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Expanding the phenotypic landscape of Gaucher disease type 3c with a novel entity - Transient neonatal cholestasis

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ABSTRACT

Gaucher disease (GD) is the most frequent lysosomal storage disorder due to biallelic pathogenic variants in *GBA* gene. Only homozygous D409H variant has been associated with the cardiovascular phenotype which is also known as Gaucher disease type 3c. In this descriptive study, we presented phenotypic heterogeneity and a novel clinical finding among 13 patients with GD type 3c. Patients presented with varying degrees of cardiac valve and/or aortic calcifications (84,6%) and corneal opacities (76,9%) in addition to visceral (100%), hematological (92,3%), neurological (92,3%), and skeletal (30%) manifestations. Also, cervical dystonia (38,4%) and psychiatric disorders (46,1%) were not infrequent entities with respect to neurological involvement in GD type 3c. In this report, we highlight transient neonatal cholestasis (38,4%) as a novel finding in GD type 3c. Neonatal cholestasis is a finding associated with Gaucher type 2, but transient neonatal cholestasis has not been reported in GD patients, so far. The clinical features of GD type 3c are highly heterogeneous, from disease severity or age of onset to disease progression. Also, we concluded that phenotypic spectrum may be associated with age at onset of clinical symptoms. As, patients presenting in infancy or childhood had mainly visceral and hematological involvement and patients presenting in adolescence and adulthood had mainly cardiac, neurological involvement, and psychiatric behavioral disorders. Identifying the heterogeneous clinical course of these patients in this fatal disease, may lead a sufficient understanding of the pathophysiology which will enable targeted therapeutic interventions.

1. Introduction

Gaucher disease (GD) is the most prevalent lysosomal storage disorder which originates from β-glucocerebrosidase enzyme deficiency due to biallelic pathogenic variants in *GBA* gene (MIM #606463). GD has been categorized according to neurological status of the patients. GD type I (GD1) is the non-neuronopathic form which presents with hematological, visceral and skeletal involvement (Stirnemann et al., 2017; Cox and Schofield, 1997). Frequency of GD1 amongst GD patients is reported as 90–95% (Stirnemann et al., 2017; Cox and Schofield, 1997; Zimran et al., 2018). GD type II (GD2) is the acute neuronopathic form with severe and early neurological manifestations and associated with high mortality (Stirneman et al., 2017). GD type 3 (GD3) is the chronic neuronopathic form with heterogenous clinical course. GD3 is further categorized into 3 groups. Patients with GD3a have severe and predominant neurological involvement, whereas patients with GD3b have predominant visceral and skeletal involvement with horizontal supranuclear gaze palsy (Stirneman et al., 2017). GD3c (MIM #231005) is the

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cardiovascular phenotype which is characterized with aortic and cardiac valve calcifications, corneal opacities, supranuclear ophthalmoplegia and variable hematological, visceral and skeletal involvement (Stirneman et al., 2017; Kurolap et al., 2019). So far, 261 pathogenic variants associated with *GBA* gene were reported in the literature and only homozygous D409H (p.Asp448His) variant has been associated with GD3c (Stirneman et al., 2017; Kurolap et al., 2019). Casta et al. (1984), reported the first patient in the literature with suspected GD3c who had calcification of the mitral and aortic valves and corneal deposits in addition to visceral involvement and growth retardation. Since the first patient was described with confirmed homozygous D409H variant, 48 patients were reported in the literature (Kurolap et al., 2019; Chabas et al., 1995; Gumus et al., 2021; Karakoyun et al., 2019). In this manuscript, we aimed to present clinical findings of 13 GD type 3c patients and provide better insight into the progression of these findings over time in different age groups.

2. Methods

2.1. Study design and patients

This is a retrospective, descriptive study. Out of 125 patients followed-up in our center with GD diagnosis (both enzymatically and genetically confirmed), homozygous D409H variant in *GBA* gene was detected in 13 patients between 2001 and 2022. All available medical records of these GD3c patients were evaluated for hematologic, visceral, bone, neurological, cardiac and ophthalmological involvement. Patients' data regarding demographic characteristics, parental consanguinity, family history, surgical interventions, age at first complaint, age at diagnosis, clinical findings at presentation, anthropometric data, physical examination, laboratory and radiological evaluations were recorded. Anthropometric data was evaluated according to the standards proposed by Neyzi et al. (2015) for Turkish children and calculated as standard deviation scores (SDS). Hematological involvement was reported as having anemia and/or thrombocytopenia. Anemia was described as absent or present according to the following age and gender norms for hemoglobin concentration: <12 g/dL for males older than 12 years; <11 g/dL for females older than 12 years; <10.5 g/dL for children ages >2–12 years; <9.5 g/dL for children ages 6 months to 2 years; <10.1 g/dL for children younger than 6 months of age. Thrombocytopenia was reported categorically as mild or none (≥120 × 109/L), moderate (60 to <120 × 109/L) and severe (<60 × 109/L). Splenomegaly and hepatomegaly were described as having spleen and liver sizes more than the uppermost levels of normal for longitudinal dimensions according to age, respectively (Konus et al., 1998). Cholestasis was defined by the presence of jaundice with increased serum conjugated bilirubin levels (conjugated bilirubin either ≥1 mg/dL or > 20% of total bilirubin, if total bilirubin >5.0 mg/dL) (Fawaz et al., 2017). Informed consent for publication of clinical data was obtained from patients and their parents. This study was approved by the Non-Interventional Clinical Studies Ethics Committee of the Cukurova University Faculty of Medicine (2022/123-3). This study was performed in accordance with the Declaration of Helsinki.

2.2. DNA extraction and variant analysis

Two mL of peripheral blood samples were collected from patients whom were referred to Cukurova University Department of Medical Genetics of Medicine Faculty. DNAs were isolated using automatized DNA isolation system (QIAcube, Qiagen, Germany) via Qiagen DNA Blood Mini Kit (Qiagen, Germany). Concentrations were measured using a fluorometer (Qubit 3.0). All samples were proceeded to fragmentation and sample specific molecular barcodes were added by adapter ligation. Barcoded samples were targeted enriched for GBA gene (all exons and exon-intron junctions) with a custom designed kit containing gene specific primers. Amplicons were labeled with universal adapter prior to next generation sequencing and sample libraries were generated. Finally, next generation sequencing was performed via Illumina Miseq platform with the minimum coverage of 100x. Quality control and bioinformatics analyses were made using QCI-Analyze and QCI-Interpret.

2.3. Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY, USA). The normality of distribution of numerical variables was evaluated using the Kolmogorov-Smirnov test. Continuous variables were presented as means ± standard deviation or medians (minimum [min]-maximum [max]) according to distribution of data, and categorical variables as number and percentage (%).A *p*-value less than or equal to 0.05 denotes statistical significance.

3. Results

3.1. Demographic and clinical characteristics

13 GD3c patients from 10 families were included in the study. 8 were males and 5 were females. All of the patients had parental consanguinity. 6 patients were adults on admission. Median age at onset of symptoms was 75 (min-max: 3–216) months, nevertheless median age at diagnosis was 148 (min-max: 10–285) months. All of the patients presented with symptoms before the age of 18 years, but 3 patients had their diagnosis above 18 years of age.

3.2. Growth parameters and visceral, hematological and skeletal findings

For pediatric patients, mean SDS for weight was −1,09 ± 1,26 (min-max: 3,43–0,34) and mean SDS for height was −1,72 ± 1,21 (min-max: 3,41 to −0,51) at diagnosis. Only 1 patient had low height- and weight-for-age.

All of the patients had visceral involvement and median age at onset of visceral involvement was 66 (min-max: 3–286) months (Fig. 1). None of the patients had undergone splenectomy. 5 patients had transient cholestasis in the newborn period, one of them needed hospitalization in the newborn intensive care unit, all patients improved with supportive care. 12 patients had hematological involvement and median age at onset of hematological involvement was 75 (min-max: 6–255) months (Fig. 1). At diagnosis; mean hemoglobin level was 12,0 ± 2,1 (min-max: 9,0–17,7) gr/dl, and mean platelet count was 123.650 ± 45.538 (min-max: 57.000–219.000)/mm^3. 2 patients had anemia according to

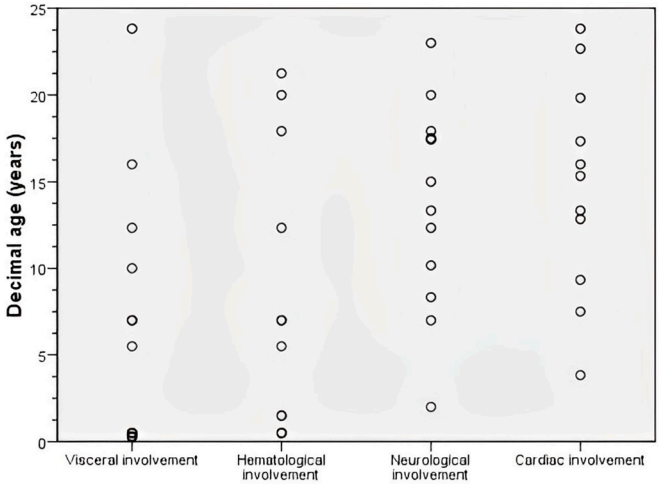


Fig. 1. Age of patients at onset of each system involvement.

normal levels for age and gender. 2 patients had normal thrombocyte levels. One patient had severe, 3 had moderate, and 7 had mild thrombocytopenia.

Evaluations for bone involvement were available for 10 patients and 3 of them had osteoporosis. Two of them had scoliosis. None of the patients needed orthopedic procedures.

3.3. Cardiac, neuropsychiatric, ophthalmological and other findings

11 patients had cardiac involvement; 1 had isolated aortic calcification, 2 had isolated cardiac valve calcifications, 5 had both cardiac valve and aortic calcifications, and 3 had left ventricular hypertrophy in addition to cardiac valve and aortic calcifications (Fig. 2). Median age at onset of cardiac involvement was 184 (min-max: 46–286) months (Fig. 1).

12 of the patients had neurological involvement, median age at onset of neurological involvement was 170 (min-max: 24–276) months (Fig. 1). On physical examination, 12 patients had oculomotor apraxia, but none of the patients had strabismus. 5 patients had cervical dystonia, 4 had epilepsy requiring antiepileptic medications, 2 of them also had myoclonus. Electroencephalography revealed epileptiform activity in 2 patients. 5 patients had fine tremor. Psychometric evaluations were abnormal in 3 patients. 4 patients had psychiatric problems, such as depression and obsessive-compulsive disorder (OCD). 3 had attention-deficit and hyperactivity disorder (ADHD). Cerebral magnetic resonance imaging detected abnormalities in 6 patients; 3 had communicating hydrocephalus, 1 had cerebellar atrophy and 1 had cerebellar venous angioma.

Ophthalmological evaluation revealed corneal opacities in 10 patients, 4 patients needed eyeglasses.

None of the patients had respiratory involvement or cholelithiasis.

3.4. Clinical outcome of the patients

Median age at the start of treatment was 156 (min-max: 12–288) months. All patients received enzyme replacement therapy (ERT) given at 60–120 units/kg body weight every two weeks. Mean duration of treatment was 62,1 ± 41,4 (min-max: 7–122) months. 6 patients deceased mainly due to cardiovascular complications, median age at death was 237 (min-max: 169–347) months. 6 patients needed cardiac valve replacement, and 4 of them were lost in the perioperative period. One died due to non-penetrating traumatic intracerebral hemorrhage while on warfarin. One patient had aortic calcification causing obstructive coronary artery calcification and died due to cardiac failure after transcatheter coronary stent deployment. The median current age of the rest of the patients was 134 (min-max: 48–403) months. Detailed clinical information of all patients are shown in Table 1.

4. Discussion

Frequency of GD3 among overall GD patients has been reported as 5–10% (Stirnemann et al., 2017; Cox and Schofield, 1997; Zimran et al., 2018). Nonetheless, detailed neurological evaluation reveals neuronopathic signs in patients who were classed as having GD type 1 (D'Amore et al., 2021). Thus, neuronopathic GD may be more frequent than is reported. Homozygous D409H variant has been reported in 48 GD patients and 12 of them were of Turkish origin (Gumus et al., 2021; Kor et al., 2017; Cindik et al., 2010; Güneş et al., 2018; Karakoyun et al., 2019). This variant was reported as one of the most common pathogenic variants in *GBA* gene in Greece and Spain but it has been reported in patients from several ethnicities (Kurolap et al., 2019; Chabas et al., 1998; Michelakakis et al., 2002).

Cardiac valve and aortic calcifications are uniquely observed in Gaucher disease type 3c patients (Stirnemann et al., 2017; Kurolap et al., 2019). Cardiovascular findings can be observed before or after visceral/hematological involvement, and neurological involvement (Kurolap et al., 2019). Cases from the literature and our cases demonstrate this clinical heterogeneity regarding both the presenting findings and disease progression. Some of our patients were diagnosed with severe cardiovascular involvement and mild visceral findings, conversely some patients admitted with severe visceral and hematological involvement. Patients in early childhood may not have any cardiovascular findings. Both cardiovascular and neurological involvement may lead to syncope, so detailed investigations are essential (Kor et al., 2017; Kurolap et al., 2019). Invasive cardiovascular interventions should be done very cautiously as the procedure itself may lead to significant morbidity and mortality.

Chronic neurological involvement is the hallmark of GD3, and GD3c patients exhibit neurological manifestations as well. These patients may not have apparent neurological signs at diagnosis and can develop these signs over time (D'Amore et al., 2021). Oculomotor apraxia and supranuclear gaze palsy are the most frequent neurological findings, on the other hand neurological findings other than neuro-ophthalmological findings are also not so rare (Kurolap et al., 2019). Progressive retroflexion of the neck, also named as cervical dystonia, is a debilitating finding in patients with GD2 (Stirnemann et al., 2017). So far, only in one patient with GD3c myoclonic-like involuntary movement of the neck was reported (Uyama et al., 1992). Gumus et al. (2021) reported two siblings presenting with dystonic tremor but specifically neck involvement was not mentioned. Interestingly, cervical dystonia was observed in 5 of our patients. This finding may be an underestimated finding due to thrusting movement for correcting supranuclear gaze palsy. Neuroimaging modalities detected hydrocephalus and cerebellar atrophy which is in accordance with the literature but none of our patients needed ventriculoperitoneal shunt (Kurolap et al., 2019; Cindik et al., 2010).

Psychiatric disorders are associated with GD3 patients and Kurolap et al. (2019) reported psychiatric findings in a patient specifically with

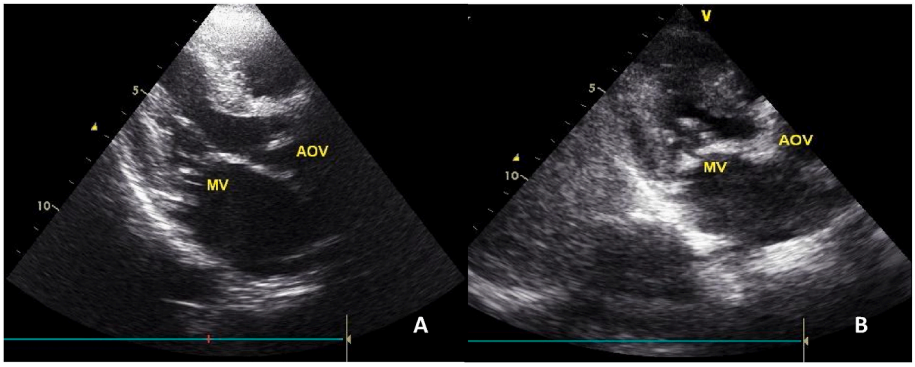


Fig. 2. Parasternal long axis view; A) mild increase in echogenicity of mitral and aortic valve leaflets, B) severe calcification of mitral and aortic valve.

Table 1
Clinical findings of the patients.

Patient	1[a]	1[b]	1[c]	2	3	4	5	6	7	8	9[a]	9[b]	11
Gender	F	F	M	M	F	F	M	M	M	F	M	M	M
Current age	25 yrs 10 mo	N/A	10 yrs 2 mo	33 yrs 7 mo	N/A	N/A	11yrs 2 mo	N/A	5yrs 5 mo	N/A	N/A	12 yrs 7 mo	4 yrs
Cause of death (age)	N/A	Cardiac failure (21 yrs)	N/A	N/A	Intracranial hemorrhage (28 yrs 11 mo)	Cardiac failure (20 yrs 10 mo)	N/A	Cardiac failure (14 yrs 1 mo)	N/A	Cardiac failure (18 yrs 9 mo)	Cardiac failure (17 yrs 7 mo)	N/A	N/A
Age at onset of hematological involvement	7 yrs	7 yrs	18 mo	20 yrs	21 yrs 3 mo	12 yrs 4 mo	6 mo	5 yrs 6 mo	N/A	17 yrs 11 mo	6 mo	6 mo	18 mo
Hematological involvement													
Anemia	–	+	–	–	–	–	–	–	–	+	–	–	–
Thrombocytopenia	Mild	–	Mild	Moderate	Mild	Mild	Mild	Mild	–	Severe	Moderate	Moderate	Mild
Age at onset of visceral involvement	7 yrs	7 yrs	3 mo	10 yrs	23 yrs 10 mo	12 yrs 4 mo	6 mo	5 yrs 6 mo	4 mo	16 yrs	6 mo	6 mo	3 mo
Transient neonatal cholestasis (age at first recognition)	+ (18 days)	+ (14 days)	–	–	–	–	–	+ (16 days)	–	–	+ (21 days)	+ (18 days)	–
Maximum total/ conjugated bilirubin (mg/dl)	6,83/1,57	5,4/1,64						19,2/13,6			5,7/2,3	3,7/2,1	
AST/ALT (U/L) (During the period of cholestasis)	97/63	89/56						282/208			88/62	66/54	
Abdominal USG (During the period of cholestasis)	Normal	Normal						Normal			Normal	Normal	
Eye involvement													
Corneal deposits	Bilateral moderate	Bilateral moderate	Bilateral moderate	Bilateral mild	Bilateral moderate	Peripheral deposits on right eye	–	Bilateral moderate	Bilateral mild	–	Bilateral moderate	Bilateral moderate	–
Refractive errors	–	–	–	+	+	+	–	–	–	–	+	–	–
Age at onset of cardiac involvement	19 yrs 10 mo	15 yrs 4 mo	N/A	22 yrs 8 mo	23 yrs 10 mo	9 yrs 4 mo	12 yrs 10 mo	7 yrs 6 mo	N/A	16 yrs	17 yrs 4 mo	13 yrs 4 mo	3 yrs 10 mo
Cardiac involvement													
Valve calcification	+	+	–	+	+	+	+	+	–	+	+	+	–
Aortic calcification	+	+	–	+	+	+	–	–	–	+	+	+	+
Left ventricular hypertrophy	+	–	–	–	–	–	–	–	–	+	+	–	–
Cardiac intervention (age)	–	MVR (18 yrs 7 mo), AVR (24 yrs 4mo)	–	AVR & MVR(24 yrs)	AVR (24 yrs), MVR (28 yrs)	AVR & MVR (15 yrs 9 mo)	–	AVR&MVR (11 yrs 3 mo), TC coronary stent (14 yrs 1 mo)	–	AVR (18 yrs 9 mo)	–	–	–
Age at onset of neurological involvement	20 yrs	17 yrs 5 mo	8 yrs 4 mo	23 yrs	15 yrs	12 yrs 4 mo	7 yrs	14 yrs	2 yrs	17 yrs 11 mo	17 yrs 6 mo	13 yrs 4 mo	N/A
Neuropsychiatric involvement													
Oculomotor apraxia	+	+	+	+	+	+	+	+	+	+	+	+	–
Epilepsy	–	–	–	+	+	+	–	–	+	–	–	–	–
Cervical dystonia	+	–	–	+	+	+	–	–	+	–	–	–	–
ADHD	–	–	+	–	–	–	–	+	+	–	–	–	–
OCD	–	–	–	+	+	+	–	+	–	–	–	–	–
Depression	–	–	–	–	+	–	–	–	–	–	–	–	–

ADHD: Attention deficit-hyperactivity disorder, ALT: alanine aminotransferase, AST: aspartate aminotransferase, AVR: Aortic valve replacement, F: Female, M: Male, mo: months, MVR: Mitral valve replacement, N: Normal, N/A: Not applicable, OCD: Obsessive-compulsive disorder, TC: Transcatheter, USG: Ultrasonography, yrs: years.
*Patients 1[a] and 1[b] were siblings and patient 1[c] were their first-degree cousin. Patients 9[a] and 9[b] were siblings.

GD3c. In our case series, 6 patients had psychiatric and/or neurobehavioural disorders (4 patients with OCD, 3 with ADHD, and 1 with depression). It was suggested that psychiatric findings may be coincidental or may be an entity directly related to neuronopathic GD (Kurolap et al., 2019). Psychiatric disorders have strong association with inherited metabolic diseases such as Niemann-Pick type C and other late-onset lysosomal storage disorders, urea cycle disorders, cerebrotendinous xanthomatosis, remethylation defects, and disorders of haem biosynthesis (Saudubray et al., 2016). Therefore, regular neuropsychiatric evaluation is essential also in this patient group.

Enzyme replacement therapy has positive outcome with regard to visceral, hematological and skeletal findings in GD3c patients. Unfortunately, it has no clear effect on cardiac, neuropsychiatric, and ophthalmological findings (Kurolap et al., 2019).

Neonatal cholestasis leading to liver failure is associated with Gaucher type 2 and liver transplantation may sometimes lead to improvement in liver disease but it is not able to prevent the neurological deterioration (Soudek et al., 2020). A 6-month-old patient with GD3c was reported to have cholestasis and liver failure treated with successful liver transplantation and enzyme replacement therapy (Karakoyun et al., 2019). To date, transient neonatal cholestasis has not been reported in GD3c patients. We observed transient neonatal cholestasis in 5 patients before the GD diagnosis was established. None of them developed liver failure, on the contrary cholestasis resolved spontaneously in all cases. Transient neonatal cholestasis in GD3c was a novel finding which was well-defined in other inherited metabolic diseases such as Niemann-Pick type C, cerebrotendinous xanthomatosis, citrin deficiency, and arginase deficiency (Saudubray et al., 2016). Clinicians should continue to monitor the patients with transient neonatal cholestasis for early recognition of visceromegaly, hematologic, and neurologic manifestations in light of these differential diagnoses, including Gaucher disease.

5. Conclusion

Cardiac manifestations are the main cause of mortality and morbidity in GD3c patients. Therefore, careful monitoring of cardiac status, comprehensive assessment before invasive cardiovascular procedures and further treatment options targeting the pathophysiology of cardiac calcifications are essential for the improved survival of these patients. Neuropsychiatric, and ophthalmological findings are more significant in GD3c patients when compared to the other GD3 patients. Transient neonatal cholestasis is a unique and an interesting finding that was observed in our patients.

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CRediT authorship contribution statement

Fatma Derya Bulut: Conceptualization, and design of study, Acquisition of data, Formal analysis, and/or interpretation of data, Drafting, the manuscript, Approval of the version of the manuscript to be published. **Deniz Kor:** Conceptualization, and design of study, Drafting, the manuscript, Approval of the version of the manuscript to be published. **Sebile Kılavuz:** Acquisition of data, Drafting, the manuscript, Approval of the version of the manuscript to be published. **Berna Şeker Yılmaz:** Acquisition of data, Drafting, the manuscript, Approval of the version of the manuscript to be published. **İrem Kaplan:** Acquisition of data, Drafting, the manuscript, Approval of the version of the manuscript to be published. **Faruk Ekinci:** Formal analysis, and/or interpretation of data, Approval of the version of the manuscript to be published. **Ezgi Burgaç:** Acquisition of data, Drafting, the manuscript, Approval of the version of the manuscript to be published. **İlknur Varol:** Acquisition of data, Drafting, the manuscript, Approval of the version of the manuscript to be published. **Burcu Köşeci:** Acquisition of data, Drafting, the manuscript, Approval of the version of the manuscript to be published. **Sevcan Tuğ Bozdoğan:** Formal analysis, and/or interpretation of data, Drafting, the manuscript, Revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published. **Esra Kara:** Acquisition of data, Drafting, the manuscript, Approval of the version of the manuscript to be published. **Fadli Demir:** Acquisition of dat, Approval of the version of the manuscript to be published. **Ali Deniz:** Acquisition of data, Drafting, the manuscript, Approval of the version of the manuscript to be published. **Fatih Temiz:** Acquisition of data, Drafting, the manuscript, Approval of the version of the manuscript to be published. **Neslihan Önenli Mungan:** Conceptualization, and design of study, Approval of the version of the manuscript to be published.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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