CASE REPORT

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Expanding the Phenotype of *TRMT10A* Mutations: Case Report and a Review of the Existing Cases

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What is already known on this topic?

The mutation of the tRNA methyltransferase 10 homologue A *(TRMT10A)* gene causes a novel recessive syndrome of abnormal glucose homeostasis associated with distinctive features. A few cases have been reported to date.

What this study adds?

Ovarian failure with small ovaries, high gonadotropins and low anti-Mullerian hormone levels can lead to pubertal delay in these patients. Growth hormone deficiency can be an additional finding of this syndrome.

Abstract

The tRNA methyltransferase 10 homologue A *(TRMT10A)* gene encodes tRNA methyl transferase, and biallelic loss of function mutations cause a recessive syndrome of intellectual disability, microcephaly, short stature and diabetes. A case with intellectual disability and distinctive features including microcephaly was admitted. She was diagnosed with epilepsy at 2.5 years old. At 3.6 years of age, severe short stature related to growth hormone (GH) deficiency was detected. She had an incidental diagnosis of diabetes at age 11.4 years which was negative for diabetes antibodies with persistent C-peptide level and she was treated with metformin. Spontaneous puberty did not begin until 15.7 years of age and she was found to have primary ovarian failure. A homozygous p.Arg127* mutation in *TRMT10A* was detected. In addition to the typical clinical features which characterize *TRMT10A* syndrome, we observed an unusual form of impaired glucose metabolism which presented in early childhood with hypoglycemia followed by diabetes in late childhood. GH deficiency and primary ovarian failure may also be additional findings of this syndrome. Patients with slow onset diabetes who are negative for auto-antibodies and have extra-pancreatic features should be tested for all known subtypes of monogenic diabetes.

Keywords: *TRMT10A*, monogenic diabetes, ovarian failure

Introduction

Human glucose metabolism can be disrupted by pathogenic mutations in numerous genes with some of them associated with distinctive clinical and laboratory features (1). Recently, a novel syndrome has been reported characterized by abnormal glucose homeostasis or non-autoimmune diabetes associated with microcephaly, epilepsy, intellectual disability, failure to thrive and delayed puberty due to biallelic pathogenic mutations in the tRNA methyltransferase 10 homologue A *(TRMT10A)* gene (2,3,4,5,6).

tRNAs are non-coding RNA molecules essential for protein synthesis. They are crucial for cellular function and can undergo modifications of their bases and sugar moieties. Reduced modifications may lead to tRNA degradation or fragmentation. TRMT10A is a tRNA modifying nuclear enzyme with methyl transferase activity and it is localized in the nucleolus where tRNA modifications occur. TRMT10A

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deficiency induces oxidative stress and initiates the apoptosis of beta cells (7).

Although short stature and delayed puberty in addition to disturbed glucose metabolism have been reported in those patients with TRMT10A deficiency, growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis has not been evaluated in the patients reported; except for one (8). We report on a patient with GH deficiency, ovarian failure, non-autoimmune diabetes and a homozygous mutation in the *TRMT10A* gene. Additionally, a review was undertaken of any existing cases for further evaluation.

Case Report

The patient was the second child born to non-consanguineous parents. The pregnancy was uneventful with the child being born at term without immediate postnatal problems. The child's birth weight was 2,100 g (z-score: -3.03) and she had microcephaly (head circumference: 30 cm, $< 3^{rd}$ centile). She was found to have difficulty in feeding during the first two years of life and was underweight (her weight was 8.8 kg at 2 years old, her z-score was -2.39). Later, she was diagnosed with delayed neuromotor development with mild intellectual disability (24 months walking, 36 months speech). This was followed by epilepsy diagnosed at 2.5 years old which was being treated with valproic acid at the time of writing. On cranial magnetic resonance imaging (MRI), a small pituitary (3 mm in length) with normal structure and an anterior arachnoid cyst (3.5x2 cm) of the left temporal lobe were detected.

Informed consent both for publication of this case report and for molecular analyses were given by the parents of the patient.

Growth and puberty of the patient: She was referred to the pediatric endocrinology clinic at 3.6 years of age for short stature. Her height was 84 cm [standard deviation score (SDS): -3.7], her weight was 11.4 kg (SDS: -2.22), her head circumference was 45 cm (SDS: -3.2) and her bone age was 2.5 years. Her mid-parental height was 153.2 cm (-1.14 SDS). Clinical examination revealed distinctive features including microcephaly, a small face and deep-set eyes.

On laboratory examination; complete blood counts, electrolytes, liver enzymes, renal function tests, thyroid function tests [thyroid stimulating hormone: 4.75 µmIU/mL (N: 0.4-5.3), free T4: 12,1 pmol/L (N: 7-16 pmol/L), prolactin level [14.2 ng/mL (N: 4-20 ng/mL)], urine and blood amino acid level results were normal. Polyuria was not observed, and urine specific gravity was 1.018. Celiac antibodies were negative and the karyotype was 46, XX. Her brainstem auditory evoked response test was also normal.

Serum IGF-1 and IGF-binding protein 3 levels were low (40.9 ng/mL, SDS: -1.44 and 2,550 ng/mL, SDS: -2.31, respectively). GH stimulation tests (L-Dopa and insulin tolerance tests) were consistent with GH deficiency (peak GH levels were 6.1 ng/mL in the L-Dopa test and 3.3 ng/mL in the insulin tolerance test) (9). Growth velocity was low during follow-up. At 5.4 years of age, her height SDS decreased to -4.38.

At that time, recombinant human GH (rhGH) therapy was initiated at a dose of 0.28 mg/kg/week. Growth velocity increased from 4 cm/year to 8 cm/year after the first year of GH therapy. At the second year of treatment, growth velocity decreased, and the dose of GH was increased to 0.35 mg/kg/week (Figure 1). IGF-1 levels often remained within normal ranges with GH treatment (annual IGF-1 levels were 117.1, 223, 254, 441, 327, 425, 254 and 234.6 ng/mL). GH could be maintained until the age of 14.7 years. Her compliance with GH treatment was low and the parents of the patient did not accept further GH treatment. At the cessation of hGH therapy, her achieved height was 142 cm, height-SDS: -3.3 (mid-parent height 153.2 cm) (Figure 1).

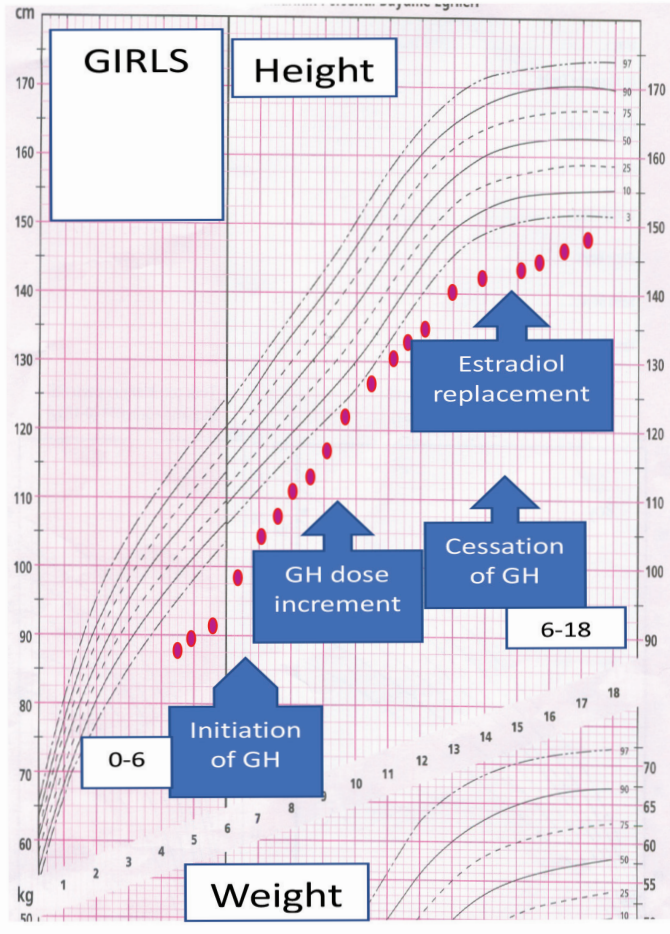

Figure 1. Growth chart of the patient

At age 13 years, she was still pre-pubertal and her bone age was 12 years. Basal luteinizing hormone (LH) levels (0.12 mIU/mL), estradiol (0.12 pg/mL) and LH response to LH-releasing hormone stimulation test (4.42 mIU/mL) were pre-pubertal. However, basal and stimulated follicle stimulating hormone (FSH) were 6.48 mIU/mL and 24.85 mIU/mL, respectively. A transabdominal pelvic ultrasound study showed that her small uterine volume (1.6 cm^3) and ovarian volumes were as low as 0.12 mL (right) and 0.06 mL (left). In both ovaries, follicles were not detected. Although it was decided to start pubertal induction, the parents did not give estrogen replacement therapy until 15.7 years of age. At this time, the following results were obtained: height: 145 cm (SDS: -2.95), weight: 35.8 kg (z-sore: -3.87), body mass index (BMI): 17.3 kg/m^2 (z-score: -2.2), relative BMI: 80%, puberty stage: still Tanner 1 and bone age: 13.5 years. Low estradiol (< 10 pg/mL), high basal LH (9.5 mIU/mL) and FSH (18.4 mIU/mL) were consistent with hypergonadotropic hypogonadism. Her serum anti-Mullerian hormone (AMH) level was found to be 0.07 pmol/L (N: 3.1-17.8 pmol/L). The small ovaries, high gonadotropins and low AMH levels were consistent with ovarian failure. After convincing the family, the patient was started with estradiol (Estrofem)® 2 mg tablets, 1/8 of a tablet once a day. It was aimed to switch to cyclic treatment within 2 years by increasing the dose at 6-month intervals. At the age of 17.5, she reached Tanner stage 3 puberty and her height was 149.8 cm (Table 1).

Glucose metabolism of the patient: At 4 years of age, on routine blood testing during a check-up at a pediatric neurology clinic, fasting blood glucose (FBG) was detected as 34 and 39 mg/dL, while fasting insulin was 2.1 IU/mL at a second blood glucose (BG) measurement. FBG was also low at GH stimulation test (35 mg/dL). Adrenocorticotropic hormone and cortisol levels were normal and ketones were negative when hypoglycemia occurred. The patient was asymptomatic during the test and remained so thereafter with no symptomatic episodes of hypoglycaemia.

She had an incidental diagnosis of diabetes at age 11.4 years. On routine examination, FBG levels were found to be 136 mg/dL. She was asymptomatic, without polyuria or polydipsia. Her oral glucose tolerance test (OGTT) results indicated diabetes (Table 1).

Hemoglobin A1c (HbA1c) at diagnosis was 7.4%. She tested negative for islet cell, anti-GAD and anti-insulin antibodies, while her C-peptide level was 1.29 ng/mL (N: 1.1-4.4), her insulin level was 7.2 mIU/mL (N: 4-16), and her BG level was 240 mg/dL. Her BMI z-score was -2.1. She was treated with metformin from the time of her diagnosis. As her C-peptide level was not low, metformin treatment was started at 2x500 mg daily. In the follow-up, it was increased to 1,500 mg/day. No side effects were observed. Her last HbA1c at age 17.1 years was 6.4% on 1.500 mg/day metformin.

Genetic analysis of our case: Sequencing analysis of all known monogenic diabetes genes by targeted next generation sequencing was undertaken as part of the Genetics of Early Onset Diabetes Study (GOOD study). The GOOD study is a cross sectional multi-center clinic-based study which aims to identify novel genetic subtypes of monogenic diabetes by excluding type 1 diabetes using a polygenic risk scores. The recruited patients undergo sequencing analysis of the known monogenic diabetes genes first, and those patients with negative tests are further investigated by whole-genome-sequencing in order to find novel genetic etiologies.

A homozygous nonsense mutation in *TRMT10A* (c.379C > T, p.Arg127*) was identified. This mutation has been reported previously in a patient with TRMT10A syndrome (2) and,

Table 1. Anthropometric and laboratory values of patients

	On admission	On GH initiation	On metformin initiation	On estrogen initiation	On last examination
Age (year)	3.6	5.4	11.4	15.7	17.5
Height (cm)	84	91	132.6	145	149.8
Height SDS	-3.6	-4.38	-2.4	-2.95	-2.23
Weight (kg)	11.4	13.7	25.2	35.8	41
Weight SDS	-2.22	-2.45	-2.56	-3.87	-3.06
Tanner stage	Telarche 1 Pubarche 1	Telarche 1 Pubarche 1	Telarche 1 Pubarche 1	Telarche 1 Pubarche 1	Telarche 3 Pubarche 2
Laboratory values	Hemogram, thyroid functions, electrolytes, renal functions and liver function tests were normal	IGF-1: 18.4 ng/mL Peak GH: 6.1 ng/mL (L-Dopa) and 3.3 ng/mL (ITT)	FBG: 136 mg/dL Fasting C-peptide: 1.29 ng/mL Fasting insulin: 7.2 mIU/mL OGTT: BG at 120': 242 mg/dL, insulin at 120': 47 mIU/mL)	E2: < 10 pg/mL LH: 9.5 mIU/mL FSH: 18.4 mIU/mL AMH: 0.07 pmol/L	

LH: luteinizing hormone, FSH: follicle stimulating hormone, AMH: anti-Mullerian hormone, OGTT: oral glucose tolerance test, SDS: standard deviation score, GH: growth hormone, IGF-1: insulin-like growth factor-1, ITT: insulin tolerance test, FBG: fasting blood glucose, BG: blood glucose

based on American College of Medical Genetics and Genomics variant classification guidelines, was considered to be a pathogenic variant. The parents could not be studied for any possible genetic mutations, and therefore, their carrier status could not be confirmed.

Discussion

There have been a total of 19 reported cases of TRMT10A syndrome within 12 families, with the first case reported by Igoillo-Esteve et al. (2) in 2013 (Table 2) (3,4,5,6,8,10,11,12,13,14). All patients, except for those cases reported by Zung et al. (4), had homozygous or compound heterozygous loss of function mutations within the *TRMT10A* gene. The cases of Zung et al. (4) also had a large deletion within the chromosomal region 4q23 which included nine genes, one of them being *TRMT10A*.

The current case was the first case in our country with TRMT10A syndrome. She was born SGA with distinctive features including microcephaly, intellectual impairment and epilepsy. At 3.65 years of age, hypoglycemia and severe short stature related to GH deficiency were detected. At 11.41 years of age, she had an incidental diagnosis of non-autoimmune diabetes. Before the development of diabetes, fasting hypoglycemia occurred. A pubertal disorder resembling primary ovarian failure was also detected at the age of 15.7 years.

Microcephaly and intellectual disability were observed in all cases. Epileptic seizures were also observed frequently in some cases. Eight out of 11 cases with cranial imaging results were found to be normal (2,3,4,5,6,10,12,13). Some minor clinical findings such as low anterior hair line, deep-set eyes with mild hypotelorism, shortened forehead and buffalo hump were also reported, which are similar to our case. In addition to findings of central nervous system involvement, in our patient, an arachnoid cyst was detected, which we believe to be an incidental finding as they are common in the population (2.6%) (15).

Growth was retarded in most of the cases. However, detailed information about the height SDS, body proportions and GH axis evaluations of patients was not fully available. Igoillo-Esteve et al. (2) reported the final adult height of their patients as being short (Table 2). The height of those cases by reported Gillis et al. (3) were below the third percentile with no given height z-scores. On the other hand, similar to our case, the height z-score of the case reported by Zung et al. (4) indicated serious short stature (-4.24). In addition, only one case had an evaluation of GH secretion (8). This case which was reported by Stern et al. (8) had short stature, low growth velocity and delayed bone age. After GH stimulations tests were performed, peak GH was found to be 7.3 mcg/l on clonidine and 1.8 mcg/l on Arginine stimulations. The MRI of the patient was found to be normal. GH replacement therapy could not be given. Our case was diagnosed with GH deficiency before the *TRMT10A* mutation was identified. Low growth velocity, inadequate responses to GH stimulation tests, retarded bone age and small hypophysis were all consistent with the diagnosis of GH deficiency. Moreover, the patient responded well to rhGH treatment as her growth velocity increased. These features suggest that the GH deficiency in our patient was caused by the *TRMT10A* mutation, although it is difficult to conclude precisely and more cases are needed to confirm if this is indeed a feature of TRMT10A syndrome. As tRNAs are crucial for cellular function and TRMT10A deficiency causes tRNA modification, all cells expressing TRMT10A would be affected. It is known that many cells in the brain including the hypothalamus and pituitary glands express TRMT10A protein. So hypothalamohypophysial functions in terms of GH secretion could be affected by TRMT10A deficiency.

Our case displayed the characteristics of hypergonadotropic hypogonadism. Puberty had not begun spontaneously when the patient was seen at 15.7 years of age. Laboratory values and pelvic ultrasound were compatible with ovarian failure. Even though pubertal delay in TRMT10A deficiency has been mentioned before, no detailed description of this was explained except by Zung et al. (3,4,5). Zung et al. (4) described the unusual pubertal progression of a female patient who showed intermittent progression with high gonadotropin levels during pubertal arrest and normal/low gonadotropin levels with estradiol elevation following pubertal progression periods. They concluded that this intermittent progression of puberty was related to the occurrence of transient episodes of gonadal failure and successive episodes of gonadal recovery. There were no detailed descriptions of pubertal progress in the other two cases.

Although gonadal expression of *TRMT10A* has not been demonstrated to date, this syndrome may lead to primary gonadal failure. We cannot be certain that primary ovarian failure is caused by the loss of TRMT10A and further validation in future cases will be required in order to be certain.

The most interesting characteristics of these cases could be the abnormalities in glucose metabolism. Eight of the reported cases with TRMT10A syndrome had diabetes. The age at diagnosis for diabetes varied between 9 and 28 years. C-peptide was detectable in all diabetic patients. Five patients were treated with insulin, three with metformin, and one case with insulin plus metformin (2,3,4,5,8,14).

Table 2. Characteristics of patients with *TRMT10A* mutations reported in the literature

	Igoillo-Esteve et al. (2), 2013			Gillis et al. (3), 2014			Zung et al. (4), 2015	Yew et al. (5), 2016
Case no	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
TRMT10A Mutation (based on RefSeq NM_152292.5)	c.379G > A, p.Arg127*	c.379G > A, p.Arg127*	c.379G > A, p.Arg127*	c.616G > A, p.Gly206Arg	c.616G > A, p.Gly206Arg	c.616G > A, p.Gly206Arg	4q23 deletion	c.79G > T, p.Glu27*
Sex	**F**	**F**	**M**	**F**	**M**	**M**	**F**	**F**
Short stature	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**
Delayed puberty	**NR***	**NR**	**NR**	**Yes**	**NR**	**NR**	**Yes**	**No**
Diabetes mellitus/age of diagnosis	**Yes/ 22 y**	**Yes/ 19 y**	**Yes/ 14 y**	**Yes/ 9 y**	**-**	**-**	**Yes/ 15 y**	**Yes/ 24y**
Diabetes treatment	**Ins****	**Ins**	**Ins**	**Diet**	**-**	**-**	**Ins**	**Ins + Met**
Hypoglycemia	**NR**	**NR**	**NR**	**Yes**	**Yes**	**Yes**	**Yes**	**No**
Other clinical features	Short neck, wide nose, low hairline, buffalo hump, retraction of right 5th toe, scoliosis, joint laxity, microcephaly, epilepsy	Microcephaly	Microcephaly	Microcephaly, epilepsy	Microcephaly, epilepsy	Microcephaly, epilepsy	Small face, clinodactyly, sensorineural hearing impairment, microcephaly	Buffalo hump, Microcephaly, epilepsy

NR*: not reported, Ins**: insulin, Met***: metformin, F: female, M: male, y: year

TRMT10A syndrome patients have persistent insulin secretion similar to Maturity Onset Diabetes of the Young (MODY) and contrary to type 1 diabetes. The clinical picture of diabetes was usually slow onset as seen in our case. Since diabetes appeared at 11.4 years of age, the patient responded well to metformin and subsequently HbA1c decreased. This suggested that there was a persistence of endogenous insulin. Our case highlighted that *TMRT10A* mutations are an important cause of non-obesity related and non-insulin dependent diabetes in childhood. Genetic testing for *TRMT10A* along with common MODY genes should be undertaken in patients with non-insulin treated diabetes, particularly in the presence of other extra-pancreatic features.

Interestingly, loss of function mutations in *TRMT10A* can cause hyperinsulinism (HI) as well as diabetes in the same subject (3,4,14). Fasting hypoglycemia developed before diabetes in two cases (3,4). Another two cases within the family reported by Gillis et al. (3) only had fasting hypoglycemia and high fasting insulin was also detected in those cases (4). Lin et al. (14) reported a diabetic child with high insulin and C-peptide levels to OGTT. They suggested that according to the OGTT results, insulin resistance appeared to be the dominant pathophysiological mechanism in their patient. In their case, spontaneous mild hypoglycemia was also detected.

Childhood onset hypoglycemia prior to developing diabetes has been reported in HNF4A MODY. The exact mechanism of this bidirectional glucose variability is unknown (16,17). Our patient had an incidental finding of low BG with no clear symptoms. The previously reported case by Zung et al. (4) had HI between 2.5 and 7.4 years of age and developed diabetes at 15.2 years of age.

TRMT10A deficiency leads to oxidative stress mediated apoptosis in the pancreatic beta cells. In an elegant study, Cosentino et al. (7) showed that tRNA guanosin 9 hypomethylation induces tRNAGln fragmentation. These fragments mediated TRMT10A-deficient beta cell death. The clinical hallmark of *TRMT10A* related diabetes is slow onset with non-autoimmunity.

Our knowledge and understanding of TRMT10A syndrome is increasing rapidly, despite it being recently described. However, some questions remain unanswered with regards to early hypoglycemic events and its characteristics of pubertal delay.

	Narayanan et al. (6), 2015		Boonsawat et al. (10), 2019	Duerinckx et al. (11), 2020	Hu et al. (12), 2019	Reuter et al. (13), 2017	Lin et al (14), 2020	Stern et al. (8), 2021	Presented case
9	10	11	12	13	14/15	16/ 17	18	19	20
c.79G > T, p.Glu27*	c.277C > T (p.Arg93*) c.397C > T (p.Arg133*)	c.277C > T (p.Arg93*) c.397C > T (p.Arg133*)	c.379C > T, p.Arg127*	c.379C > T, p.R127*	c.370 > A p.Q124K	c.348G > C p.K116N	c.496–1G > A)	c.616G > A, p.G206R	c.379C > T, p.(Arg127*)
M	F	M	NR	NR	NR/NR	M/M	NR	F	F
No	NR	Yes	Yes	NR	NR/NR	Yes /yes	Yes	Yes	Yes
Yes	NR	NR	NR	NR	NR/NR	NR/NR	NR	No	Yes
Yes/ 28 y	-	-	NR	NR	NR/NR	NR/NR	Yes/ NR	Yes/ 11 y	Yes/ 11.4 y
Met***	-	-	-	-	-	-	Met	Ins	Met
No	NR	NR	NR	NR	NR/NR	NR/NR	NR	NR	Yes
Microcephaly, epilepsy	low anterior hair line, deep set eyes with mild hypotelorism, shortened forehead, microcephaly	low anterior hair line, deep set eyes with mild hypotelorism, microcephaly, epilepsy				Hypotonia, uvula bifida, mild turuncal adiposit, microcephaly, epilepsy	Microcephaly	Microcephaly in both	Small face and deeply located eyes, microcephaly, epilepsy

Conclusion

TRMT10A gene mutations cause a syndrome of intellectual disability, microcephaly and delayed puberty resulting from ovarian failure, such as in our case. These characteristics are associated with non-autoimmune diabetes with persistent insulin secretion. GH deficiency can be an additional finding of this syndrome. *TRMT10A* should be tested in children from populations with higher rates of consanguinity when the patient has slow onset, auto-antibody negative diabetes and extra-pancreatic features.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Zeynep Şıklar, Tuğba Kontbay, Kevin Colclough, Kashyap A. Patel, Merih Berberoğlu, Concept: Zeynep Şıklar, Merih Berberoğlu, Design: Zeynep Şıklar, Merih Berberoğlu, Data Collection or Processing: Zeynep Şıklar, Tuğba Kontbay, Kevin Colclough, Kashyap A. Patel, Merih Berberoğlu, Analysis or Interpretation: Zeynep Şıklar, Kevin Colclough, Kashyap A. Patel, Merih Berberoğlu, Literature Search: Zeynep Şıklar, Tuğba Kontbay, Writing: Zeynep Şıklar, Kevin Colclough, Kashyap A. Patel, Merih Berberoğlu.

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