CASE REPORT

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A New Variant of the *IER3IP1* Gene: The First Case of Microcephaly, Epilepsy, and Diabetes Syndrome 1 from Turkey

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What is already known on this topic?

MEDS1 manifests as microcephaly with simplified gyral pattern in combination with severe infantile epileptic encephalopathy and early-onset permanent diabetes.

What this study adds?

This is the first case reported from Turkey. It differs from previously reported cases due to the absence of a typical simplified gyral pattern on early brain magnetic resonance imaging, the late onset of diabetes, and the presence of a new genetic variant.

Abstract

Microcephaly, epilepsy and diabetes syndrome 1 (MEDS1) is a rare autosomal recessive disorder caused by defects in the immediate early response 3 interacting protein 1 *(IER3IP1)* gene. Only nine cases have been described in the literature. MEDS1 manifests as microcephaly with simplified gyral pattern in combination with severe infantile epileptic encephalopathy and early-onset permanent diabetes. A simplified gyral pattern has been described in all cases reported to date. Diagnosis is made by demonstration of specific mutations in the *IER3IP1* gene. In this study, we present an additional case of a patient with MEDS1 who was homozygous for the c.53C > T p.(Ala18Val) variant. This case, the first to be reported from Turkey, differs from other cases due to the absence of a typical simplified gyral pattern on early brain magnetic resonance imaging, the late onset of diabetes, and the presence of a new genetic variant. The triad of microcephaly, generalized seizures and permanent neonatal diabetes should prompt screening for mutations in *IER3IP1*.
Keywords: Developmental delay, diabetes mellitus, epilepsy, *IER3IP1*, MEDS1

Introduction

The term "monogenic diabetes (infantile-onset diabetes)" refers to diabetes associated with a monogenic defect and is diagnosed in the first six months of life (1). Recent developments in the field of molecular genetics indicate that diabetes occurring very early in life is mostly caused by underlying monogenic defects (2,3). Current studies suggest that monogenic diabetes should be considered in cases of diabetes diagnosed in the first two years of life, and these studies report that approximately 1-6 % of pediatric diabetes cases are actually neonatal diabetes (2,3,4). Microcephaly, epilepsy, and diabetes syndrome 1 (MEDS1) is an autosomal recessive neurodevelopmental disorder that was first described by Poulton et al. (5) in 2011 and is characterized by microcephaly, simplified gyral pattern, severe epilepsy, and infantile diabetes. The disease is known to result from

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homozygous and compound heterozygous mutations in the immediate early response 3 interacting protein 1 (*IER3IP1)* gene, and it has so far been reported in a total of nine cases (5,6,7,8,9).

In this study, we present an additional case of a patient with MEDS1 who was homozygous for the c.53C > T p.(Ala18Val) variant. The case, the first to be reported from Turkey, differs from the other previously reported cases due to the absence of a typical simplified gyral pattern on early brain magnetic resonance imaging (MRI), the late onset of diabetes, and the presence of a new genetic variant. The triad of microcephaly, generalized seizures and permanent neonatal diabetes should prompt screening for mutations in *IER3IP1*.

Case Report

The patient was the first live singleton birth from the first pregnancy of a healthy father and mother, who were first cousins. He was born at term, and had no complications during pregnancy or the perinatal period. He had a birth weight of 3.400 kg [-0.24 standard deviation (SD)] with a length of 49 cm (-0.37 SD) and a head circumference of 34 cm (-0.42 SD). At the age of 11 weeks, he presented to the pediatric neurology outpatient clinic with complaints of spasms, crying, and restlessness. Neurological examination performed at presentation revealed that he had no eye contact, object tracking, and head control and that he had central hypotonia and flexor spasms. On physical examination he weighed 4,700 kg (-0.83 SD), measured 55 cm (-1.31 SD), and had a head circumference of 35.5 cm (-2.46 SD) with a conspicuous microcephaly. He had hypertelorism, depressed nasal bridge and micrognathia (Figure 1). Laboratory tests revealed blood amino acid, cerebrospinal fluid (CSF) amino acid, acyl-carnitine, and urine organic acid levels within normal limits. Electroencephalogram showed a burst suppression pattern. Brain MRI performed at the age of two months revealed normal cortical sulci and gyri with normal widths for age, as well as normal ventricular system with normal width for age (Figure 2). Diagnosed with epilepsy, he was started on vigabatrin and pyridoxal 5 phosphate therapy. Owing to first-degree consanguineous marriage in the family and the co-occurrence of epilepsy and dysmorphic features, whole-exome sequencing (WES) was performed on DNA obtained from the proband and parents. He was found to have a homozygous missense variation (c.53C > T/p.Ala18Val) in *IER3IP1*. We could not find any phenotype-genotype study about this mutation in the literature. Homozygous pathogenic variants of this gene have been associated with autosomal recessive microcephaly, epilepsy, and diabetes syndrome type 1 (OMIM: 614231), and *IER3IP1* is a highly conserved protein with marked expression in the cerebral cortex and in beta cells. As the patient's seizures did not respond to the initial treatment, other drugs were introduced in the following order: levatiracetam, topiramate, clonazepam, and clobazam. Brain computed tomography (CT) performed at the age of nine months revealed increased distance in the CSF space, particularly remarkable in the frontal lobe (Figure 3).

While there were no clinical signs of hypogonadism that might occur with MEDS1, thyroid function tests revealed a thyroid stimulating hormone level of 0.89 IU/mL (normal range: 0.27-4.2) and free T4 level of 0.96 ng/mL (normal range: 0.87-1.76). At the age of 18 months, he presented with

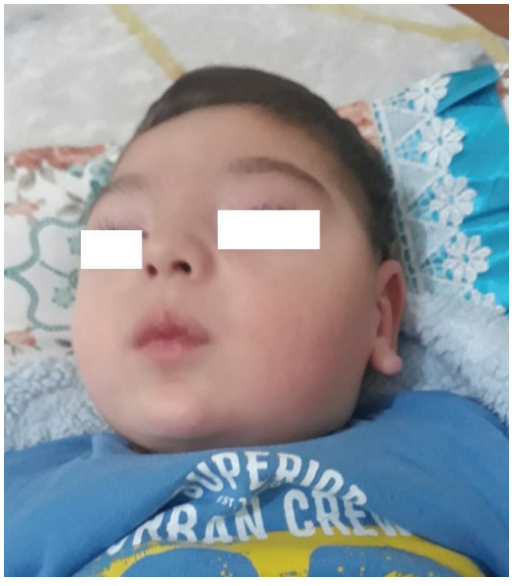

Figure 1. Patient's facial appearance

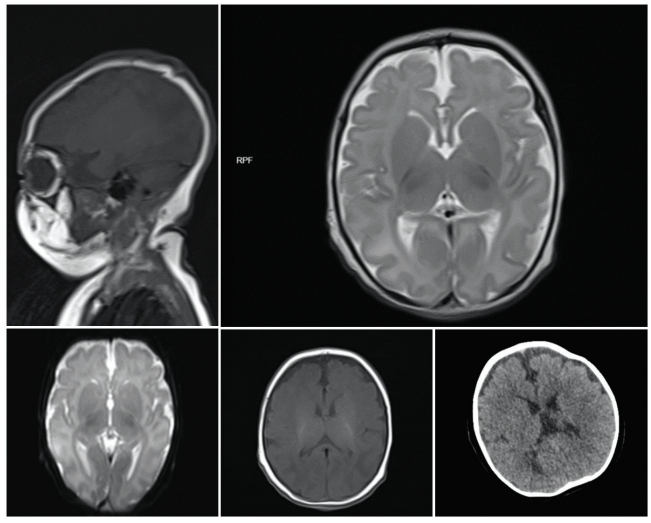

Figure 2. Brain magnetic resonance imaging of the patient at the age of three months old

rapid breathing, and further tests revealed a blood glucose level of 311 mg/dL, insulin level of 4.9 mIU/L, C-peptide level of 0.43 µg/L, and HbA1c level of 7.09%. Upon establishing a diagnosis of diabetes, insulin therapy was started at a dose of 0.4 U/kg. Diabetes antibodies (anti-glutamic acid decaboxylase, anti-insulin, and islet antibodies) were negative. There was no acidosis or ketonuria. Medical history was negative for polydipsia, polyuria, and significant weight loss. The c.53C>T/p.Ala18Val variant in *IER3IP1* has not been previously reported. Both parents were found to be heterozygous for the mutation.

The patient's parents provided informed consent for publication of this case report.

Preparation for Genetic Analysis

Genomic DNA extraction was performed according to manufacturer's instruction (Maxwell RSC Blood DNA Kit, Promega, USA) using Maxwell RSC Instrument (Promega, USA). 30 µL of proteinase K (PK) solution was added into a 200 µL blood sample. Then 300 µL of lysis buffer was added to the blood and PK mix and incubated at 56 °C for 20 minutes. After this step, each blood lysate sample was transferred to the cartridges. At the end of assay in the instrument, 50 µL of DNA was eluted. The concentration of DNA was determined spectrophotometrically by measurement of the absorbance at 260/280 nm using a Nanodrop 1000 apparatus (Thermo Fisher Scientific, Waltham, Massachusetts, USA). The concentration of DNA samples for libraries were determined by using Qubit 3.0 (Thermo Fisher Scientific). The sequencing libraries for exome sequencing were prepared according to Twist Human Core Exome Kit protocol (Twist Bioscience, South San Francisco, USA) Paired-end 150 bp read sequencing was performed on a NovaSeq system (Illumina, San Diego, USA).

Results

Raw data were uploaded to the Sophia DDM (Sophia Genetics, Lausanne, Switzerland) platform for further analysis, which detected a homozygous *c.53C>T* p.(Ala18Val) (NM_016097) variation in *IER3IP1*. This detected variant could not be found in any literature report or in the healthy population database (gnomAD; https://gnomad.broadinstitute.org/). However, *in silico* prediction databases (MutationTaster, PROVEAN, SIFT) stated, in consensus, that the variation was "deleterious." The American College of Medical Genetics 2015 criteria qualified the variant as "Class 3 - variant of uncertain clinical significance" (10). The segregation analysis for the variation was performed with Sanger sequencing and Integrative Genomics Viewer using samples collected from the patient's parents, and both parents were found to be heterozygous carriers of the mutation (Figures 4, 5). As the patient's clinical findings were similar to the expected symptoms of MEDS1 (OMIM: 614231) phenotype, known to be caused by homozygous pathogenic variants in *IER3IP1*, this mutation was thought to account for the patient's phenotypic features.

Discussion

This case report presents a male patient with homozygous variation in *IER3IP1* and this is the first case reported from Turkey and the 10th case reported globally. The present case differs from other previously reported cases due to the absence of the typical simplified gyral pattern on brain MRI and the presented case had a later onset of diabetes compared with other reported cases.

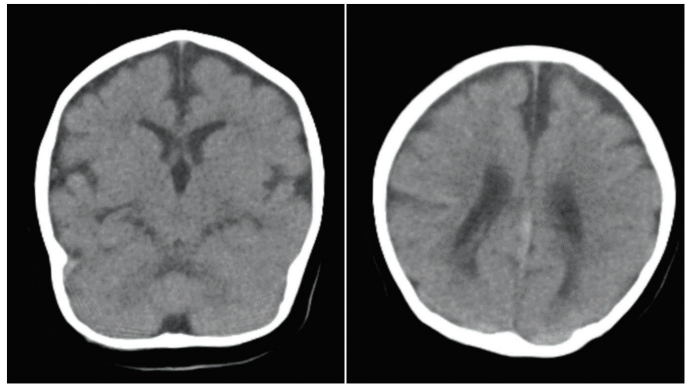

Figure 3. Brain computed tomography at the age of 9 months old

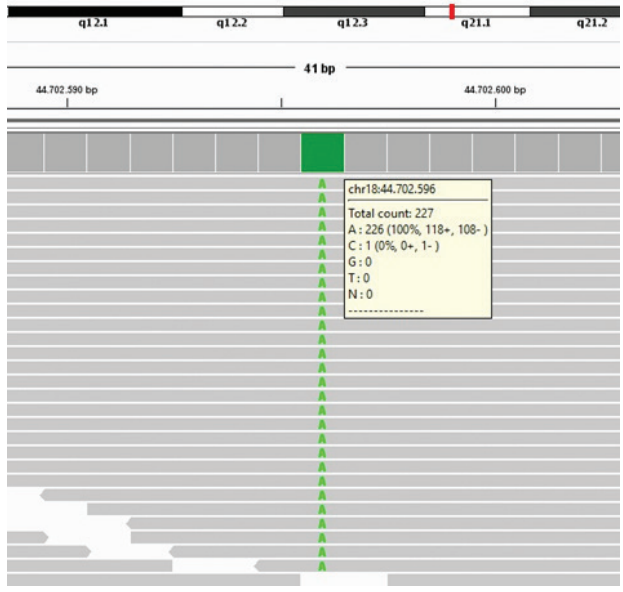

Figure 4. Results of next-generation sequencing at the mutation locus c.53C>T p.(Ala18Val)

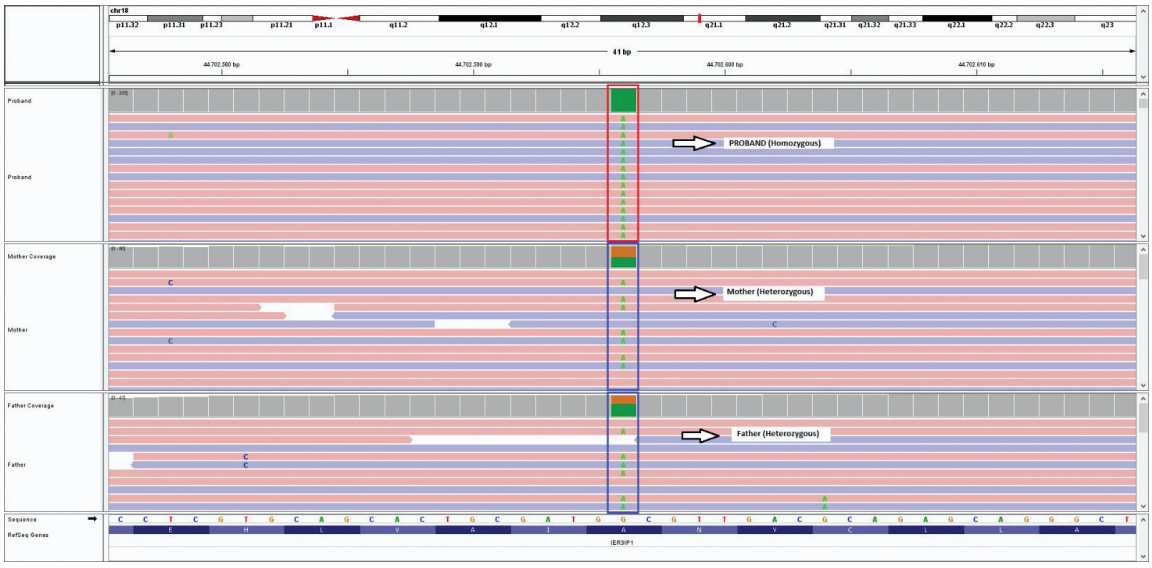

Figure 5. Integrative Genomics Viewer were used to analyse the characteristics of the mutated MEDS1 protein

MEDS1: microcephaly, epilepsy, and diabetes syndrome 1

MEDS1 syndrome was first reported by Poulton et al. (5) in 2011 in two cases from two unrelated families. Common findings in these cases were microcephaly with simplified gyral pattern in combination with severe infantile epileptic encephalopathy and early-onset permanent diabetes. An autopsy specimen from one patient showed increased apoptosis in the cerebral cortex and pancreas beta cells, implicating premature cell death as the pathogenetic mechanism (5).

MEDS1 (OMIM: 614231), which shows an autosomal recessive pattern of inheritance, results from a defect in the production of *IER3IP1* expressed in beta cells of the cerebral cortex and pancreas. *IER3IP1* is localized to the endoplasmic reticulum (ER) and is thought to play a role in the transport of proteins between the ER and Golgi apparatus and to be involved in the ER stress response (5). The association of neonatal diabetes with *IER3IP1* mutations suggests that *IER3IP1* regulates β-cell survival and/or function. Increased apoptosis in the cerebral cortex and pancreatic beta cells in autopsy samples with *IER3IP1* mutation points to early apoptosis as the pathogenic mechanism (5,7).

Neonatal diabetes refers to diabetes that is associated with a monogenic defect and is usually diagnosed in the first six months of life. The age at diagnosis of diabetes in the reported MEDS1 cases ranges from 14 days to 2 months (Table 1). In our case, however, diabetes emerged at the age of 18 months, substantially later than in other reported cases (6,7,9). Although current studies have shown that monogenic diabetes usually occurs in the first six months, recent studies have shown that it can rarely occur at the age of 12 or even 24 months (3,11,12). The important characteristics of the cases reported in the literature are summarized in Table 1.

The detection of c.62 T > G and c.233 T > C variants in all but one of the cases reported to date, and the fact that most of the cases are in Middle Eastern and North African countries or in countries receiving immigration from these regions, indicate that these variants are probably not mutational hotspots, but rather are rare ancestral variants unique to these regions. In the case reported by Shalev et al. (8), the common c.62 T > G missense variant and the novel c.79delT frameshift variant were compound heterozygous, and although this novel variant was a frameshift variant, the patient was more mildly affected than previously reported ones and survived to 8 years of age. This shows that variants other than the two most common mutations can result in different phenotypes. The c.62 T > G (p.Val21Gly) variant affects the first transmembrane hydrophobic domain of the protein, and the c.233T > C (p.Leu78Pro) variant affects the second transmembrane hydrophobic domain of the protein, impairing the protein's expression and/or function. The variant in our patient affects amino acid at position 18 in the first transmembrane hydrophobic domain, probably its mechanism of action is similar to c.62T > G, which affects amino acid at position 21. In addition, the c.62T > G variant is adjacent to the protein cleavage site. The milder phenotype of our case may be due to the fact that the variant found in the presented case was not so close to this cleavage site (5). Another piece of evidence supporting the pathogenicity of the variant in our patient is that the residues affected by both our patient's variant (18^{th} residue) and the c.62T > G (21^{st} residue) variant are located within a highly conserved 12-residue region across species, as shown below.

Table 1. The important characteristics of the cases reported in the literature

	Poulton et al. (5) (2011)		Abdel-Salam et al. (6) (2012)				Shalev et al. (8) (2015)	Valenzuela et al. (7) (2017)	Rjiba et al. (9) (2021)	Current case
			Family 1251		Family 1578					
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Gender	M	M	M	F	F	F	M	M	M	M
Consanguinity	+	+	+	+	+	+	-	-	+	+
MRI	Simplified gyral pattern	Simplified gyral pattern	Simplified gyration, cortical atrophy, hypoplastic corpus callosum, cerebellar vermis hypoplasia	Simplified gyral pattern and agenesis of corpus callosum with mild cerebellar vermis hypoplasia without atrophy	Cerebral atrophywith simplified gyral pattern, and agenesis of the corpus callosum	Simplified gyral pattern and agenesis of corpus callosum with normal cerebellum	Simplified gyral pattern	Simplified gyral pattern, ventriculomegaly and hypoplastic corpus callosum	Atrophy of the supra-tentorial level without pituitary anomaly	Normal
EEG	High voltage asymmetric multifocal activity with abnormal background	Hypsarrythmia	Polyspikes and slow waves with burst suppression	Generalized epileptic abnormalities with sharp and slow-waves	Burst suppression pattern	Burst suppression pattern	Hypsarrythmia	Low-amplitude background in the theta-delta range, suggesting diffuse neuronal dysfunction, with no epileptiform discharges	NA	Burst suppression pattern
Genetic analysis	c.62 T > G p.Val21Gly Homozygous	c.233 T > C p.Leu78Pro Homozygous	c.233 T > C p.Leu78Pro Homozygous	c.233 T > C p.Leu78Pro Homozygous	c.233 T > C p.Leu78Pro Homozygous	c.233 T > C p.Leu78Pro Homozygous	c.62 T > G/ p.Val21Gly and c.79delT/p. Phe27fsSer*25 Compound heterozygous	c.233 T > C p.Leu78Pro Homozygous	c.62 T > G p.Val21Gly Homozygous	c.53C > T p.(Ala18Val) Homozygous
Diabetes	+	+	+	+	+	+	+	+	+	+
Age at diabetes onset	NA	NA	NA	NA	40 days	14 days	NA	5 weeks	2 months	18 months
Hypogonadism	+	NA	Bilateral undescended testes	NA	NA	NA	Retractile testes	NA	Unilateral cryptorchidism and small genitalia	-
Skeletal findings	NA	NA	Osteoporosis, metaphyseal changes	Pathological fracture	Poor modeling of long bones and osteopenia	NA	NA	-	NA	-
Death	18 months	27 months	5 1/2 years	26 months	3 1/2 years	-	8 years	7 weeks	1 year	-

MRI: magnetic resonance imaging, EEG: electroencephalogram, NA: not available, M: male, F: female

11	18	21	32
AALLCVN	A	IA	V	LHEERFLKNIG	human
AALLCVN	A	IA	V	LHEERFLKNIG	mouse
TAILFTN	A	IA	V	LHEERFLSKIG	zebrafish
AALLCVN	A	IA	V	LHEERFLKNIG	cow
AALLFVN	A	IA	V	LHEERFLRR	blue-ringed sea krait

In differential diagnosis, Wolcott-Rallison syndrome has been reported to be the most common cause of neonatal diabetes in families with consanguineous marriages (13). This syndrome, which results from a homozygous mutation in *EIF2AK3*, is characterized by insulin-dependent diabetes mellitus before six months of age, skeletal dysplasia after six months of age, and liver failure. This syndrome manifests as renal failure, microcephaly, epilepsy, and central hypothyroidism and it must be ruled out in the differential diagnosis of MEDS1 (14). Increased ER stress, and thus beta-cell death, constitutes the pathogenesis of the disease, and management requires insulin replacement (15). This syndrome may also include episodes of liver failure and skeletal anomaly in later ages, indicating the importance of early genetic diagnosis. A study that presented four cases of MEDS1 reported that three of the patients had skeletal findings, including osteoporosis, metaphyseal changes, osteopenia, pathological fractures, and poor modeling of long bones (6). Our patient had no skeletal anomaly.

IER3IP1 has an unclear role in the development of the cortex and in the pathogenesis of epilepsy and diabetes, but it is thought to be required during early stages of neural development, for instance, during neural progenitor proliferation. Presence of microcephaly with simplified gyration has a distinctive role in differential diagnosis and already exists during gestation. Severe infantile epileptic encephalopathy is highly unusual in primary microcephaly and has been reported only in patients with *WDR62* mutations (16). In addition, a rare combination of primary microcephaly and severe infantile epilepsy in patients with *PNKP* mutations has been reported (17).

As our patient had refractory epilepsy, microcephaly, and axial hypotonia at the time of presentation, no specific complication at birth, and was born of parents who were first cousins, he underwent early WES and was subsequently diagnosed with MEDS1. The patient's family was asked to be vigilant about symptoms of potential diabetes with blood glucose being monitored. Diabetes emerged later than reported in other cases in the literature, but early genetic analysis allowed for diagnosing diabetes before acidosis developed. The patient did not present with microcephaly at birth, but with increasing age, it became evident. It was remarkable that the simplified gyral pattern, which was detected in all other cases, was absent on early MRI. Continued apoptosis in the postnatal period was thought to be the cause of MRI findings and microcephaly. This hypothesis was supported by increased distance in the CSF space detected on brain CT performed at the age of nine months.

Conclusion

In conclusion, this is the first case of MEDS1 from Turkey and is the first report of a variant that has not been previously described. Although the simplified gyral pattern, which co-occurs with the triad of microcephaly, epilepsy, and diabetes, may guide the diagnosis of MEDS1, manifestation of the symptoms may sometimes take time. Early genetic counseling should be considered in families where consanguineous marriage is accompanied by epilepsy and microcephaly.

Ethics

Informed Consent: The patient's parents provided informed consent for publication of this case report.

Authorship Contributions

Surgical and Medical Practices: Elif Söbü, Gül Demet Kaya Özçora, Bahtiyar Şahinoğlu, Feride Tahmiscioğlu Bucak, Concept: Gül Demet Kaya Özçora, Feride Tahmiscioğlu Bucak, Design: Elif Söbü, Data Collection or Processing: Elif Söbü, Gül Demet Kaya Özçora, Bahtiyar Şahinoğlu, Analysis or Interpretation: Elif Söbü, Gül Demet Kaya Özçora, Bahtiyar Şahinoğlu, Feride Tahmiscioğlu Bucak, Elif Yılmaz Güleç, Literature Search: Elif Söbü, Gül Demet Kaya Özçora, Writing: Elif Söbü, Feride Tahmiscioğlu Bucak, Elif Yılmaz Güleç.

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