Alternating Hemiplegia of Childhood in a Child Harboring a Novel TBC1D24 Mutation: Case Report and Literature Review

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Abstract

Alternating Hemiplegia of Childhood (AHC) is a rare neurological disease characterized by early-onset recurrent paroxysmal events and persistent neurological deficits. TBC1D24 gene variants have been associated with a phenotypic spectrum having epilepsy as the main clinical manifestation. Herein, we report the case of a child affected by developmental delay, polymorphic seizures, and nonepileptic episodes characterized by hemiplegia or bilateral plegia, pallor, hypotonia, and dystonic postures without loss of consciousness that resolved with sleep. Noteworthy, the patient fulfills all the diagnostic criteria for AHC. An epilepsy gene panel revealed a novel TBC1D24 mutation. This variant may be considered a PM5, according to the American College of Medical Genetics and Genomics guidelines. TBC1D24 gene variants are associated with various clinical features, and increasing data confirms the association with permanent and paroxysmal movement disorders. Our report suggests that the TBC1D24 molecular analysis could be considered in the diagnostic workup of AHC patients.

Keywords

► Alternating Hemiplegia of Childhood
► TBC1D24 gene
► movement disorders
► epilepsy

Introduction

Alternating Hemiplegia of Childhood (AHC) is a rare neurological disease characterized by early-onset recurrent paroxysmal events of alternating hemiplegia/hemiparesis, dystonic attacks, paroxysmal abnormal ocular movements, and persistent neurological deficits.1 Epilepsy and episodes of autonomic dysfunction may also be associated. Paroxysmal episodes are often triggered by contact with water, changes in temperature, physical or psychological

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stress, or intense emotions and anxiety. The disorder is caused by ATP1A3 gene mutations in up to 80% of patients.¹ Research for other causative genes is currently ongoing.

Several drugs have been administered as prophylaxis for paroxysmal attacks. Although no therapy is completely effective, flunarizine, a nonselective blocker of voltage-dependent calcium channels, reduces attacks’ frequency and duration.²

The TBC1D24 gene is involved in regulating synaptic vesicle transport and cellular oxidative stress response, and its mutations are related to several phenotypes. TBC1D24-related clinical features include deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures (DOORS) syndrome. Epilepsy ranges from benign patterns to epileptic encephalopathies. Myoclonic seizures and status epilepticus may be frequent.³

Permanent movement disorders such as dystonia and ataxia have also been described in a review of the literature with several series of TBC1D24 patients.⁴ Moreover, recent reports have shown an association between TBC1D24 gene mutations and paroxysmal, nonepileptic, disorders.⁵⁻¹¹

We report a child harboring a novel TBC1D24 mutation with paroxysmal and nonparoxysmal features overlapping with AHC.

Case Report

This 5-year-old girl is the first-born child of unrelated parents of Italian origin (from two small neighboring towns), with a healthy sister. Hypotonia and abnormal rotatory eye movements have been observed very early during the child’s life. Right focal clonic seizures, generalized tonic-clonic, and myoclonic seizures appeared at 5 months of age. After several therapeutic approaches (clonazepam, clobazam, levetiracetam), zonisamide (3.5 mg pro Kg every day) and oxcarbazepine (20 mg pro Kg every day) led to complete seizure control.

At 5 months of age, episodes characterized by hypotonia, bilateral plegia or hemiplegia, pallor, and sometimes dystonia without loss of consciousness appeared. These events were both bilateral and, more often, unilateral, presenting an alternation of laterality affecting the left or, more commonly, the right side. Epileptic origin was excluded by performing neurophysiological studies (EEG, video-EEG). The concomitant video-EEG showed slight amplitude asymmetry (right > left) but no epileptiform discharge. During sleep, the paroxysmal episode resolved and upon awakening, the child had no more symptoms and reactivity and interaction improve.

Flunarizine was started at a very low dosage (1.25 mg) but was discontinued after about 3 weeks due to drowsiness.

Discussion

This report describes paroxysmal episodes and chronic movement disorder in a child harboring a novel TBC1D24 gene mutation. Epileptic origin of the episodes was excluded on the basis of clinical features and EEG recording.

Regarding the genetic findings, the c.545C > T variant has never previously been reported in the literature; nevertheless, recessive missense variants in the same domain have been described in TBC1D24-related disorders by Balestrini et al.³ The substitution affects a highly conserved threonine residue in the Rab GTPase activating protein TBC domain of the gene; multiple in silico prediction tools support possible pathogenicity. Moreover, an analysis of the specific exon of the TBC1D24 gene by genomic DNA Sanger sequencing revealed that both of the patient’s parents are heterozygous for the c.545C > T (p.Thr182Met) variant, thus confirming biparental inheritance of the patient’s TBC1D24 missense variant. Based on this data, this variant may be considered a PM5, according to the American College of Medical Genetics and Genomics guidelines.

Recent reports have shown an association between the TBC1D24 gene mutation and paroxysmal movement disorders (→Table 1). Duru et al.⁵ and Guven et al.⁶ reported...
polymorphic episodic phenomena, postictal hemiparesis, dystonia, alternating and migrating jerks, and neurovegetative episodes within the same family. Luthy et al described a family with Rolandic epilepsy and dystonia triggered by sustained exercise: after a 20-year-long follow-up period, epilepsy was found to have a benign course, and exercise-induced dystonia was the most prominent and long-lasting manifestation.\(^7\) Zimmern et al reported a boy with a complex movement disorder, mainly triggered by fever and fatigue, characterized by facial myoclonus involving a single eyelid and generalizing to the entire face, and occasionally accompanied by alternating limb tremors. These episodes eventually evolved into left-sided ataxic episodes, tremor of the left upper limb, confusion, and diminished speech.\(^8\) Zhou et al reported a case of Epilepsia Partialis Continua (EPC) with a homozygous TBC1D24 mutation. The patient developed episodes of jerks triggered by fatigue, emotions, or fever that lasted from minutes to hours.\(^9\) Ngho et al described two siblings with infantile-onset multifocal polymyoclonus, developmental delay, atrophy of the lateral parts of the cerebellar hemispheres, and symmetrical signaling abnormalities on MRI.\(^10\) Paroxysmal manifestations represented the main characteristic shared by all these subjects. However, the only patient presenting a constellation of symptoms consistent with AHC in association with a TBC1D24 variant was reported by Ragona et al.\(^11\) These authors described a 5-year-old girl affected by daily episodes of unresponsiveness and hypotonia, variably associated with abnormal eye movements and hemi- or tetraplegia, all of which resolved with sleep. In this case, the child also presented rhythmic clonic jerks of a body part that persisted during sleep, consistent with EPC. Unlike our patient, this girl showed poor response to antiepileptic drugs but a partial response to florazine. It is worth pointing out that florazine’s efficacy could not be adequately tested in our patient, since the drug had to be discontinued due to intense sedation. Similarly to this girl, our patient fulfills the clinical diagnostic criteria for AHC described by Neville and Ninan in 2007.\(^12\) She presented (1) onset before 18 months of age, (2) repeated episodes of hemiplegia, (3) episodes of bilateral hemiplegia or quadriplegia, starting either as a generalization of a hemiplegic episode or bilaterally, (4) other paroxysmal disturbances including tonic/dystonic attacks, nystagmus, strabismus, dyspnea, and other autonomic phenomena occurring during hemiplegic attacks or in isolation, (5) immediate disappearance of all symptoms upon going to sleep, with recurrence 10 to 20 minutes after awakening in long-lasting attacks, and (6) evidence of developmental delay and neurological abnormalities.

Interestingly, our patient also presented spells of lethargy and drowsiness lasting minutes to hours, which were variably associated with hemiplegia along with staring and reduced responsiveness. These episodes, described by her parents and recorded during video-EEG (\(\text{Videos} 1\) and \(\text{2}\)), are very similar to Reduced Awareness Spells, which have recently been reported as non-epileptic paroxysmal episodes in about one-third of AHC cases.\(^13\) It is important to remark that the disappearance of paroxysmal symptoms after sleep is typical of AHC; however, since the first reports of this disorder, it has been reported that the long-lasting episodes would reappear after a few minutes from sleep, as occurs in our patient, in particular after brief episodes of daytime sleep.\(^14\)

**Fig. 1** Coronal fluid-attenuated inversion recovery (FLAIR) images demonstrate localized gliotic changes along the cortical regions of both cerebellar hemispheres (thick white arrows, A, B) with mild widening of the adjacent cerebellar sulci on T2- and T1-weighted images (not shown). Coronal T2-weighted (C, E) and FLAIR (D, F) images also show left-sided incomplete hippocampal inversion (arrowheads, C, D) with reduced volume and definition of the normal architecture of the hippocampal head (thin arrow, E), mild increase in FLAIR signal (thin arrow, F), and enlargement of the ipsilateral temporal horn, suggestive of concomitant mesial temporal sclerosis.
Fig. 2  (A) 24h Holter EEG recording. SI 10–20, longitudinal montage, 10 uV/m, HF 70 Hz, LF 0.1 second. Non-rapid eye movement (REM) sleep: there are generalized sharp waves. (B-C) Video-EEG during an episode characterized by weakness of the right side of the body, followed by dystonic posturing of the right upper limb associated to anarthria. During the episode comprehension was maintained and the child responded with gestures to simple requests. During the episode, the child was initially drowsy, later she fell asleep. EEG showed slight hemispheric voltage asymmetry (right > left) but no epileptic discharges.
<table>
<thead>
<tr>
<th>Mutation (reference)</th>
<th>Country of origin</th>
<th>Consanguinity</th>
<th>Family members</th>
<th>Permanent movement Disorder</th>
<th>Paroxysmal Movement Disorder</th>
<th>Age at onset (movement disorder)</th>
<th>EEG correlation</th>
<th>Treatment</th>
<th>Response to treatment</th>
<th>Sleep response</th>
<th>Brain imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.I81_K84del + c.1499C &gt; T (brother and sister) c.545CAT + c.1531GAA (cousin)</td>
<td>Italy</td>
<td>+</td>
<td>2 (1 M, 1 F) and 1 cousin</td>
<td>Dystonic episodes and tremor, brief jerking episodes</td>
<td>&lt; 18 months</td>
<td>–</td>
<td>Anti-epileptic drugs, flunarizine, acetazolamide</td>
<td>–</td>
<td>+</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>c.116C &gt; T + c.457G &gt; A&lt;sup&gt;½&lt;/sup&gt;</td>
<td>Italy</td>
<td>–</td>
<td>1 F</td>
<td>Abnormal eye movements, hemi or tetraplegia, jerks</td>
<td>&lt; 18 months</td>
<td>–</td>
<td>Flunarizine</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>c.229_240del&lt;sup&gt;½&lt;/sup&gt;</td>
<td>China</td>
<td>+</td>
<td>1 F and 1 relative</td>
<td>Hemilateral jerks</td>
<td>5 years</td>
<td>–</td>
<td>Anti-epileptic drugs</td>
<td>–</td>
<td>+</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>p.I81_K84del + c.1499C &gt; T (brother and sister) c.545CAT + c.1531GAA (cousin)</td>
<td>Italy</td>
<td>+</td>
<td>2 (1 M, 1 F) and 1 cousin</td>
<td>Dystonic episodes and tremor, brief jerking episodes</td>
<td>&lt; 18 months</td>
<td>–</td>
<td>Anti-epileptic drugs, flunarizine, acetazolamide</td>
<td>–</td>
<td>+</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>c.304C &gt; T + c.410T &gt; C&lt;sup&gt;°&lt;/sup&gt;</td>
<td>Switzerland</td>
<td>+</td>
<td>1 M and 3 relatives</td>
<td>Facial myelosclerosis, alternating hemidystonic attacks sometimes associated to tremor, anarthria and confusion</td>
<td>22 months (first evaluation)</td>
<td>–</td>
<td>Anti-epileptic drugs</td>
<td>+</td>
<td>NA</td>
<td>Cerebellar T2 hyperintensity</td>
<td></td>
</tr>
<tr>
<td>NA&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>Turkey</td>
<td>+</td>
<td>5 (4 M, 1 F)</td>
<td>Dystonic attacks, post-ictal hemiparesis, startles</td>
<td>&lt; 18 months</td>
<td>–</td>
<td>Antiepileptic drugs, tetracosactrin, vitamin B6, coenzyme Q, IVIG</td>
<td>–</td>
<td>NA</td>
<td>Diffuse delay in myelination and thin corpus callosum</td>
<td></td>
</tr>
<tr>
<td>c.457G &gt; A + c.545del&lt;sup&gt;°&lt;/sup&gt;</td>
<td>Poland</td>
<td>–</td>
<td>2 (1 M, 1 F)</td>
<td>Myoclonic twitching and jerking movements involving different muscle groups</td>
<td>&lt; 18 months</td>
<td>–</td>
<td>Anti-epileptic drugs, coenzyme Q10, biotin, niacin, levodopa, piracetam, ketogenic diet, bromocriptine</td>
<td>–</td>
<td>+</td>
<td>Hypoplasia of frontal and temporal lobes in the first and cerebellar atrophy in the 2nd patient</td>
<td></td>
</tr>
</tbody>
</table>

F, female; M, male; +, present; –, not present; EEG correlation, epileptic discharge during paroxysmal attacks; response to treatment, improvement of paroxysmal movement disorders after therapies indicated in "treatment" column; IVIG, intravenous immunoglobulin; NA, data not available.
Regarding neuroradiological features, two other patients with TBC1D24 mutations reportedly had cerebellar sequelae characterized by gliosis and/or atrophy and showed gliotic changes similar to the ones we observed in our patient (→ Table 1). MRI also revealed the presence of mesial temporal sclerosis: interestingly, concomitant mesial temporal sclerosis (→ Fig. 1) has been described in other AHC patients\(^1,\)\(^16\) and may be linked to severe epilepsy.

AHC is caused by mutations in ATP1A3 gene in approximately 80% of patients. Although a second major causative gene has not yet been identified, other gene mutations (ATP1A2, CACNA1A, ADCYS, TANGO2, SLC1A3) have occasionally been related to AHC.\(^15\)\(^,\)\(^16\) In our patient, the majority of “non-conventional” AHC genes were tested by the NGS epilepsy gene panel (ATP1A2, CACNA1A, SLC2A1, SCN1A), while ATP1A3 and ADCYS genes were tested afterward. Therefore, based on the possible pathogenicity of the TBC1D24 variant, and as per similar TBC1D24 phenotypes already described in the literature, we assume that the genetic variant suffices to explain the clinical features of our patient.

Conclusions

Our report further expands the broad phenotypic spectrum of TBC1D24-related disorders and suggests considering an analysis of this gene in the diagnostic workup of patients fulfilling AHC clinical criteria, especially for ATP1A3-negative subjects. Further researchers on this topic could clarify the role of TBC1D24 gene mutation in AHC.

Conflicts of Interests

The authors declare that they have no conflicts of interests.

Acknowledgments

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