Case Report

A rare *de novo* mutation, m.1630A>G, in the mitochondrial tRNAVal (*MT-TV*) gene in a child with epilepsy: case report and review of the literature

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Background: Mitochondrial diseases represent a diverse group of disorders caused by defects in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA), leading to a wide range of clinical manifestations. These diseases can affect multiple organs, particularly the nervous system, and present with symptoms such as epilepsy, neurodevelopmental delays, and muscular disorders. Over 300 genetic mutations have been linked to these conditions, with clinical heterogeneity being a hallmark of mitochondrial diseases. Early diagnosis and management are crucial, especially in pediatric cases where the disease burden may evolve with age. The aim of this study is to explore the variability in clinical presentation and progression associated with specific genetic mutations, using the case of a rare *de novo* mutation in the *MT-TV* gene as an illustrative example, and to discuss the implications for clinical diagnosis.

Case Description: This paper reports on a rare *de novo* mutation, m.1630A>G, in the *MT-TV* gene of a 3-year-old boy with epilepsy. In contrast to previously reported cases of the mitochondrial neurogastrointestinal encephalopathy (MNGIE)-like disease/the mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) associated with the m.1630A>G mutation, this patient exhibited an earlier age of onset, simpler clinical manifestations, and lower heterogeneity levels in the blood.

Conclusions: This case offers significant insights into the intricate nature of mitochondrial diseases, especially in pediatric populations. It highlights the critical importance of regular physical examinations and vigilant monitoring for potential multi-system involvement, which are essential for early detection and timely symptomatic intervention to mitigate further damage. Furthermore, this case underscores the necessity to investigate factors influencing clinical penetrance, such as the interplay between mitochondrial and nuclear gene mutations, heterogeneity levels, and age-related accumulation of cellular damage, to better understand disease progression and optimize therapeutic strategies.

Keywords: Mitochondrial disease; m.1630A>G; *MT-TV*; case report

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Introduction

Mitochondrial disease is an umbrella term encompassing a wide array of clinical syndromes and features, with onset spanning from neonatal to late adulthood and affecting various organs, prominently the nervous system. These symptoms include epilepsy, neurodevelopmental delays, growth retardation, mobility impairments, optic neuropathy, sensorineural deafness, muscular disorders, and more (1-4). Over 300 genetic defects, involving both mitochondrial DNA (mtDNA) and nuclear DNA (nDNA), have been associated with mitochondrial diseases (5). Patients with mitochondrial onset during childhood may not have a typical syndrome, particularly in the early stages of disease onset, and may have involvement of only a single organ (3). We present this case in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-462/rc).

Case presentation

We present a novel mutation in the mitochondrial tRNAVal (*MT-TV*) gene in a male child displaying clinical symptoms of seizures. The patient, a three-year-old boy, sought care at the Pediatric Neurology Department of our hospital due to recurrent seizures lasting three months. Without discernible triggers, the patient experienced seizures characterized by binocular strabismus, loss of consciousness, flexion and tremors in both upper limbs, absence of lip cyanosis, no incontinence, and lasting approximately 1–2 minutes. After each episode, the child felt fatigued and weak. Brain magnetic resonance imaging (MRI) revealed no significant abnormalities, but video electroencephalogram (VEEG) showed aberrant electroencephalography (EEG) patterns, including a slow background rhythm, widespread spike-slow wave, polyspike-slow wave, and slow wave discharges during wakefulness and sleep, primarily in the bilateral frontal region, notably on the left. Additionally, several myoclonic and atonic seizures were captured during the waking EEG. The patient received a diagnosis of epilepsy with focal, myoclonic, and atonic seizures. The child was a G2P2, born at term, and had enjoyed good health since birth, with typical motor and linguistic development for his age. There was no family history of the disease, and the child's 12-year-old brother was in good health. Routine laboratory tests, including blood lactate levels, complete blood count (CBC), liver function tests (LFTs), and renal function tests (RFTs), returned normal results. To further investigate the cause of the disease, the child and his parents underwent genetic testing, including nuclear DNA and mtDNA testing. The results indicated the presence of a rare *de novo* mutation, m.1630A>G, in the *MT-TV* gene with a 7.3% heteroplasmy level. In contrast, the mother had a 0% heteroplasmy. Based on the child's clinical presentation and diagnostic evaluation, structural abnormalities, infectious etiologies, immune-mediated disorders and other related factors were systematically ruled out. The findings collectively indicated that the child's epilepsy was likely attributable to mitochondrial dysfunction resulting from pathogenic mutations in mitochondrial genes. Despite receiving treatment with antiepileptic drugs, the child continued to experience seizures, primarily manifesting as atonic seizures several times daily, characterized by nodding and sighing and lasting 5–6 seconds. A Gessel developmental assessment was conducted, but it revealed no significant abnormalities.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's legal guardian for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Highlight box

Key findings

- This case report presents a rare, *de novo* mutation (m.1630A>G) in the mitochondrial tRNAVal (*MT-TV*) gene in a child with epilepsy.

What is known and what is new?

- Mitochondrial diseases are a diverse group of disorders affecting multiple organs, often involving the nervous system, and frequently associated with mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) mutations.
- Providing new insights into the phenotypic diversity of mitochondrial tRNA mutations, expanding the recognized spectrum of mitochondrial mutations associated with pediatric.

What is the implication, and what should change now?

- This report supports the need for clinicians to consider mitochondrial dysfunction in pediatric epilepsy cases, especially those with atypical or isolated symptoms. Early genetic testing for mitochondrial mutations, including rare variants, could improve diagnosis and inform tailored management and genetic counseling for affected families.

Table 1 Clinical characteristics

Characteristics	Patient 1[a]	Patient 2[b]	Patient 3[c]
Onset-age, years	3	Early childhood	15
Sex	Male	Female	Female
Seizure	+	–	+
Headache	–	+	–
Sensorineural hearing loss	–	+	+
Visual impairment	–	+	+
Development retardation	–	+	+
Muscular hypotonia	–	–	+
Gastrointestinal disorder	–	+	–
Abnormal EEG	+	+	NA
Hyperlactatemia	–	–	–
Brain MRI	–	–	+
Family history	–	–	–
Premature labour	–	+	–

[a], the patient we report in this case, a 3-year-old boy with epilepsy. [b], the patient reported by Horváth *et al.*, a girl with an MNGIE-like syndrome (8). [c], the patient reported by Glatz *et al.*, an adolescent-onset female with MELAS syndrome (6). + indicates a positive result for the corresponding indicator. – indicates no abnormality. NA indicates no data. EEG, electroencephalogram; MRI, magnetic resonance imaging.

Discussion

The m.1630A>G mutation resides in the anticodon stem of the tRNAVal (*MT-TV*) gene, substituting adenine with guanine, potentially disrupting the secondary structure of the anticodon stem. Analysis of the *MT-TV* secondary structure predicted that the mutation leads to impaired function mainly by destabilising the tRNA and consequently impeding the folding ability of the tRNA (6-8). Glatz *et al.* generated a Cybrid cell line from patient-derived fibroblasts and demonstrated through *in vitro* experiments that the mutation led to impaired electron transport in these cells. Further research of the mitochondrial electron transport chain showed a marked reduction in both the activity and protein expression levels of cytochrome C oxidase (Complex IV), with these effects being significantly more pronounced compared to other components of the electron transport system (6).

To date, only two instances of the m.1630A>G mutation have been reported. Initially described in 2009 by Horváth *et al.*, the mutation was identified in a girl with the mitochondrial neurogastrointestinal encephalopathy (MNGIE)-like syndrome, establishing its pathogenicity (8). Another case involved an adolescent-onset female with the mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) (6). The patient that we reported differs from the previous two cases in that: (I) a male child, (II) *de novo* mutation, (III) the level of heterogeneity in the blood is only 7.3%, (IV) a single affected system. A detailed description of the clinical features of our case and comparisons with other patients are shown in *Table 1*.

Clinical manifestations of mitochondrial gene mutations are highly heterogeneous (9). Different mutation sites can lead to distinct clinical syndromes. For instance, MELAS is frequently linked to the Mitochondrial tRNALeu (*MT-TL1*) gene m.3243A>G mutation, accounting for 80% of mutation cases, while mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is primarily caused by mutations in *TYMP* gene (10,11). Furthermore, various tissues and organs exhibit varying the mutational burden of the mitochondrial genome (12,13). High energy demands in the brain make it susceptible to mitochondrial dysfunction (9,14). Mitochondrial dysfunction can disruption channels and neurotransmitters in neurons, rendering them hyperexcitable and contributing to abnormal electrical activity and seizures (4,14). Additionally, previous cases reported elevated lactic acid levels, which can disrupt brain pH balance and affect neuronal function (6,8,15,16). Our patient exhibited symptoms that were exclusively neurological in nature, with seizures being a distinguishing feature. This presentation may be linked to the individual's low heterozygosity, along with the central nervous system's vulnerability to mitochondrial mutations. Besides, given the current paucity of reported cases involving this mitochondrial gene mutation and the lack of in-depth research into it, it cannot be entirely dismissed that this presentation may be associated with more complex pathogenic mechanisms.

The burden of the same mtDNA mutation can vary significantly among individuals, depending on the distribution of mutated mitochondria within their cell populations. More mutation loads in specific cell populations can lead to heavier symptoms (17-19). Our patient exhibits a remarkably low mutation level, with only 7.3% heteroplasmy in his bloodstream. In contrast, the previously reported two cases had an average heteroplasmy level exceeding 60% in their blood, and both cases manifested multisystem symptoms, as detailed in *Tables 1,2*.

Table 2 Homogeneous distribution of the m1630A<G mutation in the patients' different tissues

Patient	Blood	Muscle	Urinary
Patient 1[a]	7.3%	NA	7.2%
Patient 2[b]	70%	90%	NA
Patient 3[c]	75%	60%	95%
Pt1 mother[d]	0	NA	0
Pt2 mother[e]	60%	NA	NA
Pt3 mother[f]	93%	NA	98%

[a], the patient we report on in this case, a 3-year-old boy with epilepsy. [b], the patient reported by Horváth *et al.*, a girl with an MNGIE-like syndrome (8). [c], the patient reported by Glatz *et al.*, an adolescent-onset female with MELAS syndrome (6). [d], the mother of the patient we report on in this case, with 0 heteroplasmy both in her bloodstream and urinary. [e], the mother of the patient reported by Horvath *et al.*, with 60% heteroplasmy in her bloodstream (8). [f], the mother of the patient reported by Glatz *et al.*, with 93% heteroplasmy in her bloodstream and 98% heteroplasmy in her urinary (6). NA indicates no data. Pt, patient.

Nevertheless, the degree of heterogeneity can only partially explain the severity of mitochondrial disease (4). There are still perplexing aspects. In the two earlier reported cases, the mothers of the patients had blood heteroplasmy levels of 60% and 93%, respectively, which surpass the 7.3% heteroplasmy level observed in this current case (*Table 2*). Strikingly, neither of them exhibited any clinical symptoms (6,8). Some studies have shown that the mutation rate in patients' urine is stable and more correlated with the disease (20,21). It has been shown that the mutation level of mitochondrial gene mutations in the blood disappears over time, so the diagnosis of DNA in urine is very important, especially in this case of a child with a very low level of mutation but still symptomatic (22). Therefore, we took further urine and performed high depth point unit sequencing. Notably, the child's urine exhibited a point mutation rate of 7.2116%, while the mother's showed 0% (*Table 2*), further confirming a *de novo* mutation unrelated to maternal inheritance and demonstrating the low heteroplasmy level, which ruled out high mitochondrial mutation heterogeneity in urine. Accumulated clinical case reports and scientific research literatures have indicated that low-heteroplasmy levels of mitochondrial gene mutations play a pivotal role in the pathogenic mechanisms of specific diseases (23-25). Hence, evaluating the disease threshold solely based on heteroplasmy levels is evidently imprecise. Some researchers have conducted a deeper analysis of the mother-daughter pair in Case 2 and have concluded that nuclear gene mutations can modulate the expressivity of mtDNA variations (7). Consequently, it cannot be ruled out that this particular patient may have undergone specific nuclear gene interventions, enabling clinical manifestations to occur despite a low mutation level (26).

The progression of mitochondrial encephalomyopathy may be age-related, manifested by changes in the level of tissue heterogeneity with age and by the progressive accumulation of damage. In Case 2, the girl has experienced bilateral deafness since childhood, and as she has grown older, she has progressively developed symptoms related to the gastrointestinal tract and strokes (8). Mitochondrial disease in childhood, especially in the early stage of onset, may have a single clinical manifestation, often involving only one system (3). Seizures may be the first—or even the only—sign of mitochondrial dysfunction (27). The mother of our child said that the child has occasionally spoken in a long tone since the onset of the disease. Frequent abnormal discharges in the brain during epileptic seizures may lead to regression of language development. In particular, studies have shown that Abnormal tone including hypotonia is a prominent and early feature of childhood-onset mitochondrial disease (1). Therefore, we cannot rule out whether it is the progression of the disease in children. The single atypical symptom in the child we reported may be related to the young age at which the damage has not accumulated to a certain extent, and the progression of the disease may involve other systems as the child grows older.

Conclusions

In summary, we have reported a rare case of mitochondrial encephalomyopathy in a child with a low level of heteroplasmy carrying the *MT-TV* m1630A<G mutation, with epilepsy as the primary clinical manifestation. This provides powerful insight into the clinical heterogeneity and genotype-phenotype correlations in *MT-TV*-related diseases. When children with mitochondrial disease have low heterogeneous mitochondrial gene mutations, we need to look for possible nuclear gene mutations that affect their penetrance, and recognize that the disease burden of mitochondrial encephalomyopathy may be related to age. It is related to the accumulation of damage. We should pay close attention to other system damages that may occur during the growth of these young patients. Regular physical examinations can detect potential diseases in time and treat them symptomatically to avoid greater damage.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-462/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's legal guardian for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

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