phosphorylated STAT1 in both non-stimulated and IFN-α- and IFN-γ-stimulated monocytes from 45 DS patients. They suggested that the decrease in T cells may be linked to their overactivation and subsequent premature senescence (4).

Our study was notable for a higher frequency of CD8 lymphopenia than previously reported. While most of the mechanisms described above have traditionally been invoked to explain CD4+ T-cell lymphopenia, they are not necessarily restricted to the CD4+ compartment. Thymic hypoplasia (38), increased apoptosis (42), chronic type I interferon signaling, and premature immunosenescence (4) likely affect both CD4+ and CD8+ T-cell subsets. In addition, deficiencies in essential trace elements such as zinc and selenium-frequently reported in individuals with DS-may further impair T-cell proliferation and survival, thereby impacting CD8+ T cells as well (27,39,40). Thus, CD8+ lymphopenia, though less frequently reported, may emerge in some individuals as a result of a more global disruption of T-cell homeostasis in DS.

Respiratory tract infections were the most common infectious complication in our cohort, consistent with findings from most studies (15,21,25). Although T-cell and B-cell impairments are consistently observed in DS, the variations noted are moderate and do not fully explain the heightened susceptibility to infections. A Brazilian study comparing the immunological profiles of DS patients with and without recurrent infections found no significant immunological differences between the two groups, despite a diminished response to the pneumococcal vaccine in those with recurrent infections (24). Both groups showed normal Ig levels and T cell counts, with only a slight reduction in B lymphocytes. Recurrent infections in DS may be influenced by other DS-related conditions, such as airway malformations (e.g., laryngomalacia, tracheal stenosis, tracheomalacia, bronchomalacia, and tracheal bronchus), as well as associated comorbidities, including cardiovascular and musculoskeletal complications (43).

Conclusion

Down syndrome is a multifaceted condition that affects various organ systems, including the immune system. Children with DS typically present with diminished T- and B-cell counts, while maintaining generally normal levels of IgG, IgA, and IgM. Our findings suggest that T cell lymphopenia in DS is less pronounced compared to patients with combined immunodeficiency. Furthermore, the increased susceptibility to infections in DS appears to be the result of a confluence of factors inherent to trisomy 21, rather than being solely attributable to intrinsic dysfunctions of T and B cells.

References

1. Antonarakis SE, Skotko BG, Rafii MS, Strydom A, Pape SE, Bianchi DW, et al. Down syndrome. Nat Rev Dis Primers. 2020 Feb 6;6(1):9.
2. Marilyn J. Bull M. D. Down Syndrome. Ropper AH, editor. N Engl J Med. 2020 Jun 11;382(24):2344–52.
3. Moyer AJ, Gardiner K, Reeves RH. All Creatures Great and Small: New Approaches for Understanding Down Syndrome Genetics. Trends Genet. 2021 May;37(5):444–59.
4. Kong XF, Worley L, Rinchai D, Bondet V, Jithesh PV, Goulet M, et al. Three Copies of Four Interferon Receptor Genes Underlie a Mild Type I Interferonopathy in Down Syndrome. J Clin Immunol. 2020 Aug;40(6):807–19.
5. Letourneau A, Santoni FA, Bonilla X, Sailani MR, Gonzalez D, Kind J, et al. Domains of genome- wide gene expression dysregulation in Down's syndrome. Nature. 2014 Apr 17;508(7496):345– 50.
6. Pelleri MC, Cattani C, Vitale L, Antonaros F, Strippoli P, Locatelli C, et al. Integrated Quantitative Transcriptome Maps of Human Trisomy 21 Tissues and Cells. Front Genet. 2018 Apr 24;9:125.
7. Verstegen RHJ, Kusters MAA. Inborn Errors of Adaptive Immunity in Down Syndrome. J Clin Immunol. 2020 Aug;40(6):791–806.
8. Lagan N, Huggard D, Mc Grane F, Leahy TR, Franklin O, Roche E, et al. Multiorgan involvemen and management in children with Down syndrome. Acta Paediatrica. 2020 Jun;109(6):1096–111.
9. Englund A, Jonsson B, Zander CS, Gustafsson J, Annerén G. Changes in mortality and causes of death in the Swedish Down syndrome population. American J of Med Genetics Pt A. 2013 Apr;161(4):642–9.
10. Bittles AH, Bower C, Hussain R, Glasson EJ. The four ages of Down syndrome. The Europea Journal of Public Health. 2007 Feb 13;17(2):221–5.
11. Day SM, Strauss DJ, Shavelle RM, Reynolds RJ. Mortality and causes of death in persons with Down syndrome in California. Developmental Medicine & Child Neurology. 2007 Feb 13;47(3):171–6.
12. 12. O'Leary L, Hughes-McCormack L, Dunn K, Cooper S. Early death and causes of death of people with Down syndrome: A systematic review. Research Intellect Disabil. 2018 Sep;31(5):687–708.
13. Da Rosa Utiyama SR, Nisihara RM, Nass FR, Oliveira NP, Fiedler PT, De Messias-Reason IT. Autoantibodies in patients with Down Syndrome: Early senescence of the immune system or precocious markers for immunological diseases? J Paediatrics Child Health. 2008 Apr;44(4):182– 6.
14. Henry E, Walker D, Wiedmeier SE, Christensen RD. Hematological abnormalities during the first week of life among neonates with Down syndrome: Data from a multihospital healthcare system. American J of Med Genetics Pt A. 2007 Jan;143A(1):42–50.
15. Ram G, Chinen J. Infections and immunodeficiency in Down syndrome. Clinical and Experimental Immunology. 2011 Mar 10;164(1):9–16.
16. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022 Oct;42(7):1473–507.
17. Joshi AY, Abraham RS, Snyder MR, Boyce TG. Immune evaluation and vaccine responses in Down syndrome: Evidence of immunodeficiency? Vaccine. 2011 Jul;29(31):5040–6.
18. Dieudonné Y, Uring-Lambert B, Jeljeli MM, Gies V, Alembik Y, Korganow AS, et al. Immune Defect in Adults With Down Syndrome: Insights Into a Complex Issue. Front Immunol. 2020 May 8;11:840.
19. Cocchi G, Mastrocola M, Capelli M, Bastelli A, Vitali F, Corvaglia L. Immunological patterns in young children with Down syndrome: is there a temporal trend? Acta Paediatrica. 2007 Oct;96(10):1479–82.
20. Yılmaz C, Doğan M, Başarslan F, Yılmaz N, Yuca S, Bulan K, et al. Evaluation of Lymphocyte Subgroups in Children With Down Syndrome. Clin Appl Thromb Hemost. 2015 Sep;21(6):546–9.
21. Mitwalli M, Wahba Y, Shaltout A, Gouida M. Lymphocyte subgroups and recurrent infections in children with Down syndrome – a prospective case control study. cejoi. 2018;43(3):248–54.
22. de Hingh YCM, van der Vossen PW, Gemen EFA, Mulder AB, Hop WCJ, Brus F, et al. Intrinsic abnormalities of lymphocyte counts in children with down syndrome. J Pediatr. 2005 Dec;147(6):744–7.
23. Claudia M. Merhar, Diana I. Liberatore. Immune compromise in patients with Down syndrome. A case series. Arch Argent Pediat [Internet]. 2024 Jun 1 [cited 2024 Sep 20];122(3). Available from: https://www.sap.org.ar/docs/publicaciones/archivosarg/2024/v122n3a11e.pdf
24. Martins KR, Alves FA, Silva LRD, Silva LOAD, Segundo GRS. Different immunological patterns of Down syndrome patients with and without recurrent infections. Jornal de Pediatria. 2024 Jul;S0021755724000883.
25. Martínez E, Castañeda D, Jaramillo S, Iregui A, Quiñonez T, Rodríguez JA, et al. Altered immune parameters correlate with infection-related hospitalizations in children with Down syndrome. Human Immunology. 2016 Jul;77(7):594–9.
26. Huggard D, Worrall AP, Kirkham C, McGrane F, Mandira R, Casey L, et al. Immune screening in children with Down Syndrome. Acta Paediatrica. 2022 Oct;111(10):2025–8.
27. Stabile A, Pesaresi MA, Stabile AM, Pastore M, Sopo SM, Ricci R, et al. Immunodeficiency and plasma zinc levels in children with Down's syndrome: a long-term follow-up of oral zinc supplementation. Clin Immunol Immunopathol. 1991 Feb;58(2):207–16.
28. Tahiat A, Belbouab R, Yagoubi A, Hakem S, Fernini F, Keddari M, et al. Flow cytometry-based diagnostic approach for inborn errors of immunity: experience from Algeria. Front Immunol. 2024 Jul 12;15:1402038.
29. Nespoli L, Burgio GR, Ugazio AG, Maccario R. Immunological features of Down's syndrome: a review. J Intellect Disabil Res. 1993 Dec;37 (Pt 6):543–51.
30. Ugazio AG, Maccario R, Notarangelo LD, Burgio GR. Immunology of Down syndrome: A review. Am J Med Genet. 2005 Jun 3;37(S7):204–12.
31. Broers CJ, Gemke RJ, Weijerman ME, Kuik D, Van Hoogstraten IM, Van Furth AM. Frequency of lower respiratory tract infections in relation to adaptive immunity in children with Down syndrome compared to their healthy siblings. Acta Paediatrica. 2012 Aug;101(8):862–7.
32. Kusters MAA, Verstegen RHJ, Gemen EFA, De Vries E. Intrinsic defect of the immune system in children with Down syndrome: a review. Clinical and Experimental Immunology. 2009 Apr 8;156(2):189–93.
33. Szczawińska-Popłonyk A, Popłonyk N, Awdi K. Down Syndrome in Children: A Primary Immunodeficiency with Immune Dysregulation. Children. 2024 Oct 17;11(10):1251.
34. Schoch J, Rohrer TR, Kaestner M, Abdul-Khaliq H, Gortner L, Sester U, et al. Quantitative, Phenotypical, and Functional Characterization of Cellular Immunity in Children and Adolescents With Down Syndrome. The Journal of Infectious Diseases. 2017 May 15;215(10):1619–28.
35. Verstegen RHJ, Driessen GJ, Bartol SJW, Van Noesel CJM, Boon L, Van Der Burg M, et al. Defective B-cell memory in patients with

Down syndrome. Journal of Allergy and Clinical Immunology. 2014 Dec;134(6):1346-1353.e9.

36. Carsetti R et al. The immune system of children with Down syndrome. Front Pediatr. 2020;8:73.
37. Kusters MA et al. Immunological studies in children with Down syndrome: evidence for defective memory T cell generation. J Immunol. 2010;185(11):6621–7.
38. Musiani P, Valitutti S, Castellino F, Larocca LM, Maggiano N, Piantelli M. Intrathymic deficient expansion of T cell precursors in Down syndrome. Am J Med Genet. 2005 Jun 3;37(S7):219–24.
39. Lockitch G, Puterman M, Godolphin W, Sheps S, Tingle AJ, Quigley G. Infection and immunity in Down syndrome: a trial of long-term low oral doses of zinc. J Pediatr. 1989 May;114(5):781–7.
40. Levin S, Nir E, Mogilner BM. T system immune-deficiency in Down's syndrome. Pediatrics. 1975 Jul;56(1):123–6.
41. Franceschi C, Chiricolo M, Licastro F, Zannotti M, Masi M, Mocchegiani E, et al. Oral zinc supplementation in Down's syndrome: restoration of thymic endocrine activity and of some immune defects. J intellect Disabil Res. 1988 Jun;32(3):169–81.
42. Elsayed SM, Elsayed GM. Phenotype of apoptotic lymphocytes in children with Down syndrome. Immun Ageing. 2009 Mar 6;6:2.
43. Ghezzi M, Garancini N, De Santis R, Gianolio L, Zirpoli S, Mandelli A, et al. Recurrent Respiratory Infections in Children with Down Syndrome: A Review. Children. 2024 Feb 15;11(2):246.