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ORIGINAL ARTICLE

# Clinical and laboratory findings and etiologies of genetic homocystinemia: a single-center experience

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## Abstract

**Background** Homocysteine (Hcy) is an endogenous nonprotein sulfur-containing amino acid biosynthesized from methionine by the removal of its terminal methyl group. Hyperhomocysteinemia (HHcy) has been linked to many systemic disorders, including stroke, proteinuria, epilepsy, psychosis, diabetes, lung disease, and liver disease. The clinical effects of high serum Hcy level, also known as hyperhomocysteinemia, have been explained by different mechanisms. However, little has been reported on the clinical and laboratory findings and etiologies of genetic HHcy in children. This study aimed to examine the relationships between clinical features, laboratory findings, and genetic defects of HHcy.

**Methods** We retrospectively evaluated 20 consecutive children and adolescents with inherited HHcy at the pediatric neurology division of Baskent University, Adana Hospital (Adana, Turkey) between December 2011 and December 2022.

**Results** Our main finding is that the most common cause of genetic HHcy is MTHFR mutation. The other main finding is that the Hcy level was higher in patients with CBS deficiency and intracellular cbl defects than in MTHFR mutations. We also found that clinical presentations of genetic HHcy vary widely, and the most common clinical finding is seizures. Here, we report the first and only case of a cbl defect with nonepileptic myoclonus. We also observed that mild and intermediate HHcy associated with the MTHFR mutation may be related to migraine, vertigo, tension-type headache, and idiopathic intracranial hypertension. Although some of the patients were followed up in tertiary care centers for a long time, they were not diagnosed with HHcy. Therefore, we suggest evaluating Hcy levels in children with unexplained neurological symptoms.

**Conclusions** Our findings suggest that genetic HHcy might be associated with different clinical manifestations and etiologies. Therefore, we suggest evaluating Hcy levels in children with unexplained neurologic symptoms.

**Keywords** Hyperhomocysteinemia · Neurologic symptoms · Children

## Abbreviations

| | |
|---|---|
| Hcy | Homocysteine |
| HHcy | Hyperhomocysteinemia |
| EEG | Electroencephalographic |
| MRI | Magnetic resonance imaging |
| PPH | Primary pulmonary hypertension |
| FSGS | Focal glomerular sclerosis |
| CBS | Cystathionine b-synthase |
| CSF | Cerebrospinal fluid pressure |
| IIH | İDiopathic cranial hypertension |
| RAO | Retinal artery occlusion |
| MR | Mental retardation |

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## Introduction

Homocysteine (Hcy) is an endogenous nonprotein sulfur-containing amino acid biosynthesized from methionine by the removal of its terminal methyl group and can be recycled into methionine via the remethylation pathway or converted into cysteine by the transsulfuration pathway. Elevations in the plasma Hcy concentration can occur because of genetic

defects in the enzymes involved in the remethylation or transsulfuration pathway, nutritional deficiencies in vitamin cofactors (folate, vitamin B6, or vitamin B12), or other factors, including some chronic medical conditions and use of certain drugs (methotrexate, 6-azauridine, nicotinic acid). However, one-third of the cases are caused by genetic defects in the enzymes involved in Hcy metabolism [1]. Very little has been reported about genetic hyperhomocysteinemia (HHcy). We evaluated 20 consecutive children and adolescents diagnosed with HHcy from a single institution in Adana, Turkey, to examine the relationships between clinical features, laboratory findings, and genetic defects of HHcy in this region.

## Materials and methods

We retrospectively evaluated 20 consecutive children and adolescents with inherited HHcy at the pediatric neurology division of Baskent University, Adana Hospital (Adana, Turkey) between December 2011 and December 2022. We usually measure homocysteine levels in patients with suspected inborn errors of metabolism or homocystinemia. After we detect homocystinemia, extensive workup for homocystinemia was performed for all patients, including genetic and metabolic screening. The exclusion criteria were as follows: confirmed chronic renal disease, liver disease, malabsorption syndrome, nutritional deficiency of biotin (B6), vitamin B12, and folate, hypothyroidism, and the use of any drugs associated with the metabolism of Hcy. 2- Five of the patients (Patients 4, 8, 13, 18 and 19) were using enzyme-inducing antiepileptic drugs at the time of admission. Since the interaction between enzyme-inducing antiepileptic drugs could lead to low plasma folate and high Hcy levels in approximately 20–40% of epileptic patients, we measured vitamin B12, folate and Hcy level before genetic investigation and only patients within normal limits were included in the study. In addition, seven of patients use one of these drugs still (Table 2). Demographic data, clinical findings, genetic and metabolic results, electroencephalographic (EEG) findings, neuropsychologic profiles, and cranial magnetic resonance imaging (MRI) results were recorded during presentation. At the time of diagnosis, serum Hcy, plasma methionine, urinary organic acid, B12, and folate levels were obtained and monitored during treatment. Hyperhomocysteinemia is classified in relation to the total plasma concentrations: moderate (15–30 µmol/L), intermediate (31–100 µmol/L), or severe (> 100 µmol/L) [2]. Appropriate doses of B6, B12, and folate were initiated for all children according to possible underlying causes. After the final diagnosis, appropriate treatment added (for MTHFR mutation, oral 5 mg folic acid, 250 mg B6 and 250 mcg B12 daily and for homocystinuria and cobalamin deficiencies, we administered oral 5 mg folic acid, 250 mg B6 and 250 mcg B12 daily with betaine treatment). All of the patients were regularly followed at the outpatient clinic at 1 week after discharge and every 1 to 6 months thereafter until preparation of this article, depending on clinical conditions. All patients underwent genetic analysis after a specific preliminary diagnosis. All physical and neurologic examinations performed in the hospital and during outpatient follow-up were performed by the same pediatric neurologists (IE).

### Testing

For all 20 patients, a single fasting blood sample was drawn from the antecubital vein. Fasting time ranged from 4 h to overnight. Laboratory testing included complete blood count, serum levels of vitamin B12, folic acid, and Hcy, and liver, kidney, and thyroid function tests. Serum testing was performed via a chemiluminescent microparticle immunoassay using a commercial kit (Abbott Laboratories, Abbott Park, IL, USA), and an Abbott Architect I2000 system (Abbott Inc., IL, USA). Organic acid analysis was performed by capillary gas chromatography-mass spectrometry. Thrombophilic polymorphisms; MTHFR c.677 C > T and c.1298 A > C were analyzed with commercial kits by RT-PCR method (LightCycler® 2.0 Instrument, Roche).

### Statistical analyses

Statistical analysis was performed using the statistical package SPSS software (Version 22.0, SPSS Inc., and Chicago, IL, USA). Descriptive statistics regarding age, sex, symptoms, neurologic findings, and the results of laboratory tests, neuroimaging, and genetic analysis were evaluated.

## Results

Twenty patients (age range 7 months to 16 years 10 months, 5 girls) were diagnosed with genetic Hcy. The demographic and clinical data and serum levels of vitamin B12, folic acid, and Hcy are presented in Table 1.

The most common final diagnoses were homozygote MTHFR mutation in 75% (15/20) of cases (Table 1). Eight of 13 children with homozygous MTHFR C677T mutations had seizures. One of 12 children with a homozygous MTHFR C677T mutation had retinal artery occlusion (RAO) (case 1). Initially, she received low molecular weight heparin for treatment. Appropriate doses of B6, B12, and folate were also added after the diagnosis of HHcy. This case was previously reported as a central RAO possibly due to HHcy caused by a MTHFR C677T mutation and high

**Table 1** The demographic, clinical and genetic findings of patients with hyperhomocysteinemia

| Patient no. | Age(y) /sex | Age at the time of diagnosis | Follow up time | Symptoms at presentation | Initial diagnosis | Final diagnosis | Serum Hcy level (μmol/L) | Serum B12 level (pg/dL) | Serum folate level (ng/mL) | Serum methionine level (μmol/L) | Urine organic acid | MRI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 21 y/F | 13y 10m | 7y 9m | Blindness on the left eye | RAO | MTHFR C677T | 45.27 | 267 | 9.2 | – | – | – |
| 2 | 8.5 y/M | 1y 4m | 7y4m | Seizure | Nonepileptic myoclonus | Cbl C | 106.5 | 238 | 8.37 | N | MMA + | + |
| 3 | 23 y/M | 15y10m | 7y | Small head, MR | Microcephaly MR | MTHFR C677T | 41.75 | 243 | 3 | 22.09 | N | + |
| 4 | 21 y/M | 14y11m | 7y4m | Seizure,MR | Epilepsy, MR | Combined form Cbl | 197 | 714 | 17.8 | Low | MMA + | + |
| 5 | 21 y/M | 16y | 5y10m | Seizure conduct disorder | Epilepsy conduct disorder | MTHFR C677T | 37.38 | 247 | 17.42 | – | – | – |
| 6 | 16y3 m/M | 12y10m | 4y8m | Seizure | Epilepsy | MTHFR C677T | 29.7 | 238 | 3.6 | – | – | + |
| 7 | 16y6 m/F | 12y3m | 4y3m | Headache, blurred vision | Papiledema Pseudotumor cerebri | MTHFR C677T | 28.5 | 302 | 4.04 | – | – | – |
| 8 | 21y3 m/F | 17y | 4y3m | Seizure | Epilepsy | MTHFR C677T | 21.3 | 346 | 6.92 | – | – | + |
| 9 | 2y2 m/M | 2y2m | 1mo | Seizure left sided weakness | Stroke sepsis | Classic Homocystinuria | 198 | 406 | 3.3 | 259 | N | + |
| 10 | 14y4 m/F | 12y1m | 3y | Seizure | Epilepsy | MTHFR C677T | 31.8 | 419 | 3.5 | – | – | + |
| 11 | 18 y/M | 12y10m | 3y | Headache | Migraine | MTHFR C677T | 58.1 | 255 | 5.01 | 33 | N | + |
| 12 | 11y6 m/F | 9y9m | 2y6m | Proteinuria | Pulmonary hypertension FSGS | Cbl C | 165.4 | 628 | 18.9 | 9.7 | MMA + | – |
| 13 | 15y6 m/M | 13y9m | 2y6m | Seizure,MR | Epilepsy, MR | MTHFR C677T | 28.55 | 579 | 9.09 | – | – | + |
| 14 | 17y1 m/M | 16y1m | 1y9m | Headache | Migraine | MTHFR A1298C | 29.15 | 238 | 11.97 | – | – | + |
| 15 | 17 y/M | 16y8m | 1y1m | Dizziness | Vertigo | MTHFR A1298C | 43.97 | 357 | 9.56 | – | – | – |
| 16 | 1y6 m/M | 7m | 1y1m | Hypotonia growth retardation | Congenital hypotonia | Classic Homocystinuria | 242.6 | 542 | 15.4 | 1265 | N | + |
| 17 | 15y8 m/M | 15y4m | 1y | Headache | Tension Headache, | MTHFR C677T | 26.42 | 376 | 4.7 | – | – | + |
| 18 | 17y5 m/M | 12y6m | 9m | Seizure mental retardation | Epilepsy mental retardation | MTHFR C677T | 17.8 | 619 | 7.73 | – | – | + |
| 19 | 12y3 m/M | 10y2m | 6m | Seizure | Epilepsy | MTHFR C677T | 26.7 | 847 | 2.8 | – | – | + |
| 20 | 15y2 m/M | 14y10m | 6m | Seizure | Epilepsy | MTHFR C677T | 39.73 | 1030 | 4.3 | – | – | + |

*RAO* retinal artery occlusion; *m* month; *MR* mental retardation; *M* male; *F* female; *y* year; *MRI* magnetic resonance imaging

**Table 2** Characteristic features of patients with epileptic seizures

| Patient no. | Age(y) /sex | Age at the time of diagnosis | Symptoms at presentation | Initial diagnosis | Final diagnosis | Seizure type | Last seizure time | Type of EEG findings | Anti-epileptic drug | MRI findings |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 8y6 m/M | 1y4m | Seizure | Nonepileptic myoclonus | Cbl C | Myoclonus | – | Normal | – | + |
| 4 | 21 y/M | 11y | Seizure, MR | Epilepsy, MR | Combined form Cbl | Generalized | Daily | Slow background activity and left occipital dominant, generalized spike-waves discharges | LEV,CLB,PHE,OXC | + |
| 5 | 21 y/M | 11y | Seizure behavioral | Epilepsy conduct disorder | MTHFR C677T | Focal | 1y ago | Normal | LEV,VPA | – |
| 6 | 16y3 m/M | 12y10m | Seizure | Epilepsy | MTHFR C677T | Focal | 4y ago | Normal | CBZ | + |
| 8 | 21y3 m/F | 17y | Seizure | Epilepsy | MTHFR C677T | Generalized | 3y3m ago | Generalized 3–4 Hz SWs of frontal predominance, polyspike-waves discharges | VPA,LTG | – |
| 9 | 2y2 m/ M | 2y1m | Seizure left sided weakness | Epilepsy, stroke, sepsis | Classic Homocystinuria | Generalized | – | Generalized slow background activity | LEV,PHE | + |
| 10 | 14y4 m/F | 12y1m | Seizure | Epilepsy | MTHFR C677T | Generalized | 3y ago | 3–4 Hz diffuse polyspike-wave discharges | LEV | – |
| 13 | 15y6 m/M | 14y | Seizure,MR | Epilepsy, MR | MTHFR C677T | Focal | 2y7m ago | Normal | VPA | + |
| 18 | 17y5 m/M | 12y6m | Seizure,MR | Epilepsy, MR | MTHFR C677T | Focal | 2y6m ago | Normal | VPA | + |
| 19 | 12y10 m/M | 10y9m | Seizure | Epilepsy | MTHFR C677T | Focal | 1m ago | Bilaterally, spike and wave discharges at frontotemporal regions | OXC,LEV | – |
| 20 | 15y7 m/M | 15y4m | Seizure | Epilepsy | MTHFR C677T | Focal | 1m ago | Normal | LEV | |

*m* month; *MR* mental retardation; *M* male; *F* female; *y* year; *VPA* valproic acid; *PHE* Phenytoin; *OXC* oxcarbazepine; *CBZ* carbamazepine; *CLB* clobazam; *LEV* levetiracetam; *LTG* Lamotrigin; *MRI* magnetic resonance imaging

lipoprotein (a) level [3]. One of 13 children (case 7) with a homozygous MTHFR C677T mutation was diagnosed with idiopathic cranial hypertension (IIH). There was no history of any preceding head injury, chronic systemic disease, viral illness, or use of any medication. On physical examination, she weighed 71 kg and had a height of 163 cm (body mass İndex (BMI) of 26.7 kg/m$^2$). Neurologic examination revealed only bilateral papilledema. Brain MRI and MR venography were normal. The laboratory and genetic tests of the patients are given in Table 1. She was diagnosed with IIH according to the Modified Dandy's Criteria [4]. She was put on 750 mg/day acetazolamide together with appropriate doses of B6, B12, and folate. In the follow-up, she showed complete resolution of symptoms and signs. Two children with homozygous MTHFR C677T mutations (cases 11 and 17) and one with MTHFR A1298C mutations (case 14) were admitted to the hospital with chronic headache. Cases 11 and 14 met the diagnostic criteria of the İnternational Headache Society (2013) for migraine [5]. Case 17 was diagnosed as tension type headache. The only patient who suffered from dizziness was case15 a with homozygous MTHFR A1298C mutation. His EEG and brain MRI were normal and diagnosed as peripheral vertigo. He was given appropriate doses of B6, B12, and folate and he was symptom-free for nearly two and a half years.

Three patients (15%) of cases (cases 2, 4, 12) with intracellular cobalamin (cbl) defects were combined form, and genetic analysis revealed cblC defects. Although the fourth case had been followed up in another center for a long time because of resistant epilepsy and mental retardation (MR), it was not diagnosed, because Hcy level was not analysed. We observed proteinuria in twelfth case with a cblC defect. She presented with cyanotic spells at the age of 3 and was diagnosed with primary pulmonary hypertension ((PPH) and secondary focal glomerular sclerosis (FSGS) at another center. At the age of 7, HHcy was detected and she was diagnosed as cblC defect. We observed nonepileptic myoclonus in case 2 with cblC defect (Table 1).

Two patients (10%) had classic homocystinuria (cases 9 and 16). Case 9 was referred to our pediatric intensive care unit (PICU) from another hospital due stroke in the left hemisphere. Treatment with appropriate doses of B6, B12, folate, and betaine was initiated for HHcy. He died at the seventeenth day of admission because of septicemia. The case 16 was a 10-month-old boy who presented with hypotonia and failure to thrive. On his medical history, he was admitted to another clinic twice at the age of 3 months and 5 months with fever and rapidly needed transfer to the PICU and he was diagnosed as septicemia and discharged after treatment. He had a sister who died at the age of 2 years due to MR and drug-resistant epilepsy and his parents are consanguineous. He was symptom-free for 24 months and also gained weight after appropriate treatment (Table 2).

Eleven of 20 patients presented with suspected seizure and 10 of them were diagnosed with epilepsy. Seizure type, EEG features and treatments are summarized on Table 2. In addition, the EEG findings of the patient with resistant epilepsy (case 4) before and after treatment are presented in Figs. 1 and 2.

## Discussion

Our main finding is that the most common cause of genetic HHcy is MTHFR mutation. The other main finding is that the Hcy level was higher in patients with cystathionine

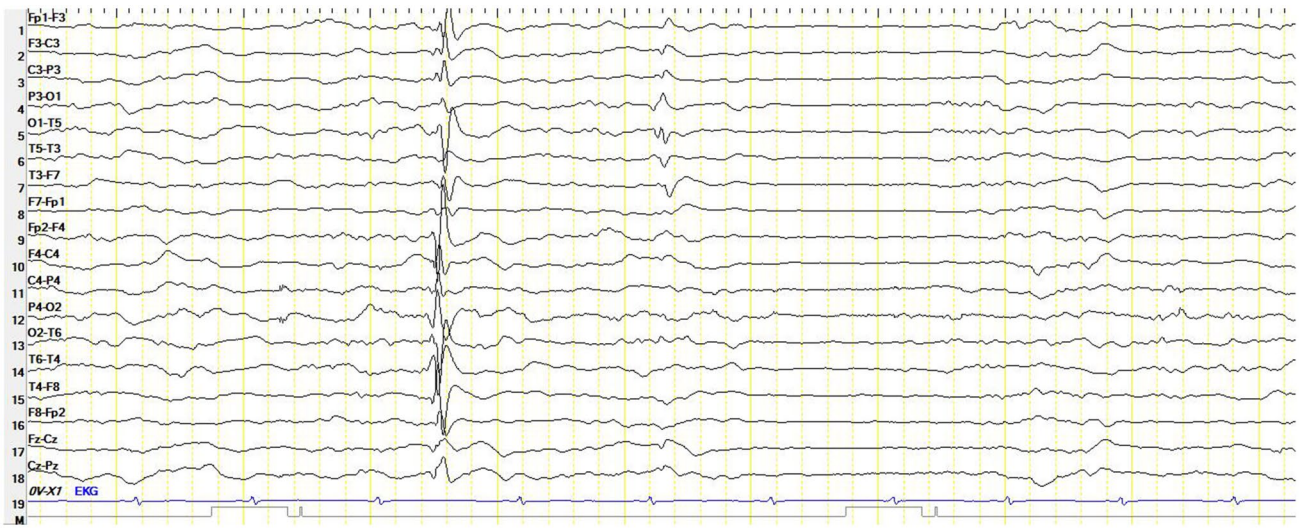


**Fig. 1** Patient 4′s EEG consistent with abnormal background activity and left occipital dominant, generalized epileptic discharges

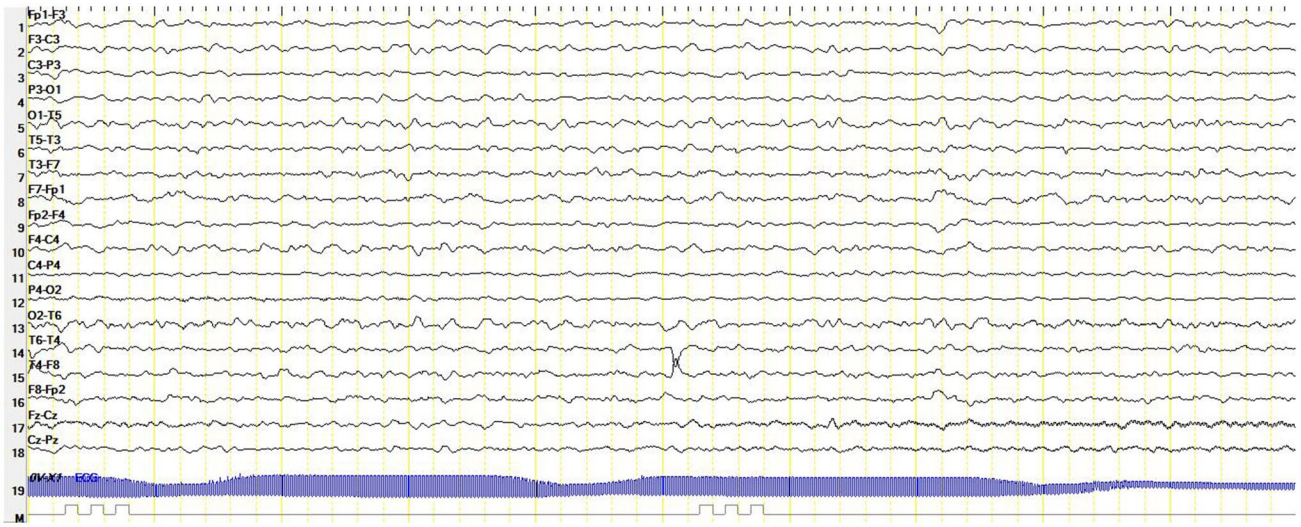


**Fig. 2** Patient 4′s EEG consistent with abnormal background activity without any epileptic discharges

b-synthase (CBS) deficiency and intracellular cbl defects than in MTHFR mutations. We also found that clinical presentations of genetic HHcy vary widely, and the most common clinical finding is seizures.

MTHFR deficiency is a severe disease primarily affecting the central nervous system. Age at presentation and clinical pattern are correlated with residual enzyme activity of MTHFR deficiency. The MTHFR C677T polymorphism reduces enzyme activity by 70% and 35% in homozygous and heterozygous individuals, respectively. Therefore, mutation of the MTHFR gene may cause mild clinical presentation [6–9]. Fifteen of our patients had HHcy and MTHFR mutations, and only 2 of the patients had the MTHFR A1298C genotype (Table 1).

The data of children associated with MTHFR mutations in the literature are insufficient[10]. In some studies, the relationship between the C677T polymorphism and low serum folate levels was reported, while other studies reported that serum folate levels were normal in individuals carrying this polymorphism [10–16]. Van der Put et al. reported that serum folate levels were lower in individuals with C677T mutations but normal in individuals with the A1298C polymorphism [13]. We observed that serum folate levels were lower in patients with the MTHFR C677T mutation than in those with the A1298C mutation. On the other hand, serum folate levels were within normal limits in all of our cases with MTHFR mutations, although some of them were within the lower limit of the normal range. Therefore, we thought that there was no relationship between the clinical findings and folate levels in our patients with MTHFR mutations.

In previous studies, the MTHFR C677T and A1298C polymorphisms were reported to be associated with an increased risk of epilepsy due to acting as NMDA receptor agonists or metabolites of Hcy including homocysteic acid and L-Hcy sulfinic acid which interacts with glutamate receptors [17–19]. Cases 5, 6, 8,10,13, 18, 19, and 20 presented with seizures and the MTHFR C677T mutation. The interaction between enzyme-inducing antiepileptic drugs and MTHFR polymorphisms could lead to low plasma folate and high Hcy levels in approximately 20–40% of epileptic patients [20, 21]. Measuring the level of Hcy before starting drug treatment may guide drug selection.

It has been reported that the C677T polymorphism of the MTHFR gene is associated with stroke, coronary artery disease, psychiatric disorders, and migraine [22]. Our first patient was diagnosed with RAO due to HHcy caused by the MTHFR C677T mutation and elevated levels of lipoprotein A. Although RAO primarily affects patients older than 60 years old, it is rarely reported in children. Therefore, it should be kept in mind that HHcy is probably an independent risk factor for RAO in children (Table 3) [3].

The data on vertigo in children associated with Hhyc in the literature are limited. Recently, high plasma levels of Hcy were reported to be associated with acute peripheral vertigo, sudden sensorineural hearing loss, and impaired cochlear perfusion [23, 24]. A microvascular disorder or the neurotoxic effects of HHcy have been considered possible causal factors [25]. Case 15 presented with dizziness and was diagnosed as peripheral vertigo associated with HHcy (Table 3).

Patient six presented with papilledema and blurred vision. All evaluations for IIH were normal except for MTHFR 6C77T mutation. It is known that increased cerebrospinal fluid pressure (CSF) pressure can be caused by unrecognized nonocclusive venous thrombosis by impeding CSF drainage

**Table 3** Different features of our study from the literature

| Number of patient | Age | Diagnosis | Final diagnosis | Clinical findings | Our cases |
|---|---|---|---|---|---|
| Case 1 | 21 y/F | Retinal artery occlusion | Due to HHcy caused by the MTHFR C677T | C677T polymorphism of the MTHFR gene is associated with stroke, coronary artery disease, psychiatric disorders, and migraine | HHcy is probably an independent risk factor for retinal artery occlusion in children |
| Case 2 | 8.5 y/M | Nonepileptic myoclonus | Due to Cbl C | Failure to thrive, hypotonia, seizures, microcephaly, developmental delay, neuropsychiatric symptoms, myelopathy/peripheral neuropathy, thromboembolism, and kidney disease | This case was the first and only with a cbl defect who presented with nonepileptic myoclonus |
| Case 7 | 16y6 m/ F | Idiopathic cranial hypertension | Due to MTHFR C677T | Thrombophilia, stroke, venous thromboembolism, hyperlipidaemia, essential hypertension, | Nonocclusive venous thrombosis |
| Case 17 | 15y8 m/M | Tension Headache | Due to MTHFR C677T | Migraine | No relationship between HHcy and tension-type headache has been described in the children in the literature until now. Studies are needed to establish cause-effect relationships |
| Case 15 | 17 y/M | Vertigo | Due to MTHFR A1298C | Rarely acute peripheral vertigo, sudden sensorineural hearing loss, and impaired cochlear perfusion | The data on vertigo in children associated with HHycin the literature are limited |

[26]. In the literature, one pediatric case with recurrent IIH and vitamin B12 deficiency was reported. Although her MR venography was normal at the first attack, sinus thrombosis was detected at the recurrent attack. The cause was reported as vitamin B12 deficiency-related HHcy [27]. Therefore, we speculate that the sixth case of IIH was caused by nonocclusive venous thrombosis associated with the MTHFR 6C77T mutation and relsated to HHcy. We also thought that platelet-rich microthrombi associated with HHcy occlude arachnoid sinus villi and lead to IIH by reducing resorption of CSF. Therefore, investigation of the level of Hcy may be useful in patients with IIH (Table 3).

The MTHFR-C677T polymorphism was found to be associated with migraine in Turkish patients [28]. Another study reported that Hcy and folate-related functional gene polymorphisms may influence the presence of aura among migraineurs [29]. These studies explain the pathogenesis of migraine by HHcy and vascular theory. Another theory is that Hcy derivatives may act as NMDA receptor agonists and may enhance glutamatergic neurotransmission. As a result, spontaneous trigeminal cell firing increases and predisposes cortical neurons to hyperexcitability [30]. Moreover, Rainero et al. suggested the use of folate, vitamin B6, and vitamin B12 for the prevention of migraine [31]. Case 11 with the MTHFR C677T mutation and case 14 with the MTHFR A1298C mutation presented with headache and were diagnosed with migraine according to IHCS [5]. Case 17 with the MTHFR 6C77T mutation also presented with headache, and he was diagnosed with tension-type headache. No relationship between HHcy and tension-type headache has been described in the literature until now (Table 3).

Later-onset disease in patients with higher residual activity of MTHFR usually presents with MR and psychiatric disease in children, adolescents, and adults [32–35]. Several studies have shown an association between elevated plasma Hcy levels and cognitive impairment, indicating that it may play a role in the pathophysiology of dementia [36]. Although we cannot clearly state the relationship between hyperhomocysteinemia and the clinic of our case 3 and 13 who had MR with microcephaly and epilepsy, respectively (Table 1). We suggest evaluating the serum levels of Hcy, folate, and vitamin B12 in patients with idiopathic MR.

Our three patients (cases 2, 4, and 12) were diagnosed with a combined form of cbl-related remethylation disorders according to biochemical analysis. Genetic analysis revealed cblC defects in cases 4 and 12 (Table 1). Our fourth patient was admitted with seizures and MR at the age of 12 years old in our clinic and was diagnosed with cobalamin C defects. Although he was evaluated at other tertiary centers with MR and drug-resistant epilepsy, his diagnosis was delayed since no laboratory testing for Hcy levels was performed. After HHcy treatment, his seizure frequency decreased gradually. He was seizure-free. Evaluation of the serum Hcy level in

all patients with intractable seizures may help the patient to get the correct diagnosis.

The twelfth patient had also a cblC defect. She was being followed up for PPH and secondary FSGS. Cardiopulmonary signs are increasingly observed in cblC patients, including congenital heart diseases, cardiomyopathy, pulmonary thromboembolism, and pulmonary hypertension. Some cblC patients present with renal disease including renal thrombotic microangiopathy, hemolytic uremic syndrome, and primary glomerular disease, such as segmental glomerulosclerosis or atypical glomerulopathy [37]. Although patient 11 was diagnosed with PPH at the age of three years, she was diagnosed as cblC defect when she had proteinuria at the age of 7. Evaluation of the serum Hcy level in all patients with PHT may help the patient to get the early diagnosis and may prevents kidney injury.

Case 2 was diagnosed as nonepileptic myoclonus with combined remethylation disorders due to intracellular cbl defects according to biochemical analysis (Table 1). To the best of our knowledge, this case was the first and only with a cbl defect who presented with nonepileptic myoclonus. Our case was symptom-free and showed normal development with appropriate treatment (Table 3).

CBS deficiency is another rare genetic disorder in the methionine catabolic pathway in which the impaired synthesis of cystathionine leads to the accumulation of Hcy [38]. The usual presentations of classical homocystinuria are mental retardation and developmental delay, seizures, ocular lens dislocation, and thromboembolic events [39]. Two of our patients had homozygous CBS deficiency. As we mentioned, high-dose pyridoxine, B12, and folate were given to our patients with CBS deficiency, and betaine was administered after the final diagnosis. Case 8 with CBS deficiency had stroke on presentation, and unfortunately, he was lost due to septicemia. The second patient with CBS deficiency (case 15) presented with hypotonia and developmental delay. Since he was 6 months old at the time of diagnosis, we did not observe any stroke under appropriate treatment during the 12-month follow-up. We think that neurological sequelae can be prevented with early diagnosis.

## Conclusion

Our findings suggest that genetic HHcy might be associated with different clinical manifestations and etiologies. The most common cause of genetic HHcy in our study was the MTHFR mutation. We observed that the Hcy level was higher in patients with CBS deficiency and intracellular cbl defects than in those with MTHFR mutations. We also found that clinical presentations of genetic HHcy vary widely, and the most common clinical finding is seizures. Here, we also report the first and only case of a cbl defect with nonepileptic myoclonus. We also observed that mild and intermediate HHcy associated with the MTHFR mutation may be related to migraine, vertigo, tension-type headache, and IIH. Although some of the patients were followed up in tertiary care centers for a long time, they.

**Author contributions** ŞB wrote the manuscript. ŞB, YÖ, İE, SC, and AN were involved in patient care, including administration of medication and routine clinical follow-up. İE, YÖ, ŞB reviewed the results and approved the final version of the manuscript.

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**Data availability** The data that support the findings of this study are available on request from the corresponding author.

## Declarations

**Conflict of interest** The authors declare there are no conflicts of interest financial or otherwise related to the material presented herein.

**Ethical approval** Our study was approved by the Baskent University Institutional Review Board and Ethics Committee. The approvement number is KA20/120. Written informed consent was obtained from the parents of all participants.

**Copyright form disclosure** The authors disclosed government work.

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