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Immune system defects in DiGeorge syndrome and association with clinical course

Ercan Nain MD[1] | **Ayca Kiykim MD**[1] | **Ismail Ogulur PhD**[1] | **Nurhan Kasap MD**[1] | **Elif Karakoc-Aydiner MD**[1,2] | **Ahmet Ozen MD**[1,2] | **Safa Baris MD**[1,2]

[1]Faculty of Medicine, Pediatric Allergy and Immunology, Marmara University, Istanbul, Turkey

[2]Istanbul Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Istanbul, Turkey

Correspondence
Safa Baris, Pediatric Allergy and Immunology, Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Marmara University Hospital, Istanbul, Turkey.
Emails: safabaris@hotmail.com, sbaris@marmara.edu.tr

Abstract

We evaluated 18 DiGeorge syndrome (DGS) patients and aimed to investigate the immunological changes in this population. DGS patients with low naive $CD4^+$T and $CD8^+$T cells were defined as high-risk (HR) patients, whereas patients with normal numbers of naive $CD4^+$ and $CD8^+$T cells were defined as standard risk (SR) patients. Level of serum IgM, $CD3^+$ T cell counts and percentages of class-switched memory B cells were significantly low in HR group compared to SR ones. Severe infections and persistent hypoparathyroidism were detected significantly higher in HR group. Patients with reduced percentages of class-switched B cells had earlier onset of infection, lower blood IgM, lower $CD4^+$ and $CD8^+$T counts than patients with normal class-switched memory B cells. Decreased levels of IgM were associated with low numbers of naive $CD4^+$ and recent thymic emigrants T cells. Monitoring the immune changes of patients with DGS would be useful to predict the severe phenotype of disease.

1 | INTRODUCTION

DiGeorge syndrome (DGS) is a common genetic disorder, also known as chromosome 22q11.2 deletion syndrome, with a prevalence of 1:4000–1:6000.[1,2] The phenotypic features include conotruncal heart defects, hypoparathyroidism, characteristic facies, a wide degree of immune deficiency[3,4] and autoimmunity.[5] Many patients have low T cells numbers due to thymic hypoplasia,[6,7] and this condition is prominent in paediatric age group and renders the patients susceptible to infections.[8] Although the T cell counts raise with age, recurrent infections may be still observed in one third of adolescent DGS patients.[9]

Previously, longitudinal immunological studies were conducted to predict the outcome of DGS.[9-13] Sediva et al[10] demonstrated normalization of $CD4^+$T cells numbers in the majority of patients up to the 3 years. In another observational study, the $CD8^+$T cells reached normal levels at 2 years in 81% of patients when compared to the healthy controls.[11] Interestingly, beyond the T-cell compartments, B-cell abnormalities were also described in DGS and the median recovery time of B cells was found as 1.4 years.[11] Another study conducted with partial DGS patients displayed that 20 out of 25 patients had recurrent bacterial and viral infections in the presence of low $CD8^+$T cells.[12] DGS patients characterized by persistent low numbers of $CD4^+CD45RA^+$ and $CD8^+$T cells during the follow-up were prone more to lethal infections and lymphoproliferative disorders.[13] Although all these studies denote the alleviation of the clinical and immunological phenotypes of DGS patients with age, some patients continue to suffer from severe infections. In this study, we aimed to investigate the immunological changes and their association with the clinical features in DGS patients.

2 | MATERIAL AND METHODS

2.1 | Subject characteristics

Eighteen patients with 22q11.2 deletion syndrome who were diagnosed by florescent in situ hybridization method and followed up at the Pediatric Allergy and Immunology Outpatient Clinic of Marmara University were included in the study. Detailed description of patients and laboratory data were collected from patients' files and evaluated retrospectively. The study protocol was approved by the local ethics committee of Marmara University (IRB number: 00009067).

2.2 | Laboratory findings

Serum immunoglobulin levels (IgG, IgA, IgM, IgG subclasses) were determined by nephelometric immunoassay (BN2; Dade Behring) and compared with age-matched reference ranges for Turkish children.[14] Serum total IgE level was measured by Immulite immunoassay method (Euro/DPC).

For the immunophenotyping, blood lymphocytes were stained with the following antibodies at optimal concentrations: fluorescein isothiocyanate (FITC)-conjugated anti-CD3, CD4, CD45, CD45RA, IgM, TCRαβ; phycoerythrin (PE)-conjugated anti-CD4, CD8, CD14, CD16+56, CD19, CD21, CD31, CD45RA, CD45RO, IgD; peridin chlorophyll protein (PreCP)-conjugated anti-CD3, CD4, CD8, CD14, CD19; allophycocyanin (APC)-conjugated anti-CD8, CD20 and CD27. All antibodies were purchased from Becton Dickinson (San Jose, CA, USA), except for CD197 (CCR7) (Biolegend). Naive T cells were defined as $CD45RA^{+}RO^{-}$, memory T cells as $CD45RA^{-}RO^{+}$ and recent thymic emigrants (RTE) as $CD4^{+}CD45RA^{+}CD31^{+}$ T cells. B cells were grouped as naïve ($CD27^{-}IgD^{+}$), non-class-switched memory ($CD27^{+}IgD^{+}$) and class-switched memory ($CD27^{+}IgD^{-}$) B cells. Lymphocyte subgroup results were compared with age-matched reference ranges.[15,16]

2.3 | Statistical analysis

The normality of the distribution was assessed by Kolmogorov-Smirnov test. Descriptive statistics were expressed as frequency, percentage, mean ± SD (standard deviation) and median with interquartile range (IQR). Continuous variables were analysed by independent Student's *t* test and Mann-Whitney *U* tests as appropriate. For categorical variables, differences between the groups were assessed by chi-square analysis. All analyses were performed by the Statistical Package for the Social Sciences (SPSS) program (version 16.0; SPSS Inc) using default settings. Statistical significance level was set as $P < .05$.

3 | RESULTS

3.1 | Clinical features of DGS patients

Eighteen patients (9 males and 9 females) with a diagnosis of DGS were included into the study. The median age of symptoms onset was 2 days (range: 1-30); the median age at diagnosis was 1 month (range: 1-18) with a median delay of 2 months. The patients were referred to our clinic for immunological evaluation at a median age of 19 months (range: 9.5-61). The demographic and clinical features of the patients are summarized in Table 1.

3.2 | Immunological evaluation of DGS patients

Seventeen patients were evaluated immunologically by immunoglobulin levels, antibody responses and lymphocyte subset analysis. The majority of the patients had normal IgG, IgM and IgA levels (n:14, n:11 and n:12, respectively) compared to the age-matched Turkish healthy controls.[14] Hepatitis B antisurface antibody titres were negative in 14 patients (77.7%). Baseline lymphocyte subsets were evaluated and compared with age-matched healthy donors in 17 patients, and decreased percentages of T cells in 41% (n:7), $CD4^{+}$T cells in 29% (n:5), $CD8^{+}$T cells in 35% (n:6) and $CD19^{+}$B cells in 11.7% (n:2) patients were detected (Figure 1A-D).

3.3 | Immunological defects that relate to the disease course of DGS patients

In our cohort, the final categorization of patients was adjusted according to the Eberle et al[13] criteria, which defined the DGS patients with persistent low naive $CD4^{+}$T cells and $CD8^{+}$T cells as high-risk (HR) group at the period between 12 and 72 months. However, patients with normal numbers of naive $CD4^{+}$ and $CD8^{+}$T cells were defined as standard risk (SR) group. The lower normal cut-off values for the naive $CD4^{+}$T cells and $CD8^{+}$T cells were accepted as 430 and 490 cells/μL, respectively.[13] The HR patients have more documented lethal infections and lymphoproliferative complications.[13] In our cohort, during the last clinical examination of the study, six patients were classified as HR (patients 2, 3, 6, 8, 12, 13), while the rest as SR (patients 1, 4, 5, 7, 9, 10, 11, 14, 15, 17, 18) (Table 1). Patient 16 was excluded from the evaluation due to the loss of follow-up. There were no differences between the final ages of patients in SR and HR groups (8.0 ± 6.1 vs 7.1 ± 4.5 years). The comparison between two groups revealed significantly lower levels of serum IgM, $CD3^{+}$T-cell counts and percentages of class-switched B cells in HR groups ($P = .030$, $P = .034$, $P = .004$, respectively). On the other hand, naive B cells were increased

TABLE 1 The demographic and clinical features of patients with 22q.11.2 deletion syndrome

Patient	Current age (yrs/sex)	AOO (mo)	Risk group	Congenital heart disease	Other abnormalities
1	3.5/female	1	SR	Secundum ASD, perimembranous VSD, PFO	HPT
2	5/female	1	HR	Tetralogy of Fallot, right arcus aorta, aberrant left subclavian artery	GER, tracheomalacia, HPT
3	27/male	3	HR	Undetectable	Sliding hiatal hernia, HPT
4	6/male	2	SR	VSD, ASD	HPT, umbilical hernia, scoliosis, cleft palate, swallow difficulty
5	4/male	2	SR	Tetralogy of Fallot	Undetectable
6	1.5/male	2	HR	Tetralogy of Fallot, PDA	GER, tracheomalacia, diaphragmatic hernia, coloboma iridis, sensorineural hearing loss
7	6/male	2	SR	AS, aortic valve insufficiency, arcus aorta anomaly	Right renal agenesis, scoliosis
8	5.5/male	1	HR	Double arcus aorta	HPT, cleft palate
9	15.5/male	1	SR	VSD	Scoliosis
10	11/male	12	SR	VSD, complete AV block	HPT, bilateral Inguinal hernia, cleft palate
11	2/female	1	SR	Undetectable	GER, HPT
12	1/male	1	HR	Tetralogy of Fallot	GER, HPT, left hydroureteronephrosis, diaphragmatic hernia
13	1/female	1	HR	ASD, VSD	Left pelvicaliectasis, laryngeal web, accessory finger
14	2/female	1	SR	Circumflex aorta, high venosum ASD, PDA, Kommerell diverticulum	Laryngomalacia, laryngeal web
15	1.5/female	1	SR	Interrupted aortic arcus type B, VSD, AS	Failure to thrive, benign external hydrocephalus
16	1/female	1	UK	Truncus arteriosus	Left multicystic kidney, right pelvicaliectasis, HPT
17	12/female	3	SR	Mitral valve insufficiency	Right pelvicaliectasis, cleft palate
18	2/female	1	SR	Undetectable	Undetectable

Abbreviations: AOO, Age of onset; AS, aortic valve stenosis; ASD, atrial septal defect; GER, gastroesophageal reflux; HPT, hypoparathyroidism; HR, high risk; PDA, patent ductus arteriosus; PFO, patent foramen ovale; SR, standard risk; UK, unknown; VSD, ventricular septal defect.

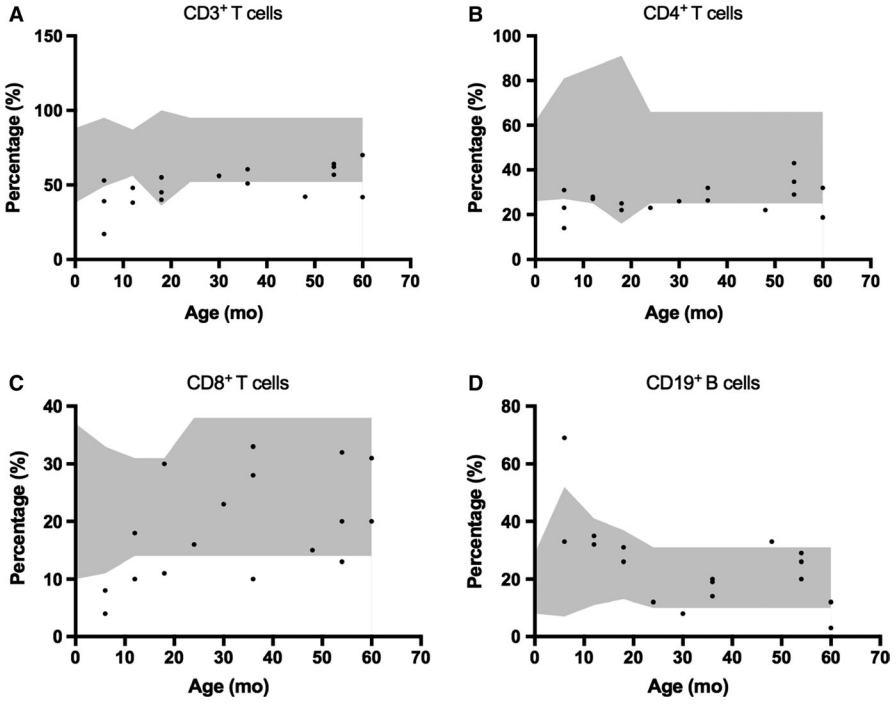

FIGURE 1 Percentages of several lymphocyte subtypes in peripheral blood of DGS patients. $CD3^+$ (A), $CD4^+$ (B), $CD8^+$ (C) T cells and $CD19^+$ B cells (D). Grey areas represent age-adjusted normal ranges according to Schatorje et al[15]

TABLE 2 Comparison of the immunological properties and IVIG treatment of patients with SR and HR groups

Parameters	SR patients	HR patients	*P*-value
Age at the evaluation (y)	8.0 ± 6.1	7.1 ± 4.5	n.s.
IgM (mg/dL) (mean ± SD)	87 ± 32	45 ± 25	.030*
$CD3^+$T (cells/μL) (mean ± SD) (median/IQR)	1731 ± 645 1609 (1462-2166)	970 ± 476 791 (630-1536)	.034*
$CD8^+$T (cells/μL) (mean ± SD) (median/IQR)	816 ± 387 668 (639-848)	238 ± 68 216 (199-312)	.010*
$CD4^+CD45RA^+$T (cells/μL) (mean ± SD) (median/IQR)	379 ± 127 431 (259-492)	196 ± 111 208 (82-278)	.015*
Naive B cells (%) (mean ± SD) (median/IQR)	66.3 ± 15.2 68 (57.3-76.5)	88.8 ± 4.5 87.9 (84.6-91.8)	.010*
B class-switched cells (%) (mean ± SD) (median/IQR)	14.5 ± 8.3 12 (7.2-24.6)	2.8 ± 2.2 2.4 (1-4.35)	.004*
IVIG treatment (n (%))	2/11 (18%)	5/6 (83.3%)	.035**

Note: Normal ranges of IgM for 7-8 y: 69-387 mg/dL.
Abbreviations: IQR, Interquartile range; IVIG, intravenous immunoglobulin; n.s., non-significant; SD, standard deviation.
*Mann-Whitney *U* test.
**Chi-square test.

in HR patients compared to the SR ones ($P = .010$) (Table 2). In our study, patients received intravenous immunoglobulin (IVIG) with a dose of 300-800 mg/kg (median: 500 mg/kg) every 3-4 weeks. Interestingly, compared to the SR patients (n:2, 18%), HR patients (n:5, 83.3%) required more IVIG replacement therapy ($P = .035$, Table 2).

To further characterize the immune phenotype of DGS patients, we evaluated the last percentages of class-switched memory B cells as a marker to guide the outcome of patients. Accordingly, age at infection onset, the last evaluated age-matched $CD3^+$ and $CD8^+$T cells counts were found statistically low in patients with reduced class-switched B cells compared to the normal ones ($P = .037$, $P = .016$, $P = .006$, Figure 2A, Table 3). The final levels of IgA and IgG were not different between two groups; however, serum IgM was lower in patients with reduced class-switched memory B cells ($P = .030$). During the last evaluation, patients with persistent low IgM were found to have decreased naive $CD4^+$T cells counts (214 ± 112/mm^3 vs 430 ± 208/mm^3) and RTE counts (176 ± 135/mm^3 vs 368 ± 179/mm^3) compared to patients with normal serum IgM levels ($P = .028$, $P = .040$, respectively, Figure 2B).

3.4 | Infections, autoimmunity and other complications and their association with the defined immunological markers

Infections and non-infection complications occurred in both SR and HR groups (Table 4). Invasive candida infections were detected only in HR patients (Patient 3 had *Candida* spp. pneumonia and Patient 6 had *Candida* spp. septicaemia). One HR patient (Patient 3) experienced pulmonary *Mycobacterium tuberculosis*. Overall, the rate of these described infections was statistically higher in HR compared to the SR group ($P = .020$).

We have detected a high frequency (27.7%) of autoimmune disease in our cohort (patients 2, 3, 8, 10 and 18). Three patients in HR group manifested with autoimmune diseases (Patient 2 had psoriasis, Patient 3 had idiopathic thrombocytopenic purpura (ITP), and Patient 8 had autoimmune haemolytic anaemia). Two patients of SR patients suffered from autoimmune diseases (Patient 10 had ITP and Patient 18 had Juvenile idiopathic arthritis). There was no significant difference in terms of autoimmune diseases between two groups.

Hypoparathyroidism was observed in nine patients (52.9%). Hypoparathyroidism was recorded in four of six HR patients (patients 2, 3, 8, 12) and in four of 10 SR patients (patients 1, 4, 10, 11). During the follow-up, persistent hypoparathyroidism was detected only in HR group (patients 3, 8, 12) and was significantly higher than SR group ($P = .035$, Table 1).

4 | DISCUSSION

In this study, we evaluated the clinical and immunological features of patients with DGS and aimed to investigate

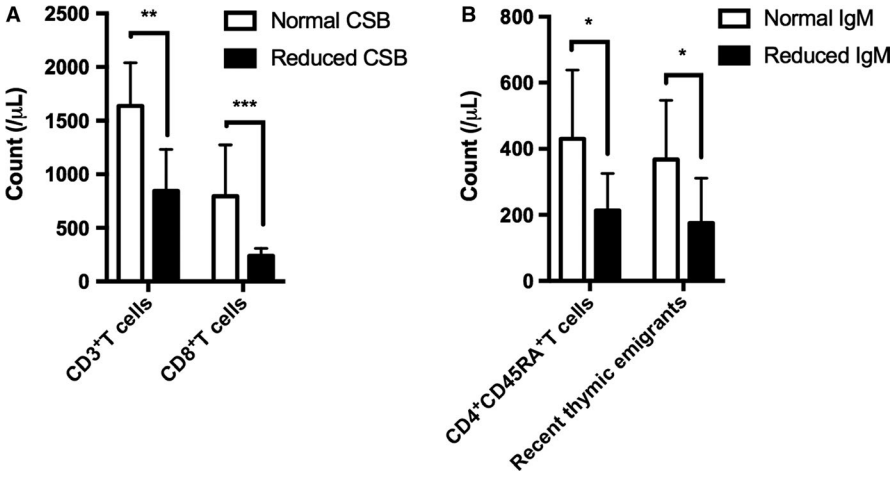

FIGURE 2 Class-switched memory B cells and serum IgM levels as risk factors in DGS. The $CD3^+$ and $CD8^+$ T cells counts were statistically decreased in patients with reduced class-switched memory B cells (A). Low IgM levels were associated with reduced numbers of naive $CD4^+$ and recent thymic emigrants T cells (B).*P < .05, **P < .01, ***P < .001. CSB, Class-switched memory B cells

TABLE 3 Comparison of the clinical and immunological findings of patients according to the class-switched memory B-cell levels

Parameters	Patients with normal % of CSB cells (n = 7)	Patients with reduced % of CSB cells (n = 6)	*P*-value
Age at the evaluation (y)	9.1 ± 7.4	7.9 ± 5.5	n.s.
Age at infection onset (mo) (mean ± SD)	3 ± 4	1 ± 1	.037*
$CD3^+$T (cells/μL) (mean ± SD) (median/IQR)	1637 ± 405 1573 (1493-1652)	845 ± 388 753 (630-862)	.016*
$CD8^+$T (cells/μL) (mean ± SD) (median/IQR)	710 ± 294 656 (639-748)	239 ± 71 216 (199-312)	.006*
IgA (mg/dL) (mean ± SD) (median/IQR)	127 ± 83 108 (67-190)	44 ± 40 33 (17-59)	.050*
IgM (mg/dL) (mean ± SD) (median/IQR)	187 ± 32 80 (57-113)	45 ± 25 47 (18-65)	.030*

Abbreviations: CSB, Class-switched B cells; IQR, interquartile range; n.s., non-significant; SD, standard deviation.
*Mann-Whitney *U* test.

the immunological changes in this population. Apart from low naive $CD4^+$ and $CD8^+$T cells, which are known as risk factors for HR patients, the current study demonstrated that patients with reduced percentages of class-switched B cells had earlier onset of infection, lower blood IgM, lower $CD4^+$ and $CD8^+$T counts than patients with normal class-switched memory B cells. Decreased levels of IgM were associated with low numbers of naive $CD4^+$ and recent thymic emigrants T cells.

Reduced class-switched B cells were observed in patients with common variable immune deficiencies, CD40L and ICOS deficiencies and were linked with splenomegaly, granulomatous disease, chronic lung disease and autoimmunity.[17,18] Recently, low class-switched B cells were also defined in some DGS patients.[19,20] In our cohort, some DGS patients demonstrated abnormalities in B-cell pool, which were characterized by significant low class-switched B cells and increased naive B cells. Patients with persistent low class-switched memory B cells had earlier infection presentation than patients with normal levels of class-switched B cells.

Low levels of IgG, IgA, IgM and impaired antibody responses to vaccines were described before in DGS.[12,21-23] Severe infections observed in DGS were attributed to humoral immune deficiency.[12,21] Our results showed significantly lower serum IgM levels in HR patients. Previously,

TABLE 4 Infections, autoimmunity and other complications of patients with 22q.11.2 deletion syndrome

Groups	Infections and complications	Autoimmunity	Failure to thrive	IVIG tx
HR patients				
2	Recurrent bronchiolitis	Psoriasis	(+)	(+)
3	Recurrent pneumonia *Candida* spp. Pulmonary tuberculosis BE	ITP	(+)	(+)
6	Recurrent bronchiolitis Pneumonia Candida sepsis Pneumothorax Tracheostomy	—	(+)	(+)
8	Recurrent bronchiolitis	AIHA	(−)	(−)
12	Pneumonia	—	(+)	(+)
13	Pneumonia	—	(+)	(+)
SR patients				
1	Recurrent bronchiolitis	—	(−)	(−)
4	Pneumonia Moniliasis	—	(+)	(−)
5	Diarrhoea	—	(−)	(−)
7	Recurrent bronchiolitis	—	(+)	(−)
9	Pneumonia BE	—	(+)	(−)
10	Pneumonia	ITP	(+)	(+)
11	Moniliasis	—	(+)	(−)
14	Recurrent bronchiolitis	—	(+)	(−)
15	Pneumonia	—	(+)	(−)
17	Pneumonia Diarrhoea BE	—	(+)	(−)
18	Recurrent bronchiolitis	JIA	(−)	(+)

Abbreviations: AIHA, Autoimmune haemolytic anaemia; BE, bronchiectasis; HR, high risk; ITP, idiopathic thrombocytopenic purpura, JIA, juvenile idiopathic arthritis; SR, standard risk; Tx, therapy.

Eberle et al[13] showed $CD4^+CD45RA^+CD31^+$T cells as a useful marker for early detection of persistent impaired thymic activity in DGS patients. In line with Eberle et al study, our patients with reduced IgM showed lower numbers of naive $CD4^+$ and RTE T cells compared to the patients with normal IgM levels. Our results indicate that in patients with low IgM levels, analysis of RTE could help to determine the persistent defective thymic output at early stage of disease. Further studies are required to straight this association.

In our study, infections were observed in both SR and HR groups. The most common infection was noted as pneumonia, which was similar to other reports.[11,12] In HR group, two patients suffered from invasive candida infection and one from pulmonary tuberculosis. Eberle et al[13] detected that fatal infections and lymphoproliferative complications were observed more frequently in HR patients. Another study showed that three DGS patients had septicaemia due to fungal pathogens (*Candida tropicalis* and *Cryptococcus neoformans*). In accordance with our patients, $CD3^+$, $CD4^+$ and $CD8^+$T cells were found to be low in these described patients.[11]

Autoimmune diseases in patients with DGS have been reported sporadically with a frequency range from 10% to 18%.[4,24,25] Autoimmunity is more common in DGS patients with recurrent severe infection.[24] On the other hand, less autoimmune diseases were observed in patients with high number of naive $CD4^+$ T cells.[25] High frequency (27.7%) of autoimmune diseases was detected in our patients when

compared to other previous reported studies. Interestingly, autoimmune manifestations were equal in HR and SR patients. Further studies are required to uncover the risk factors, which are responsible for autoimmunity in DGS patients.

This study had some limitations, which need to be mentioned. First, the low number of patients hinders detailed analyses during the study. Therefore, further studies are required to enlighten our results. Second, since the study was carried out at a tertiary university hospital, some patients were referred to our centre after normalization of cellular immunity. Therefore, baseline immune evaluations were not possible for those patients.

In our study, apart from the known immune defects in DGS, we demonstrated that patients with low class-switched memory B cells and IgM levels had more severe immune phenotype compared to other DGS patients. Monitoring the class-switched memory B cells and IgM levels would be useful markers to detect high-risk patients at an early stage of disease. Further studies with more patients are needed to clarify these findings.

CONFLICT OF INTEREST

The author declares that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

EN followed up the patients, registered and analysed the clinical and immunological findings of patients and wrote the manuscript. IO performed flow cytometry analysis. AK, NAK, EKA, AO followed up the patients. SB designed the study and made a critical review of the manuscript. EN and SB have full access to all of the data and take responsibility for the integrity and the accuracy of the manuscript.

ORCID

Ercan Nain https://orcid.org/0000-0003-2560-9210
Ayca Kiykim https://orcid.org/0000-0001-5821-3963
Ismail Ogulur https://orcid.org/0000-0001-8282-7762
Nurhan Kasap https://orcid.org/0000-0001-5432-4076
Elif Karakoc-Aydiner https://orcid.org/0000-0003-4150-5200
Ahmet Ozen https://orcid.org/0000-0002-9065-1901
Safa Baris https://orcid.org/0000-0002-4730-9422

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