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Research Paper

Neurocognitive Evaluation of Patients With DiGeorge Syndrome

Zuhal Karali, MD [a], Yasin Karali, MD [a], Sukru Cekic, MD [a], Berfin Altinok, MD [a], Muhittin Bodur, MD [b], Mustafa Bostanci, MD [b], Sara S. Kilic, MD [a,*]

[a] Division of Pediatric Immunology, Uludag University Faculty of Medicine, Bursa, Turkey
[b] Division of Pediatric Neurology, Uludag University Faculty of Medicine, Bursa, Turkey

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ABSTRACT

Background: DiGeorge syndrome (DGS), the most common microdeletion syndrome, affects multiple organs, including the heart, the nervous system, and the immune system. In this study, we aimed to evaluate the clinical, laboratory, brain magnetic resonance imaging (MRI), and neurocognitive findings of our patients with DGS.
Methods: Clinical and laboratory data of 52 patients with DGS between June 2000 and March 2022 were evaluated retrospectively. Brain MRI and neuropsychologic tests were performed to assess the neurocognitive status of the patients.
Results: Fifty-two patients (28 males and 24 females) were included in our study. Fifteen of them died during the follow-up. All 37 patients who are alive had partial DGS. The median age of patients was 10 years and 7 months, and the median age at diagnosis was 5 years and 4 months. Bilateral conduction deceleration in the anterior visual pathways in six (20%) of 30 patients was determined by the visual evoked potentials. The auditory brainstem evoked potential test showed sensorineural hearing loss in 11 of 30 (36.6%) patients. Brain MRI disclosed brain parenchymal abnormalities in 18 of 25 (72%) patients. Impairments in executive functions, expressive language, and verbal memory were noted in 18 patients who were neuropsychologically assessed.
Conclusions: It is important to keep in mind that patients with DGS may be accompanied by neurocognitive findings. Awareness of the potential for underlying psychiatric and neurodevelopment disorders is key to anticipatory guidance, optimization of therapies, and maximizing life quality.
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Introduction

DiGeorge syndrome (DGS), also known as "22q11.2 deletion syndrome," (22q11.DS) is a genetic disorder caused by a hemizygous microdeletion of the long arm of chromosome 22. Although the prevalence of DGS varies depending on ethnicity, it is estimated to be one of 3000 to one of 6000. 22q11.2DS is the most common chromosomal microdeletion syndrome. 22q11.2DS is a syndrome affecting 50 genes and is seen with multiple system pathologies due to a deletion of the q11.2 band in one copy of chromosome 22.[1] This syndrome was first described by Dr. Angelo DiGeorge in 1965 in infants without thymus (thymic aplasia) and parathyroid glands (hypoparathyroidism); then, in the early 1980s, 22q11.2 deletion was demonstrated in cytogenetic studies. DGS can be seen in all races and ethnicities.[2,3] A wide range of multiorgan dysfunction, including cardiac and palatal abnormalities; immune and autoimmune disorders; endocrine, genitourinary, and gastrointestinal problems; and mental disorders as evinced by variable developmental delays, cognitive deficits, and psychiatric disorders (schizophrenia, depressive disorder, obsessive-compulsive disorder, anxiety disorders), was reported. The most common (82% to 100%) emerging symptoms are neurodevelopmental disorders

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* Communications should be addressed to: Dr. Kilic; Division of Pediatric Immunology; Uludag University Faculty of Medicine; Izmir Street; Bursa 16100, Turkey.
E-mail address: sebnemkl@uludag.edu.tr (S.S. Kilic).

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(behavioral disorder: autism spectrum disorder, attention-deficit/hyperactivity disorder; intellectual disability, communication disorders, and specific learning disorder).[4,5]

DGS may present with different clinical findings and organ dysfunction according to age groups. Immunodeficiency (75%), congenital cardiac anomalies (75%), and hypocalcemia (50%) due to hypoparathyroidism are mainly observed during childhood.[6] However, in adulthood and adolescence, hypocalcemia and neurodevelopmental disorders can be seen with accompanying psychiatric disorders. Psychiatric disorders seem to be diagnosed in adolescence.[7-10] About 25% of the patients with DGS have a diagnosis of schizophrenia.[11]

In this study, we aimed to evaluate the clinical, laboratory, brain magnetic resonance imaging (MRI), and neurocognitive findings of 52 patients diagnosed with DGS.

Methods

Patients

Patients with DGS who were followed up in the Bursa Uludag University Faculty of Medicine, Pediatric Immunology Division, outpatient clinic between June 2000 and March 2022 were included in the study. Clinical data (sex, age, family history, parental consanguinity, organ and system involvements of patients) and laboratory findings (immunologic tests; immunoglobulin serum levels and lymphocyte subsets) have been gathered from electronic files and evaluated retrospectively. Brain MRI and the neuropsychologic tests were performed during the study.

Neuropsychologic assessment is the performance-based evaluation of cognitive abilities performed through a battery approach involving multiple tests of various cognitive ability domains. For this purpose, a range of cognitive abilities, including reading, learning, mood, behavior, memory, attention, processing speed, reasoning, judgment and problem-solving, and spatial and language functions, are tested in our study.[12]

To evaluate the neurocognitive findings of the patients, the Denver II Test, which estimates the age-appropriate skills of children between the ages zero and six, was used to screen for asymptomatic neurodevelopmental disorders and to confirm suspicious situations with an objective criterion. Likewise, the Benton Visual Retention Test to assess age-appropriate visual perception, memory, and visuoconstructive abilities; the Bourdon Attention Test to assess a child's attention span; the Peabody Picture Vocabulary Test to determine the level of children's receptive language skills, comprehension of words via images, and vocabulary; the Serial Digit Learning Test to evaluate learning ability and short- and long-term memory; the Frankfurt Adaptive Concentration Test to determine whether the child's attention span is below, above, or at average; the KENT E-G-Y, a verbal performance test based on knowledge and language, to evaluate individuals' knowledge and to identify the pathology; and the R.B. Cattell 2A-3A Intelligence Test to rate intelligence through performance have been used.

The diagnoses associated with the patients' neurodevelopmental and psychiatric disorders were obtained retrospectively from their files. Patients were diagnosed according to the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition*, published by the American Psychiatric Association, as well as the Minnesota Multiphasic Personality Inventory test for schizophrenia over the age of 16, Maria Kovacs Children's Depression, and Beck Depression Scale according to age for depression diagnosis, family history, and psychiatric examination results.

Statistical analysis

Statistical analyses were performed using the SPSS 23 (IBM Corp.) statistical package. Categorical data were expressed as frequencies and percentages and continuous data as mean ± S.D. or median (minimum and maximum). Kolmogorov-Smirnov test and histogram were used to test the normality of the data distribution. Categorical variables were compared by using the Pearson chi-square test and Fisher exact test.

Results

Fifty-two patients, 28 males and 24 females, were included in the study; 15 died during follow-up. Of the patients who died, eight were female, seven were male, and six were with a complete DiGeorge. Fourteen patients died of heart failure due to conotruncal abnormalities, whereas one died from Hodgkin lymphoma.

All 37 patients (21 males, 16 females) under clinical follow-up had partial DGS. The mean age of the patients was 10 years and 7 months (range: 2 months to 49 years and 5 months), whereas the mean age at diagnosis was 5 years and 4 months (range: 1 month to 48 years and 1 month). All patients were under 18 years except for three adults. The parental consanguinity rate was 13.4%. The median age at diagnosis of these findings in patients with neurocognitive findings was 8 (1 to 46) years. The genetic results of 22q11 microdeletion examined by fluorescence *in situ hybridization* were positive in all our patients.

Neurodevelopmental disorders were the most common findings in 34 of 37 (91.8%) patients. Otolaryngeal findings were detected in 30 (81.0%) patients, including dysmorphic facial anomalies, bifid uvula, high-arched palate, narrow nares, prominent nasal root nasal anomalies, velopharyngeal insufficiency (hypernasal speech), feeding difficulties, hearing loss, and ear abnormalities (Table 1). Two patients had cancer, one with non-Hodgkin lymphoma (passed away) and one with mycosis fungoides.

Complete blood cell count evaluations revealed anemia in four patients, thrombocytopenia in two, and leukopenia in one patient. The median absolute lymphocyte count was 2434/mm^3, whereas absolute lymphocyte counts (10.8%) of four patients were below 1500/mm^3. CD3 lymphopenia was found in 19 of 52 (36.5%), with a low CD4 count in 11 and a low CD8 count in 17 patients. IgM levels were low in 20 (38.4%) patients, whereas IgG and IgA deficiencies were detected in five. Antibody responses to vaccines (anti-HBs or anti-tetanus IgG) were negative in 14 patients (37.8%). The absolute B cell count of all patients with low serum immunoglobulin levels was normal. Defects in the immune system, including cellular and/or humoral, were detected in 29 (55.7%) patients.

TABLE 1.
Distribution of Organ and System Involvements of 37 Patients With DGS Retrospectively

Affected Systems	Number of Patients n (%)
Neurodevelopmental disorders	34 (91.8)
Otolaryngeal	30 (81.0)
Cardiovascular	27 (72.9)
Immune-related	22 (59.4)
Psychiatric	20 (54.0)
Endocrine	17 (45.9)
Autoimmunity	13 (35.1)
Musculoskeletal	7 (18.9)
Hematological	5 (13.5)
Ophthalmologic	5 (13.5)
Genitourinary	4 (10.8)

Abbreviation:
DGS = DiGeorge syndrome

Neurological evaluation

The results of the auditory brainstem evoked potential test of 30 of 37 patients under follow-up were evaluated. Nineteen patients (63.3%) had normal results, whereas two had unilateral and seven had bilateral slowing in conduction velocity in bulbospinal excitatory pathways and two had peripheral conduction velocity defect. Bilateral conduction slowing in anterior visual pathways was detected in six of 30 patients in the analysis of visual evoked potentials. Brain MRI findings of 25 of 37 patients were included in our study, whereas MRI findings of 15 deceased patients were excluded. Brain parenchymal abnormalities were detected in 18 (72%), chronic thrombus in the right transverse sinus in one patient, and mastoiditis in one of 25 patients in brain MRI. Patients with specific pathologies in MRI are given in Table 2.

Neuropsychologic evaluation

Neuropsychologic impairments were noted in executive functions, expressive language, and verbal memory in 18 of 29 patients.

TABLE 2.
Retrospective Evaluation of Clinical Data and Laboratory Findings of Patients With Specific Pathologies on Brain MRI

Patients No.	Age, (Years)	Sex	Brain MRI	Immunologic Tests	Other Involvements
P.1	16	F	Plagiocephaly, Lateral ventricular enlargement, Thinning of the corpus callosum	ALC: 520/mm^3 Low IgM and IgG Low T cells	Autoimmune neutropenia Obsessive-compulsive disorder Attention-deficit/hyperactivity disorders
P.2	17	M	Left mastoiditis	ALC<1500/mm^3 Normal immunoglobulins	Hearing loss
P.3	14	M	Focal white matter lesions in both frontal areas	Low serum IgA	Major depression
P.4	12	M	Chronic thrombus in the right transverse sinus, along with the structures forming the right venous system	Low serum IgM Low CD3 cells	Left renal agenesis Protein C deficiency Articulation disorder
P.5	20	F	Cerebral and cerebellar atrophy Mild staining in the dura adjacent to the left parietal lesion (Langerhans cell histiocytosis)	Low serum IgM	Obsessive-compulsive disorder
P.6	17	M	*Cavum septum pellucidum* and cavum vergae, microcephaly	Low serum IgG and IgM	Anxiety disorder
P.7	8	M	Millimetric T2 hyperintensities in the cerebral white matter	Normal	-
P.8	6	F	A 6-mm nonspecific focus in the right inferior frontal crus	Low serum IgG and IgA Low CD3 cells	Introvert personality
P.9	7	F	A left parieto-occipital encephalomalacia	Low IgM and IgA Low CD4 cells	Oligoarticular JIA
P.10	46	M	Multiple millimetric nonspecific gliotic foci in periventricular deep white matter areas Asymmetric right lateral ventriculomegaly	Low serum IgM	Schizophrenia Hashimoto thyroiditis
P.11	15	F	Mild cerebellar vermis atrophy	Low serum IgM Low CD3 and CD8 cells	Attention-deficit/hyperactivity disorder Obsessive-compulsive disorder Hashimoto thyroiditis Asthma
P.12	7	F	Mild cerebellar vermis atrophy	Low serum IgM Low CD3 cells	Hashimoto thyroiditis
P.13	13	F	Mild cerebellar vermis atrophy	Normal	Hashimoto thyroiditis Behavior disorder Learning disorder
P.14	3	M	A gliotic focus in the left periventricular deep white matter	Low CD3 cells	Hearing loss Articulation disorder
P.15	1	M	Right cerebellar atrophy and right lateral ventriculomegaly	Low serum IgA and IgG	Hypothyroidism Hypoparathyroidism
P.16	12	F	Nonspecific gliotic foci in the white matter of both cerebral hemispheres	Low serum IgM	Mycosis fungoides, Introvert personality
P.17	9	M	Cavum septum pellucidum anomaly	Normal	Attention-deficit/hyperactivity disorder
P.18	18	F	Frontal horn and pineal cysts	Low CD3 cells	Epilepsy Anxiety disorder Intellectual disability
P.19	18	M	Cerebral and cerebellar atrophy	Low serum IgM	Hypothyroidism Hypoparathyroidism Hashimoto thyroiditis Intellectual disability
P.20	6	F	Cavum septum pellucidum anomaly	Normal	Autism spectrum disorder

Abbreviations:
ALC = Absolute lymphocyte count
F = Female
Ig = Immunoglobulin
JIA = Juvenile idiopathic arthritis
M = Male
MRI = Magnetic resonance imaging
P = Patient

Four patients could not complete the tests due to poor cooperation (three with severe intellectual disability and one with autism spectrum disorder). Frankfurt Adaptive Concentration Test and Bourdon Attention Test evaluated the ability to sustain attention in 17 patients according to age. According to these tests, the ability to sustain attention was 2 S.D. below the average in six patients (35.3%). Intelligence performance was tested via Kent E-G-Y and R.B Cattell 2A-3A Intelligence tests, and although the verbal intelligence quotient (IQ) scores were slightly higher than the performance IQ, as the average score, "borderline intellectual functioning" was identified in patients. Normal intellectual functioning was detected in five of 16 patients (31.2%), whereas 11 (68.8%) patients had different severities of disability in IQ scores by the Kent-Cattell average (full-scale IQ) and six (37.5%) had an IQ below 70. Benton Visual Retention Test was used to evaluate attention and perceptual memory skills, and the results were found to be below the normal score in 12 (80%) of 15 patients. According to the Peabody Picture Vocabulary Test, the receptive language age was delayed in 12 (60%) of 20 patients. Only three (20%) of 15 patients passed the Serial Digit Learning Test, which evaluates memory (Tables 3 and 4).

Discussion

DGS is associated with a high risk for neurodevelopmental disorders of intellectual disability and communication disorders. The early onset of neurocognitive findings common to 22q11.2DS disrupts the quality of life and is a potential risk factor for the later development of a psychotic disorder. Behavioral and neuropsychiatric problems may be the initial presentation of the patients.[13] Neurocognitive findings were not the first reason for admission in any of the patients in our study.

Although cardiac and immune system disorders are diagnosed on time and treated successfully in patients with DGS, there are delays in recognizing and treating neurodevelopmental and psychiatric disorders.[10] Behavioral and psychiatric disorders increase with age.[14-16] A quarter of patients with the 22q11 deletion develop psychosis, corresponding to a ~20-fold increase in risk, accounting for 1% to 2% of all schizophrenia cases.[11] In our study, a 46-year-old male patient was diagnosed with schizophrenia.

DGS is one of the etiologies of developmental delay and intellectual disability in children. Additionally, autism spectrum disorder has increased by 30% to 40%. IQ scores were <80 in 70% to 85% of patients.[17-19] Also, the average Full-Scale IQ score was 77.5 (52.5 to 110.5) in our study. Three patients had severe intellectual disability, and one had autism spectrum disorder.

Verbal IQ was higher than performance IQ in children and adolescents with DGS.[20-22] In our study, verbal IQ was found to be higher than performance IQ, similar to other studies.

In our study, 86.5% of our patients had neurocognitive findings, such as communication disorders, attention-deficit/hyperactivity disorder, behavioral disorder, obsessive-compulsive disorder, and depressive disorder. It was found that 35.3% of our patients had below-average attention span; furthermore, "low average" levels of attention, perception, and memory functioning and inadequate levels of attention skills were identified in most of them.

Language development may be delayed in children with DGS. At the same time, language disorders have been observed in those children's reading comprehension and self-expression.[23] In addition to the language development delay, calculation, verbal problem solving,[24,25] and an insight into understanding numerical values,[26] mathematical operations have recorded shortcomings.[27]

Similar to the literature, in our study, children's receptive language skills, level of understanding words with pictures, learning ability, and short- and long-term memory evaluation results were below average.

Although many patients show normal intellectual functioning in childhood, the cause of deterioration in cognitive functions at later ages may be due to defects in the developmental stage of neuronal processes.[13]

On the contrary, some authors showed that age-related improvement in cognition is attributable to the beneficial effects of lifelong supportive education aimed at improving cognitive ability and academic achievement in 22q11.2DS. The clinical data in meta-analyses are generally consistent with a loss of motor and executive functions in patients with DGS.[13] Van Aken et al. found that 62% of the primary school children with 22q11.2DS had motor dysfunction.[28] Among patients who could accomplish the tests in our study, motor dysfunction has been found in 18 (62.1%) of the 29.

Patients with 22q11.2DS are more likely to develop psychosis when they reach adulthood.[29] It has been stated that the decline in IQ with age, especially verbal IQ changes, is associated with the emergence of psychotic symptoms.[30] A group of patients with 22.q11 deletion showed early-onset cognitive disability before the onset of neurocognitive findings.[31] In our study, behavioral and psychiatric disorders in the form of hyperactivity/attention deficit, anxiety, and depression were detected in 18 (48.6%) pediatric patients.

A total of eight people in three different families had DGS. The first family was mother and daughter. The mother had no neurocognitive findings, whereas her daughter had attention-deficit/hyperactivity disorder with developmental delay. In the second family, only two children were diagnosed: the older one had intellectual disability and epilepsy, whereas the younger one had mild intellectual disability and attention-deficit/hyperactivity disorder. The third family consisted of a father and three children. The father was diagnosed as schizophrenic, whereas the youngest child had no neurocognitive findings, the middle child had aggressive

TABLE 3.
Neuropsychologic Test Results of Patients

Neuropsychologic Tests	Low Score Patient n (%)	Median Score (Min-Max)	Normal Score
Frankfurt Adaptive Concentration Test (n:6)	3 (50)	23.2 (4-32)	23-32
Bourdon Attention Test (%) (n:11)	3 (27.3)	47 (33-75)	40-60
Kent E-G-Y test (Verbal IQ) (n:16)	11 (68.8)	79 (57-120)	90-109
Cattell Test (Performance IQ) (n:14)	10 (71.4)	76 (46-117)	90-109
Kent-Cattell Average (Full-Scale IQ) (n:16)	11 (68.8)	77.5 (52.5-110.5)	90-109
Benton Visual Retention Test (n:15)	12 (80)	10 (6-13)	>12
Peabody Picture Vocabulary Test (Receptive Language) (n:20)	12 (60)	74.3 (34-98)	Age-variable normal range

Abbreviations:
IQ = Intelligence quotient
max = Maximum
min = Minimum
Normal score: Average range of intellectual functioning based on test standardization.
Low score: 2 S.D. below normal.

TABLE 4.
Evaluation of Patients' Neuropsychologic Test Findings

Patient	Sex	Age (Years)	Denver II Test	Frankfurter Adaptive Concentration Test	Bourdon Attention Test	Kent E-G-Y Test (Verbal IQ)	R.B. Cattell 2A-3A Intelligence Test (Performance IQ)	Kent-Cattell Average (Full Scale IQ)	Benton Visual Retention Test	Peabody Picture Vocabulary Test	SDLT
					Level of Attention	Verbal IQ (Mental Age; Years)	Performance IQ (Category)	Full Scale IQ (Category)	Correct Score; (Level)	Receptive Language; Years)	
P.1	F	16	N/A	N/A	N/A	57 (8)	57 (Mild intellectual disability)	57.5 (Mild intellectual disability)	9/15; (Borderline)	10.5	Failed the test
P.2	M	17	N/A	N/A	N/A	57 (8)	64 (Mild intellectual disability	60.5 (Mild intellectual disability)	7/15; (Very defective)	10	Failed the test
P.3	M	14	N/A	N/A	35% (Bad)	80 (10)	82 (Below average)	81 (Below average)	9/15; (Borderline)	9.9	Failed the test
P.4	M	12	N/A	N/A	55% (Average)	81 (9)	77 (Borderline)	79 (Borderline)	11/15; (Average)	8.1	Failed the test
P.5	F	20	N/A	N/A	45% (Average)	71 (10)	70 (Borderline)	70.5 (Borderline)	11/15; (Low Average)	10.1	Failed the test
P.6	M	17	N/A	N/A	35% (Bad)	57 (8)	48 (Moderate intellectual disability)	52.5 (Moderate intellectual disability)	7/15; (Very defective)	6.1	Failed the test
P.7	M	8	N/A	N/A	N/A	100 (7)	N/A	100 (Average)	N/A	8.1	N/A
P.8	F	6	Development appropriate to age	Above average	N/A	89 (7)	117 (Above average)	103 (Average)	N/A	N/A	N/A
P.9	F	7	Development appropriate to age	Above average	N/A	N/A	N/A	N/A	N/A	N/A	N/A
P.10	M	46	N/A	N/A	N/A	N/A	N/A	N/A	10/15; (Low average)	N/A	Failed the test
P.11	F	15	N/A	N/A	60% (Good)	92 (13)	106 (Average)	99 (Average)	13/15; (High average)	11.3	Passed the test in 6 repetitions
P.12	F	7	Development appropriate to age	Above average	N/A	120 (6)	101 (Average)	110 (Above average)	N/A	7.4	N/A
P.13	F	13	N/A	N/A	50% (Average)	92 (13)	84 (Below average)	88 (Below average)	10/15; (Borderline)	10	Failed the test
P.14	M	3	Personal-Social and Fine Motor-Adaptive: 15-16 months; Language: 8-9 months; Gross Motor: 2.5 years	N/A	N/A	N/A	N/A	N/A	N/A	8 months old	N/A
P.15	M	1	Development appropriate to age	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
P.16	F	12	N/A	N/A	75% (Good)	105 (12)	95 (Average)	100 (Average)	13/15; (High average)	12	Passed the test in 3 repetitions
P.17	M	9	N/A	N/A	N/A	88 (8)	N/A	88 (Below average)	7/15; (Defective)	8.6	Passed the test in 9 repetitions
P.22	M	15	N/A	N/A	60% (Good)	64 (9)	61 (Mild intellectual disability)	62.5 (Mild intellectual disability)	13/15; (High average)	10.1	Failed the test
P.23	F	17	N/A	N/A	35% (Bad)	55 (10)	54 (Mild intellectual disability	54.5 (Mild intellectual disability)	10/15; (Borderline.)	10.5	Failed the test
P.24	M	10	N/A	N/A	40% (Average)	72 (8)	59 (Mild intellectual disability)	65.5 (Mild intellectual disability)	6/15; (Defective)	9.8	Failed the test
P.25	F	4	Personal-Social: 3.5 years; Fine Motor-Adaptive: 3.5 years; Language: 3.5 years; Gross Motor: 3.5 years	Below average	N/A	N/A	N/A	N/A	N/A	3.6	N/A
P.26	M	4	Personal-Social: 15-16 months; Fine Motor-Adaptive: 20 months; Language: 12-13 months; Gross Motor: 19-20 months	Below average	N/A	N/A	N/A	N/A	N/A	N/A	N/A
P.27	M	7	N/A	N/A	60% (Good)	N/A	N/A	N/A	10/15; (Borderline)	3.5	N/A

TABLE 4. (*continued*)

Patient	Sex	Age (Years)	Denver II Test	Frankfurter Adaptive Concentration Test	Bourdon Attention Test	Kent E-G-Y Test (Verbal IQ)	R.B. Cattell 2A-3A Intelligence Test (Performance IQ)	Kent-Cattell Average (Full Scale IQ)	Benton Visual Retention Test	Peabody Picture Vocabulary Test	SDLT
					Level of Attention	Verbal IQ (Mental Age; Years)	Performance IQ (Category)	Full Scale IQ (Category)	Correct Score; (Level)	Receptive Language; Years)	
P.28	E	2	Personal-Social: 2 years; Fine Motor-Adaptive: 1 year; Language: 2 years; Gross Motor: 2 years	Below average	N/A	N/A	N/A	N/A	N/A	2	Failed the test
P.29	F	3	Personal-Social and Language: 2 years; Fine motor-Adaptive and Gross Motor:3 years	N/A	N/A	N/A	N/A	N/A	N/A	3	N/A

Abbreviations:
F = Female
M = Male
N/A = None assessment (Those who were not of suitable age for the test and those who could not complete the test were shown as N/A).
P = Patient
SDLT = Serial Digit Learning Test
Four patients could not perform tests, three of them (P.18, P.19, and P.21) because of intellectual disability and one patient (P.20) due to autism spectrum disorder.

behavior and depressive disorder, and the oldest child had obsessive-compulsive disorder and attention-deficit/hyperactivity disorder. The changes in phenotypic severity of neurocognitive findings in different generations in our study are similar to the findings of Crillo et al.[32]

Brain MRI revealed abnormalities in 12 (66.6%) of 18 pediatric patients with psychiatric disorders. We identified pathologies ranging from brain parenchymal abnormalities to reactive gliosis and sinus thrombosis in 18 (72%) of 25 patients in our study. Parenchymal abnormalities were seen, especially in the parietal, occipital, and frontal lobes and cerebellum on brain MRI. No significant difference was found in terms of gender. Nonspecific lesions were detected in the frontal lobe (two females, one male) in three patients. Left parieto-occipital encephalomalacia was detected in one patient, and mild staining in the dura adjacent to the left parietal lesion was detected in one. Kates et al. found that whereas the frontal lobe volume decreased in men with 22q11 deletion, the size remained the same in women.[33] In another study, it was reported that there was a decrease in parietal lobe volume in children with 22q11.2DS, whereas a larger parietal lobe volume was found in adults with the same disorder.[34,35] In a study conducted by Robin et al., in patients with 22q11.2DS, as well as polymicrogyria, corpus callosum agenesis, cerebellar atrophy, and meningomyelocele were the most frequently reported brain malformations.[36] In another study conducted by Bohm et al., in which 24 patients had brain MRI findings, it was shown that more than half of the patients (13 of 24) had persistent cavum septum pellucidum, and cavum vergae (eight of 24), abnormal cortical vessels (six of 24), and polymicrogyria or cortical dysplasia (four of 24) were also reported.[37]

The most common abnormal brain MRI findings in our study were cerebellar pathologies seen in six patients. In our study, plagiocephaly was detected in only one patient; however, no meningomyelocele was observed. Furthermore, in our study, cavum septum pellucidum (one of 20), cavum vergae anomaly (three of 20), and ventriculomegaly (three of 20) were detected.

Delays in verbal and performance IQ were detected in 16 (88.8%) of 18 patients with brain parenchymal abnormalities on brain MRI.

Mild cerebellar vermis atrophy in two of the five patients with normal IQ tests, nonspecific cerebral gliotic lesion in the other two, and right cerebellar atrophy in one patient was detected on brain MRI. Therefore we concluded that even if the IQ tests are normal, patients with DGS may have pathology on brain MRI, and vice versa.

Additionally, brain MRI detected parenchymal pathology in 11 (61.1%) of 18 pediatric patients with neuropsychiatric disorders. Sinus vein thrombosis was found in a patient with severe anxiety and aggression attacks. The brain MRI of one adult patient with schizophrenia showed multiple nonspecific gliotic foci in the periventricular deep white matter areas and asymmetric chronic ventriculomegaly in the right lateral ventricle.

T cell subset counts are mild to moderately decreased in patients with partial DGS compared with age-matched normal populations; however, “complete DiGeorge” is defined as DGS with very few or undetectable T cells secondary to congenital athymia.[38] In our study, the severity of immunodeficiency was heterogeneous, manifesting in a broad spectrum ranging from patients with normal thymic development to severe cellular immunodeficiency. Complete thymic aplasia with severe or complete T lymphopenia presenting with the severe combined immunodeficiency phenotype (T-B + NK+) was reported in less than 1.5% of patients.[29] There is usually mild to moderate antibody impairment, with T lymphocytopenia being the most prominent form in infancy.[39] There was no patient in our study with severe cellular immunodeficiency. However, CD3 lymphopenia in 19 (36.5%), CD4 lymphopenia in 11 (21.1%), and CD8 lymphopenia in 17 (32.7%) patients were detected.

Patel et al. reported that 6% of patients older than three years had hypogammaglobulinemia, 27% of whom had low IgM levels, and 3% of patients with DGS received immunoglobulin replacement therapy.[40] Gennery et al. showed that 50% of the patients with DGS had a deficiency in at least one of the IgM, IgG, and IgA values.[41] In our study, low IgM was observed in 20 (38.4%) and low IgA and IgG levels were detected in five (13%) patients. Only one (2.7%) patient was receiving an intravenous immunoglobulin treatment among all the patients. CD19 cell numbers were normal in patients who exhibited prolonged hypogammaglobulinemia.

Fourteen (73.7%) of 19 patients with immunologic defects had abnormal brain MRI. Our study shows that brain MRI should be evaluated together with immune examinations in the long-term follow-up of patients in this respect.

Our study evaluated the neurocognitive findings of the patients with both brain MRI findings and immunologic parameters. In addition, the difference of our study is that the neuropsychologic tests of the patients (ability to sustain attention, visual memory, short-term memory, receptive language skills, and intelligence [verbal, performance, full-scale]) were selected from age-appropriate tests that can be responded to in a short time considering the attention span of the patients.

Conclusion

Patients diagnosed with DGS should be monitored in a multidisciplinary manner, and it should be kept in mind that they may present with neurocognitive findings as the initial symptom in advanced age. Neuropsychologic tests should be done regularly during childhood. The prevalence of frequently seen neurodevelopmental, behavioral, and psychiatric disorders might be decreased by supporting the attention, memory, verbal IQ, and communication disorders of the patients in the early period with corrective training by psychologists and speech therapists. Therefore, a basic knowledge of this syndrome is crucial for pediatric and adult neurologists and psychiatrists who follow-up with patients with neurodevelopmental, behavioral, and psychiatric disorders.

CRediT authorship contribution statement

Zuhal Karali: Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **Yasin Karali:** Validation, Resources, Methodology, Investigation, Data curation. **Sukru Cekic:** Resources, Methodology, Investigation, Formal analysis, Data curation. **Berfin Altinok:** Resources, Investigation, Data curation. **Muhittin Bodur:** Resources, Investigation, Data curation. **Mustafa Bostanci:** Resources, Investigation, Data curation. **Sara Sebnem Kilic:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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