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MCT8 deficiency: Point of a neurological view

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Abstract

Background: Monocarboxylate Transporter 8 (MCT8) deficiency, or Allan-Herndon-Dudley Syndrome (AHDS), is a rare X-linked disorder characterized by impaired neuronal uptake of thyroid hormone, leading to severe neurodevelopmental delay and characteristic laboratory findings.

Objectives: This study aimed to delineate the clinical, radiological, and genetic features of patients with MCT8 deficiency and to assess the therapeutic outcomes of recent treatment modalities.

Methods: A retrospective, multicenter case series was conducted across seven pediatric neurology centers in Turkey. Data from 12 male patients from 10 unrelated families were analyzed. Diagnosis was genetically confirmed using Whole Exome Sequencing (WES) or Next-Generation Sequencing (NGS), followed by Sanger validation. Clinical and demographic data, thyroid hormone profiles, and cranial MRI findings were collected and evaluated using descriptive statistics.

Results: The mean age at diagnosis was 35 ± 11.9 months, with symptom onset at 5.6 ± 0.8 months. All patients presented with profound hypotonia, psychomotor delay, and absent head control. Spasticity (92%), dystonia (33%), and seizures (50%) were observed. Skeletal deformities included scoliosis (58%) and pectus excavatum (25%). MRI revealed delayed myelination in 50% and cerebral atrophy in 30%. Most patients had elevated free T3 and increased T3:T4 ratios. Two patients treated with triiodothyroacetic acid (Triac) demonstrated improved weight gain and reduced spasticity compared to untreated peers.

Conclusion: Early diagnosis and multidisciplinary management are essential in MCT8 deficiency. This study supports the potential benefits of Triac treatment in selected cases and highlights the need for further research on long-term outcomes.

Keywords: MCT8 deficiency; Allan-Herndon-Dudley Syndrome; Delayed myelination; Triac therapy; Thyroid hormone transporter; Neurological disorders.

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Introduction

Thyroid hormones play a crucial role in the development of the central nervous system. They affect neurogenesis, migration, synaptogenesis and myelination. To exert these effects, triiodothyronine (T3), the active form of thyroid hormone, must cross the blood-brain barrier and enter the central nervous system [1,2]. Monocarboxylate Transporter 8 (MCT8) is a thyroid hormone transporter encoded by the solute carrier family 16 member 2 (SLC16A2) gene on the X chromosome. MCT8 is expressed primarily in the liver, kidneys and brain. Studies have shown that in the brain MCT8 is located in glial cells, neurons, the blood-cerebrospinal fluid barrier and specifically the blood-brain barrier [1,3]. In the post-mortem study performed, delayed myelination with delayed maturation in the neocortex and cerebellum was found in 2 patients with MCT8 deficiency, which is thought to be due to the negative effect of central hypothyroidism on brain development [4]. Since MCT8 production is impaired in SLC16A2 gene mutations, T3 transport is impaired and central hypothyroidism occurs. In contrast, peripheral tissues show signs of hyperthyroidism [5]. Clinically unremarkable in the first few months after birth, lack of head control due to severe hypotonia, lack of speech development, swallowing-feeding problems, mental retardation, dystonia, development of spasticity in later stages. Drug-resistant epilepsy, microcephaly, dysmorphic findings like long face, ear anomalies, bone anomalies and thyroid hormone disorders [6-8] may be seen. Muscle wasting and inability to gain weight are explained by the effects of hyperthyroidism on peripheral tissues, as well as swallowing and feeding problems. Delayed myelination is the most common finding on cranial imaging, and cases of improved myelination have been reported. This is important for differentiation from leukodystrophic disorders. Enlarged ventricles, thin corpus callosum and cerebral atrophy may also be seen [7,9]. In most patients, elevated free T3, decreased rT3 and T4, normal/slightly elevated TSH, and elevated T3/T4 ratio are expected [10,11]. MCT8 deficiency is responsible for about 4% of X-linked mental retardation [12,13]. Although cases have been reported at an advanced age, it has been reported that life expectancy in MCT8 deficiency is significantly reduced, especially in patients who cannot control their head at the age of 1.5 years and whose weight for age is under the -2 SD [11]. The main causes of mortality are aspiration-related pneumonia and cardiac causes related to peripheral hyperthyroidism [14,15]. More than 300 affected individuals with SLC16A2 mutations have been reported, and the mutations are highly variable. Large deletions, loss of one or more exons, frameshift deletions, single amino acid deletions are some of these mutations. The severity of the clinical findings can vary according to the type of mutation [2]. Allan et al. first identified Allan-Herndon-Dudley syndrome (AHDS) in 1944 by studying the clinical features of 22 cases from 9 different families [16]. In 2006, Friesema et al. found that MCT8 deficiency due to SLC16A2 mutations led to this clinical picture [17]. Subsequently, studies of the genotype-phenotype relationship and possible treatable central hypothyroidism have been carried out in case series from different countries.

Materials and methods

This study is a retrospective, multicenter case series involving seven pediatric neurology departments across Turkey. The centers include University of Health Sciences Tepecik Training and Research Hospital, Izmir Katip Celebi University, Dokuz Eylul University, Karadeniz Technical University, Dicle University, Cerrahpasa University, and Eskisehir City Hospital. The study was conducted in accordance with the ethical guidelines set by the Declaration of Helsinki and was approved by the Institutional Ethics Committee of each participating center. Informed consent was obtained from the families of all participating patients.

The study included 12 male patients from 10 unrelated families, all diagnosed with MCT8 deficiency through genetic testing. The patients were recruited based on clinical suspicion of MCT8 deficiency due to characteristic neurological findings, including severe hypotonia, delayed motor milestones, and abnormal thyroid hormone profiles. Genetic confirmation was performed via Sanger sequencing or Next-Generation Sequencing (NGS) as described below. Inclusion criteria consisted of a genetically confirmed diagnosis of MCT8 deficiency, available clinical data, and consent for participation. Exclusion criteria included patients with incomplete medical records or those without a confirmed genetic diagnosis.

Clinical and demographic data were collected from the patients' electronic medical records, including age at diagnosis, sex, gestational age, birth weight, head circumference, and dysmorphic features. Neurological assessments such as muscle tone, motor milestones, and presence of movement disorders (e.g., dystonia, spasticity) were recorded. Radiological data, including cranial Magnetic Resonance İmaging (MRI) and Auditory Brainstem Response (ABR) findings, were also collected. Electroencephalography (EEG), Echocardiography (ECHO), and Electrocardiography (ECG) findings were noted when available.

Thyroid function was evaluated through serum levels of Thyroid-Stimulating Hormone (TSH), free T3, free T4, and the T3:T4 ratio.

Whole Exome Sequencing (WES) was performed to identify pathogenic variants in the SLC16A2 gene responsible for MCT8 deficiency. Genomic DNA was extracted from peripheral blood samples collected from the patients. Libraries were prepared using commercial exome capture kits, and sequencing was performed using high-throughput NGS platforms, such as Illumina HiSeq or NovaSeq. Sanger sequencing was used to confirm the pathogenic variants identified in the SLC16A2 gene. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Descriptive statistics were used to summarize the demographic, clinical, and laboratory characteristics of the cohort. Continuous variables were expressed as means and standard deviations or medians with interquartile ranges, depending on the distribution of the data. Categorical variables were summarized as frequencies and percentages. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Twelve patients from 10 different families were genetically diagnosed with MCT8 deficiency. The mean age at diagnosis was 35 ± 11,9 months (range 6–132), but the mean age at onset of first symptoms was 5,6 ± 0,8 months (range 1-10). Four patients were born prematurely, and low birth weight was noted in two of them (Table 1). In the other patients, low birth weight was not noted and head circumferences were within the normal range at birth. All patients had severe psychomotor retardation. The most common complaint for admission was lack of head control. Other causes include hypotonia and lack of unsupported sitting (this patient achieved head control at 4 months of age). Head control was present in only 4 pa-

tients and unsupported sitting and walking were not observed in any of them. Single word speech was observed in 1 patient at 36 months of age (Table 2). Head circumference and weight percentiles were below -2 SD in all but one patient. Dysphagia was noted in 10 patients, with concomitant gastro-oesophageal reflux in 3, and 1 patient underwent Nissen fundoplication. Seizures occurred in 6 patients, 3 of whom had generalised seizures and the others had focal seizures. One patient had antiseizure drug resistance. Extrapyramidal symptoms were common (Table 3). Dystonia was seen in 4 patients, hypomemia in 4, paroxysmal kinesigenic dyskinesia in 2, hypokinesia in 3 and opsoclonus-myoclonus in 2. Pyramidal signs were noted in 11 patients. All patients were hypotonic and deep tendon reflexes were increased in 10 patients. Spasticity was noted in 11 patients. Nystagmus was noted in 3 patients. Scoliosis was the most common skeletal abnormality in 7 patients. Everted feet were found in 3 patients and pectus excavatum in 3 patients. ABR was normal in 7 patients and sensorineural hearing loss in 1 patient. Electrocardiographic and echocardiographic findings were available for 7 patients and while all ECG findings were normal, ventricular septal defect was found in 1 patient and patent foramen ovale in 1 patient. Seven patients had Denver Developmental Scale and global growth retardation was found in all. Cranial MRI was performed in 10 patients and 3 of them had normal findings. Delayed myelination was found in 5 patients, 3 of whom had cerebral atrophy. Increased CSF space was noted in 3 patients and mild ventriculomegaly in 1 patient (Table 4). The most common dismorphological features were elongated face in 6 patients, cryptorchidism in 3 patients and inguinal hernia in 1 patient. No deaths were reported in these patients. Serum Thyroid Stimulating Hormone (TSH) concentrations were within the normal range in 12 patients. Ten patients had serum free T3 concentrations above the upper age limit for T3, resulting in a marked increase in the T3:T4 ratio. There were no abnormal laboratory findings in blood counts, electrolytes, alanine aminotransferase, aspartate aminotransferase, creatine kinase, creatinine or blood urea.

Table 1: Clinical characteristics of patients with MCT8 deficiency.

Mean age at diagnosis (months) (range, median)	5,6 ± 0,8 (1-10)
Mean gestational age (weeks) (range, median)	38 (36-40)
Mean head circumference at birth (cm) (range, median)	34 (33-35)
Mean birth weight (g) (range, median)	3248 (1880-4150)
Body weight (<3rd centile) n:11	%91,6
Microcephaly (<3rd centile) n:11	%91,6
Skoliozis n:7	%58,3
Elongated face n:6	%50
Pectus excavatum n:3	%25
Everted feet n:3	%25
Open mouth shape n:2	%16,6
Cryptorchidism n:3	%25
Inguinal hernia n:1	%8,3

Table 2: Neurological features and laboratory findings of patients with MCT8 deficiency.

Completion of head control n:4	%33,3
Able to keep sitting n:0	%0
Able to speak a word n:1	%8,3
Seizures n:6	%50
Hypotonia n:12	%100
Dystonia n:4	%33,3
Spasticity n:11	%91,6
Nystagmus n:3	%25
Increased deep tendon reflexes n:10	%83,3
Paroxysmal kynesigenic dyskinesia n:2	%16,6
Hypokinezia n:3	%25
Hypomimia n:4	%33,3
Denver developmental scale anomaly n:7	%100 (data available in 7 patients)
EEG abnormality, n:6	%100 (data available in 6 patients)
ABR abnormality n:1	%12,5 (data available in 8 patients)

Table 3: Extrapyramidal and pyramidal symptoms in patients with MCT8 deficiency.

Symptom	Number of patients	Percentage
Extrapyramidal symptoms	11	%91,6
Dystonia	4	%33,3
Hypomemia	4	%33,3
Paroxysmal kinesigenic dyskinesia	2	%16,6
Hypokinesia	3	%25
Opsoclonus myoclonus	2	%16,6
Pyramidal symptoms	11	%91,6
Increased deep tendon reflexes	10	%83,3
Spasticity	11	%91,6
Nystagmus	3	%25

Table 4: The MRI findings in patients with MCT8 deficiency.

MRI Findings	Number of Patients	Percentage
No abnormality	3	%30
Delayed myelination	5	%50
Cerebral atrophy with delayed myelination	3	%30
Increased CSF space	3	%30
Mild ventriculomegaly	1	%10

Discussion

Clinical findings and neuroimaging

The mean age of patients at diagnosis was 35 ± 11.9 months, but the mean age of first symptoms was 5.6 ± 0.8 months. This is in line with previous studies reporting that symptoms of AHDS typically appear in the first months of life [13,18].

It is important to note that head circumference in patients with AHDS may be within the normal range at birth, but usually becomes progressively smaller over time. This is due to impaired thyroid hormone transport caused by SLC16A2 mutations, which affects brain development and growth. In fact, reduced head circumference is one of the main diagnostic criteria for AHDS [7,8,11,13].

As noted in the article, all patients had severe psychomotor retardation. This is a common feature of MCT8 deficiency and AHDS, as it reflects the role of MCT8 in transporting thyroid hormones across the blood-brain barrier and into neurons. Psychomotor retardation is often the first symptom to appear in affected individuals and typically includes severe intellectual disability, delayed motor development and hypotonia [13,18,19]. Hypotonia, or low muscle tone, was a common feature among patients. This is also a hallmark of MCT8 deficiency and AHDS and is thought to result from impaired neuromuscular signalling due to the lack of thyroid hormone in affected individuals [13,20].

Seizures were observed in 6 patients, 3 with generalised seizures and 3 with focal seizures. Seizures are a common complication of MCT8 deficiency and AHDS, affecting up to 80% of affected individuals. They can be difficult to control with medication and often have a negative impact on cognitive development. In this study, one patient was resistant to antiseizure drugs. In a case series by Remerand et al, four out of seven patients with Allan-Herndon-Dudley syndrome were described as having drug resistant seizures [7]. Groeneweg et al. reported that 23% of patients had EEG-proven seizures, most of which were generalised. The pathophysiology of seizures in MCT8 deficiency and AHDS probably involves a complex interplay of factors, including excitatory-inhibitory imbalance, neuronal hyperexcitability, neurodevelopmental abnormalities and dysfunction of the GABAergic system.

Extrapyramidal symptoms such as dystonia, hypomemia and paroxysmal kinesigenic dyskinesia were seen in our patients. This is consistent with previous studies reporting extrapyramidal symptoms in individuals with Allan-Herndon-Dudley syndrome. Goeneweg et al. reported extrapyramidal findings in 25% of patients. Masnada et al found dystonia and hypokinesia in 25 of 27 patients [21]. As seen, extrapyramidal symptoms are common, but the frequency may vary. Disruption of thyroid hormone transport can affect dopaminergic and GABAergic pathways, potentially leading to dysfunction of the basal ganglia circuit and the development of dystonia and other extrapyramidal symptoms. Thyroid hormones, particularly triiodothyronine (T3), are essential for the development and maintenance of the motor cortex and corticospinal tract. Disruptions in thyroid hormone signalling can lead to abnormalities in the development and function of the motor cortex and corticospinal tract, resulting in pyramidal symptoms. Spasticity and hyperreflexia were observed in most patients. This is also consistent with previous reports of AHDS, which have noted the presence of spasticity/hyperreflexia in affected individuals. Studies have shown that the incidence of pyramidal findings is between 70-90% [7,18]. Nystagmus has been reported in a minority of patients. Previous reports of AHDS have also noted the presence of nystagmus in some individuals. Dumitrescu et al found that nystagmus was present in 33% of their cohort [19]. The development of the visual pathway, visual cortex and cerebellum is highly dependent on thyroid hormones. Disorders in these pathways can lead to phenomena such as nystagmus.

Regarding cardiac abnormalities, our study found no significant electrocardiographic or echocardiographic abnormalities in most patients, which is consistent with previous reports. However, we identified one patient with VSD and another with PFO. Van Geest et al emphasise that conditions such as tachycardia and rhythm disturbances due to peripheral hyperthyroidism may increase the risk of sudden death, and therefore cardiovascular investigation is important [22].

Dysphagia, gastroesophageal reflux, chewing and swallowing difficulties are common. Most patients are fed through a gastric tube. Aspiration pneumonia is one of the most common causes of death [11,14,15].

Thyroid hormones play a critical role in skeletal growth and development by regulating bone formation, mineralisation and remodelling. Disruption of thyroid hormone signalling can lead to dysregulation of these processes, resulting in skeletal abnormalities such as scoliosis, everted feet and pectus excavatum. Scoliosis was the most common skeletal abnormality in our patients, with everted feet and pectus excavatum also observed in some cases. Everted feet were found in 3 patients and pectus excavatum was found in 3 of our patients. Skeletal deformities such as kyphoscoliosis, pectus excavatum and flat feet have been reported in the literature with a frequency of 10-70% [7,8,18]. The most common morphological feature was an elongated face, observed in five patients. This finding is consistent with previous reports suggesting that an elongated face is a characteristic feature of AHDS. Three patients had cryptorchidism, which is also a common feature of the syndrome. One patient had an inguinal hernia, which is a rare finding in AHDS [8]. These findings may have underlying pathophysiological explanations related to the role of thyroid hormones in embryonic development and tissue differentiation.

Ten patients in our study underwent cranial MRI, and while no abnormality was found in 3 patients, delayed myelination was found in 5 patients, 3 of whom had cerebral atrophy. The myelination defect in MCT8 deficiency results from impaired thyroid hormone transport and signalling within oligodendrocytes, leading to delayed or aberrant myelination of axons in the CNS. Vancamp et al. reported that delayed myelination was seen in 84% of patients under 2 years of age, 63% of patients aged 2-6 years, and 33% of patients over 6 years [9]. This suggests that repeated cranial MRI is important in monitoring myelination.

Auditory Brainstem Response (ABR) was normal in 7 patients and only one patient had sensorineural hearing loss. This finding is consistent with the previous report of normal hearing thresholds in most patients with AHDS [20].

Diagnosis

Patients with developmental delay, hypotonia, movement disorders and abnormal thyroid function tests should be investigated for MCT8 deficiency. Definitive diagnosis is made by genetic testing to identify pathogenic variants in the SLC16A2 gene, together with clinical correlation and evaluation of thyroid function and neuroimaging findings. Early diagnosis is crucial for appropriate management and genetic counselling of affected individuals and their families.

Thyroid function tests, including serum Thyroid Stimulating Hormone (TSH) and free Thyroxine (T4), are commonly used to diagnose thyroid disorders. In this study, serum TSH concentrations were within the normal range in all patients, indicating normal thyroid function. However, serum free T3 concentrations exceeded the age-specific upper limit for T3 in ten patients, resulting in a marked increase in the T3:T4 ratio. This finding is consistent with the expected pattern of thyroid hormone dysregulation in MCT8 deficiency and AHDS, as MCT8 is responsible for transporting T3 across the blood-brain barrier [5,13]. In addition to morphological and thyroid function abnormalities, the study also reported on laboratory tests, including blood cell counts, electrolytes, alanine aminotransferase, aspartate aminotransferase, creatinine and blood urea nitrogen. No abnormalities were found in any of these tests, which is consistent with previous reports indicating that these parameters are typically normal in AHDS [7,11,23].

Recent therapies

In patients treated with T4 replacement therapy (L-thyroxine) for central hypothyroidism, it has been noted that there was no beneficial effect, and treatment was even discontinued in some patients due to an increase in peripheral hyperthyroidism [20,24]. With intranasal L-T4 treatment, it was observed that there was no increase in cerebral T3 and that peripheral thyrotoxicosis worsened [25]. Subsequently, L-T4 replacement was given together with propylthiouracil, and it was found that peripheral T3 decreased with inhibition of peripheral deiodinase 1 activity, and the clinic of hyperthyroidism improved, but no neurological effect was observed [12]. Although normal T3 levels were achieved with 3,5-Diiodothyropropionic Acid (DITPA), a thyroid hormone analogue, no neurodevelopmental progress could be demonstrated. A phase 2 study in 46 patients with triiodothyroacetic acid (triac), another thyroid hormone analogue, reported balanced T3 and T4 levels, a reduction in the effects of peripheral hyperthyroidism, and beneficial effects on heart and weight gain [5,26]. Studies of sobetirome, a thyroid hormone analogue, pharmacological chaperones and gene therapy are ongoing [27]. In our cohort, two patients received triiodothyroacetic acid (triac). Remarkably, one of these patients had percentiles for height, weight and head circumference greater than -2 SD. Interestingly, the absence of spasticity was observed only in the Triac-treated patient, suggesting a possible association between Triac administration and improvement in spasticity symptoms.

Conclusion

In conclusion, this study sheds light on the clinical and laboratory characteristics of patients with Allan-Herndon-Dudley syndrome, highlighting the high prevalence of neurological, developmental and skeletal abnormalities. Our findings confirm previous reports and emphasise the need for early diagnosis and multidisciplinary management strategies. These include close monitoring of cardiac function, developmental assessment and targeted interventions to address skeletal and neurological manifestations. Furthermore, our study highlights the importance of comprehensive clinical assessment and imaging studies to facilitate accurate diagnosis and effective management of AHDS. In the future, further research efforts are warranted to deepen our understanding of the underlying pathophysiological mechanisms of this rare disorder and to develop novel therapeutic strategies aimed at improving patient outcomes.

Declarations

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