Pediatr Pol 2023; 98 (3): 258-263
DOI: https://doi.org/10.5114/polp.2023.131763
Submitted: 23.01.2023, Accepted: 12.04.2023, Published: 29.09.2023

PEDIATRIA Polska
PISMO POLSKIEGO TOWARZYSTWA PEDIATRYCZNEGO
Polish Journal of PAEDIATRICS
OFFICIAL JOURNAL OF POLISH SOCIETY OF PAEDIATRICS

CASE REPORT

Heterozygous *de novo* mutation in the *ATP1A2* gene in a patient with alternating hemiplegia of childhood

Katarzyna Wojciechowska[1], Agata Pikulicka[2], Olga Drgas[3], Żaneta Brudkowska[4], Iwona Żarnowska[4]

[1]Independent Laboratory of Genetic Diagnostic, Medical University of Lublin, Lublin, Poland
[2]Internal Disease Department, Warsaw Southern Hospital, Warsaw, Poland
[3]MedGen Medical Centre, Warsaw, Poland.
[4]Department of Pediatric Neurology, Medical University of Lublin, Lublin, Poland

ABSTRACT

Alternating hemiplegia of childhood (AHC) is characterized by recurrent hemiplegic episodes and paroxysmal disorders, dystonia, nystagmus, epileptic seizure, mental retardation, and intellectual impairment. Alternating hemiplegia of childhood is caused by pathogenic variants in the genes encoding α-1, -2, and -3 subunits of Na,K-ATPase. Among them, pathogenic variants in ATP1A3 are responsible for almost 80% of cases. The aim of our study was to present a patient with de novo ATP1A2 mutation as the primary cause of AHC and to study the spectrum of phenotypes associated with mutation in this gene. Our study presents a case of a 9-year-old boy who was correctly diagnosed with AHC at the age of 8 years. The example of our patient proves that pathogenic variants in ATP1A2 correlate with milder phenotype.

KEY WORDS:
hemiplegia, ATP1A2, alternating hemiplegia of childhood.

INTRODUCTION

Alternating hemiplegia of childhood (AHC) is a rare neurological disorder characterized by recurrent hemiplegic episodes and paroxysmal disorders, dystonia, nystagmus, epileptic seizures, mental retardation, and intellectual impairment. Children with AHC often have a delay in diagnosis or are misdiagnosed [1]. In the differential diagnosis the following should be considered: infantile seizures due to acute causes, for example ischaemia, infection, hypoglycaemia, traumatic brain injury, epilepsy due to structural aetiologies such as malformations of cortical development, epileptic syndromes, for example Genetic epilepsy with febrile seizures plus (GEFS+), and Dravet Syndrome.

Alternating hemiplegia of childhood was first described in 1971 by Verret *et al*. [2], and in 1993 specific diagnostic criteria named Aicardi criteria were published [3]. In 2021 Mikati *et al*. [4] updated the diagnostic guidelines. The disease is caused by molecular changes in the *ATP1A3* gene, which account for more than 80% of all cases of AHC. There are only 4 reports about the role of *ATP1A2* gene in the pathogenesis of AHC [5–8]. The *ATP1A2* missense mutations are known to be responsible for different types of familiar hemiplegic migraine.

In the article, we present a patient with *de novo ATP1A2* mutation as the primary cause of AHC, and the spectrum of phenotypes associated with mutations in this gene.

Diagnosing patients with AHC is often laborious. Laboratory tests are not helpful. Structural neuroimaging might be normal or can present cerebral atrophy. Ictal electroencephalogram during episodes of hemiplegia

ADDRESS FOR CORRESPONDENCE:
Agata Pikulicka, Sieprawki 7b, 21-008 Tomaszowice, Poland, phone: +48882091657, e-mail: agapikulicka@gmail.com

TABLE 1. Current clinical criteria of alternating hemiplegia of childhood diagnosis [4]

Essential criteria	Major criteria	Minor criteria
1. Paroxysmal episodes of hemiplegia that alternate between the 2 sides and/or of quadriplegia 2. Evidence of background abnormal neurological development	1. Onset before 18 months of age 2. Episodes of dystonia 3. Different types of episodes occur independently or at the same time with evolution from one or more symptoms to others during that one episode 4. Paroxysmal episodes of abnormal eye movements such as nystagmus and especially monocular nystagmus 5. ATP1A3 mutation 6. Plegia spells improve with sleep	1. Epileptic seizures alone or in combination with other spells 2. Episodes of altered consciousness, not epileptic in nature, alone or in combination with other spells 3. Abnormal motor function such as tone abnormalities (in particular, hypotonia or dystonia that can co-exist), ataxia, choreoathetosis, and oral motor control 4. Episodes of autonomic dysfunction

may not show any abnormalities as well. That is why diagnosing AHC is almost entirely based on the clinical picture. However, symptoms can easily mislead, suggesting the other similar diseases. Consequently, children with AHC often have a delay in diagnosis or are misdiagnosed. The current clinical criteria of AHC diagnosis were developed in 2021 by Mikati *et al.* [4] (Table 1).

Alternating hemiplegia of childhood is one of the diseases in which genes are determinative. Interestingly, most mutations are sporadic. Only a few familial cases have been reported in the literature [6]. The role of the *ATP1A3* gene in the pathogenesis of AHC has already been well documented. However, studies have shown that the novel mutations in the *ATP1A2* gene also appear to be significant in AHC development (previously known only as a cause of familiar hemiplegic migraine type 2 – FHM2, and benign familial infantile convulsions – BFIC) [6].

Symptoms in both types of AHC are similar; however, patients with pathogenic variants in *ATP1A2* present a milder phenotype. Further research is required to find out the real differences between the phenotypes of the patients.

The aim of the current study is to present the case of 9-year-old Polish Caucasian boy suffering from AHC caused by *ATP1A2* gene mutation. He meets current AHC criteria stated by Mikati *et al.* [4]. Even though he has been presenting a wide range of symptoms since the age of 4 months, he was properly diagnosed at the age of 8 years.

MATERIAL AND METHODS

Sanger sequencing of all exons and intron-exon boundaries of *ATP1A2* and *ATP1A3* was performed. Genomic DNA was isolated from a peripheral blood sample of the patient using PREPITO® (PerkinElmer). Polymerase chain reaction (PCR) was performed using specific primers targeting the DNA coding region of the exons of the *ATP1A2* and *ATP1A3* genes. For confirmation, exon-specific genomic DNA sequencing was also performed using specific primers. Primer information, and PCR reaction mix and conditions are available on request. Polymerase chain reaction products were purified using EXOSAP-IT (Amersham Biosciences) according to the manufacturer's protocol. Standard sequencing reaction and capillary electrophoresis using an ABI PRISM 3730 sequencer (Applied Biosystems) were performed. Fluorochromatograms were analysed using Mutation Surveyor™ software (SoftGenetics). Sequence NM_000702.2 was used as a reference. Novel mutations were analysed with the prediction module of Alamut software. The database used in the study was ClinVar: (https://www.ncbi.nlm.nih.gov/clinvar/).

Sanger sequencing revealed heterozygous mutation p.Ala297Thr (c.889G > A) in one allele of *ATP1A2*. Testing of the parents showed that the mutation appeared *de novo*. Sanger sequencing did not reveal any pathogenic variant in *ATP1A3* gene.

Comprehensive psychological evaluation included a diagnostic interview, behavioural observations, standardized testing of intelligence and cognitive abilities, and a caregiver report on the child's behavioural, emotional, and cognitive functioning. To assess cognitive function and the current level of intellectual development of the patient the Stanford-Binet Intelligence Scales, Fifth Edition (SB5 polish version) were applied. SB5 is a standardized intelligence test, which provides a comprehensive assessment of the 5 factors of cognitive ability: fluid reasoning, knowledge, quantitative reasoning, visual-spatial processing, and working memory. Each factor was tested in 2 scales: verbal and nonverbal [9].

Ethical approval and consent to participate

All experimental protocols were approved by the Ethics Committee of the Medical University of Lublin, reference number: KE-0254/43/02/2022. All methods were performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. Written informed consent was obtained from the parents.

TABLE 2. The comparison of the symptoms of 2 patients with p.Ala297Thr variant in ATP1A2

Parameters	Alternating hemiplegia of childhood due to D801N variant in ATP1A3 reported by Masoud *et al*. [13]	The patient with p.Ala297Thr variant in ATP1A2 reported by Huang *et al*. [7]	Our patient with p.Ala297Thr variant in ATP1A2
Age of onset	0–18 months	19 months old	4 months old
Inheritance	Usually sporadic, rarely familial	Sporadic case	Sporadic case
Hemiplegia that alternates between sides or quadriplegia	+	Hemiplegia	Hemiplegia that alternatse with quadriplegia
developmental delay	+	+	+
			+
Dystonia	+	–	+
Febrile seizures	+	+	+
Epileptic seizures	+Epilepsy with focal and generalized seizure	–	+Epilepsy with focal and generalized seizures
Autonomic disturbances			
Altered consciousness	+	–	+
Anarthria	+	–	+
Dysphagia	+	–	+
Abnormal eye movement	+	Not reported	+
Triggers	+	+	+
Remission with sleep	+	+	+
Interictal symptoms	+		
Persistent motor deficits	+		–
Ataxia	+		–
Choreoathetosis	+		–

Consent for publication

Written informed consent was obtained from the parents for the research study, clinical details, and publication of this case report.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no conflict of interest that could compromise the impartiality of the research reported and that no financial support was requested for this study.

CASE REPORT

Patient data

A male neonate was born at 40 weeks' gestation as the second child to unrelated Polish parents, with birth weight 3820 g. The neonate was delivered by caesarean section due to foetal distress. Apgar score was 8 at the first minute. The mother was a 30-year-old female who had an ectopic pregnancy history, and the father was 48 years old. Both parents have no history of neurological diseases, epileptic seizures, episodes of acute paralysis, or familial migraine. There is no known family history of mental health problems. The neonatal period of our patient was uncomplicated.

Course of illness

The patient first presented with a paroxysmal episode of prolonged complex febrile seizures at 4 months of age. The episode was preceded by vaccination and mild fever (38.8°C). Left-sided jerking movements of the extremities lasted approx. 40 minutes and were aborted by the injection of lorazepam. During the episode the infant was not responsive, pale, with prominent perioral automatisms (smacking) and drooling. Electroencephalogram (EEG) monitoring as well as brain magnetic resonance imaging results showed no abnormalities. After seizure termination, left hemiparesis was apparent for 24 hours, but no other abnormalities were observed in the neurological examination.

Similar episodes of unilateral clonic movements or tonic extension of the extremities on the left side, often prolonged with secondary generalization, occurred most often in the peri-infective period in the first 3 years of life (10 episodes occurring once a week to once every 3 months). These usually started with gaze deviation, psychomotor agitation, and crying. They were sometimes reported as status epilepticus and were treated in the hospital. All episodes were followed by residual weakness and confusion for 1–3 days. A few of these episodes were generalized from the beginning. Repeat imaging

at that time was unremarkable. All EEG results showed normal waveforms. After prolonged attacks the parents reported mild global developmental regression. The patient exhibited only mild developmental delay in gross motor and language areas. Despite laborious investigations including biochemical, metabolic, and genetic analysis (microarray, sequencing of *SCN1A* gene), no causes of this relapsing encephalopathy during febrile illness were found.

At the age of 11 months, epilepsy was diagnosed. Treatment with valproic acid was started, and after a few months levetiracetam was added. No seizures were observed after the age of 3 years, and antiepileptic treatment was eventually discontinued at the age of 6 years.

At 7 years of age the boy experienced an acute episode of right-sided hemiparesis without preceding fever or convulsions. He woke up with right-sided weakness more prominent in the right upper limb, confusion, and dysarthria. The episode resolved spontaneously within 3 days.

Three months later another episode of hemiparesis occurred – this time on the left side, with a predominance of the upper limb with speech disorders. No seizures were observed, only right hemiplegia, dysphasia, and confusion. The symptoms completely regressed within 30 minutes. Electroencephalogram showed normal results. Neuroimaging tests (magnetic resonance and angiography) did not reveal any abnormalities. Laboratory test results were normal.

After the above episode, the boy vomited once. Flunarizine was included in the treatment, and after a month it was discontinued due to the poor tolerance of the drug.

A few months later the patient presented another episode characterized by left hemiparesis, dysarthric speech, and confusion with hallucinations. During this episode the boy vomited 3 times.

At the age of 8 years genetic tests were performed again, and the *de novo* mutation in the *ATP1A2* gene was diagnosed. Acetazolamide (Diuramid) was included in the treatment, with significant reduction in the frequency of paroxysmal attacks.

At present, the patient has rare paroxysmal episodes, mostly triggered by stress or tiredness, and characterized by mild hemiparesis or limb dystonic movements, drooling, and dysarthria, all lasting only a few minutes and resolving spontaneously. He has impaired neuropsychomotor development with moderate intellectual disability. In neurological examination he presents bilateral Babinski sign.

Psychological examination – description

The patient's medical record and parents' reports both indicated that his development for the first 4 months of life was within normal limits. However, after 4 months of age, the baby still did not acquire the ability to properly balance the head, i.e. he did not hold the head straight in a vertical position. Delays were also observed later in the course of motor development. The patient was able to sit unsupported at 8 months and stood up at 11 months. He began to walk unaided at 18 months. Speech and language difficulties were observed as well. The boy started uttering phrases at the age of 4 years, and he spoke his first short sentences at the age of 5 years. Additionally, behavioural difficulties were noted, including disturbances in emotional development, delayed toilet training (fully trained at the age of 4 years), or difficulties in self-dressing, which are present today. He started preschool at age of 3 years, adapted well, but the obligation to start schooling was postponed twice because of the deficits in intellectual and motor development. The child received various forms of early development therapy, including the following: sensory integration therapy, psychological, pedagogical, and speech therapy, which is still continued. At present the boy attends an integration class, where he has the assistance of a support teacher.

During the psychological examination, the boy was willing to interact and had no difficulty in separating from his mother. He acted cheerfully, and he logically answered questions. However, eye contact was generally limited, language was noticeably delayed, and he was difficult to understand at times due to articulation disorders. He had difficulty in forming words and using age-appropriate language, often building short, simple sentences. At the beginning, testing ran smoothly without incidence, but after a few minutes the patient required clear motivation to keep working. Rapidly increased mental fatigue was observed. Furthermore, the patient presented attention deficit disorder with features of hyperactivity.

To determine the current level of intellectual development of the child, a test was performed using the Standford-Binet 5 Intelligence Scale [9]. The results showed his overall level of intellectual functioning. He was in the intellectually deficient range (moderately impaired or delayed). No significant difference between his verbal and nonverbal abilities was demonstrated. In our study we found deficits in sustained attention, reduced speed of information processing, and difficulties in understanding, speaking, and working memory. In addition, his parents and teachers reported behavioural disturbances, such as decreased inhibition capability in self-control and in regulating emotions.

DISCUSSION

Alternating hemiplegia of childhood is a disease in which genetic background plays a key role. Pathogenic variants in *ATP1A3* are thought to be a major cause of the disease and to be responsible for almost 80% of all cases [8]. The most common pathogenic variants in *ATP1A3* which were found in the patients are p.Asp801Asn, p.Glu815Lys, and p.Gly947Arg. Each mutation is associated with different clinical phenotype, symp-

toms, severity, and prognosis [1]. *ATP1A3* together with *ATP1A1* and *ATP1A2* encode the α-3, -1, and -2 subunits of Na,K-ATPase and are mainly expressed in interneurons and pyramidal cells. Sweadner *et al.* [10] presented genotype-phenotype correlations between pathogenic variants in *ATP1A3, ATP1A2*, and *ATP1A1* and neurological outcomes.

The *ATP1A2* gene is located on chromosome 1q23 and encodes the α2 subunit of the plasma membrane Na/K pump, which consumes ATP to actively transport Na+ and K+ into the cell. The Na,K-ATPase is an enzyme composed of α, β, and γ subunits. Four types of α subunits independently occur in different tissues; for example, α1 is ubiquitous, α4 in testis, α3 in the brain, and α2 in both brain (neurocytes and astrocytes) and heart. The mutation in *ATP1A2* is mainly attributed to the α2 isoform between the M4 and M5 helices, which are crucial to regulate the transport system in spite of their accurate localization in the membrane. This hypothesis was supported by research on HeLa cells [10, 11].

Mutations in *ATP1A2* were previously said to be the cause of FHM2. In this syndrome, some symptoms were common to those in AHC and BFIC [6]. Todt *et al.* [12] found the E174K variant in the *ATP1A2* gene in a family with the FHM2 spectrum who experienced migraine with side-changing paraesthesia. Several authors reported that homozygous truncating mutations in *ATP1A2* were associated with polymicrogyria, microcephaly, arthrogryposis, and early lethal hydrops fetalis [13].

So far, only 4 reports have linked mutations in *ATP1A2* to AHC [5–8]. Patients suffering from AHC with *de novo ATP1A2* gene mutations have similar symptoms to those with *ATP1A3* mutations. Swoboda *et al.* [5] presented a case of a Greek family of 4 members in which the patients had hemiplegia, quadriplegia, dystonia, epileptic seizures, autonomic disturbances, anarthria, abnormal eye movements, triggers, developmental delay, and ataxia and in whom a missense variant p.Thr378Asn in *ATP1A2* was found. The members of the Greek family presented by Swoboda *et al.* [5] displayed analogous phenotypes with all 3 types of hemiplegic attacks (alternating unilateral, shifting, and bilateral). The first onset was observed in the defined age range. Moreover, all of them presented developmental delay, paraphasia, and difficulty in understanding and performing simple words and orders. Choreoathetoid movements, tremor, horizontal nystagmus, eye deviation, clumsiness, saliva dripping, and ataxia were observed as well. Interestingly, psychological examination relieved that 2 of three sons had emotional problems and were said to be "aggressive children". Our patient presented febrile clonic seizures, hemiparesis with dysarthria, dysphasia, and confusion. It is worth mentioning that the patient had hallucinations and vomited although migraine was excluded from the diagnosis. Interestingly, our patient and the members of the mentioned Greek family with the *ATP1A2* mutation had a milder phenotype in comparison to sporadic cases. Our patient is the second child reported in the literature with *de novo* heterozygous mutation p.Ala297Thr (c.889G > A) in one allele of *ATP1A2*. Calame *et al.* [8] analysed the correlation between the symptoms of patients with AHC and particular pathogenic variants in *ATP1A2*. Both patients presented by those authors had missense variant p.Met813Lys in *ATP1A2*, and both patients had hemiplegia, epileptic seizures, autonomic disturbances, dysphagia, abnormal eye movements, triggers, developmental delay, persistent motor deficits, ataxia, and choreoathetosis and there was no remission during sleep. However, the patients presented specific symptoms; according to the authors, they did not fulfil the diagnostic criteria of AHC. The 3-month-old boy with recurrent hemiplegia, epilepsy, and nonepileptic paroxysmal symptoms, presented by Wilbur *et al.* [6], had 2 missense variants in *ATP1A2*: the first one – p.Arg548Cys classified as pathogenic, and the second one – p.Arg1008Trp classified as a variant of uncertain significance. A recent article of Huang *et al.* [7] revealed that variants p.Gly324Ser and p.Ala297Thr in *ATP1A2* were responsible for AHC in 2 Chinese patients. The first boy, in whom the variant p.Gly324Ser was found, had episodes of acute hemiplegia preceded by mild fever and generalized tonic-clonic seizures followed by several days of hemiparesis. The second patient, who had the same variant as our patient, had right hemiplegia after one febrile convulsion without other neurological signs. In Table 2 we compare the features of our patient with the features of the patient presented by Huang *et al.* [7] and Masoud *et al.* [12]. Vetro *et al.* [14] characterized 6 patients with 5 different heterozygous mutations in *ATP1A2* with disrupted brain morphogenesis, who presented polymicrogyria, progressive brain atrophy, and epilepsy. Our patient did not have such severe symptoms.

CONCLUSIONS

The case of our patient showed that pathogenic variants in the *ATP1A2* gene appear to be significant in AHC development. The overall aim of this article was to raise awareness that AHC may be caused by mutations not in one but in many genes, and eventually further research on *ATP1A2* must be done. Our studies indicate that patients with AHC caused by *ATP1A2* mutations present a milder phenotype than those with *ATP1A3* mutation. Further research on genes and their correlation with phenotypes would enable scientists to divide AHC into different, more specific classes with appropriate diagnostic criteria. Actual figures of AHC might be much higher than those we already know, with far more patients suffering and needing professional help. Promoting knowledge among physicians is crucial to diagnose AHC in the early stages and protect children from development disorders.

ACKNOWLEDGMENTS

We thank the family of our patient for their trust and collaboration.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Rosewich H, Thiele H, Ohlenbusch A, et al. Heterozygous de-novo mutations in ATP1A3 in patients with alternating hemiplegia of childhood: a whole-exome sequencing gene-identification study. Lancet Neurol 2012; 11: 764-773.
2. Verret S, Steele JC. Alternating hemiplegia in childhood: a report of eight patients with complicated migraine beginning in infancy. Pediatrics 1971; 47: 675–680.
3. Krägeloh I, Aicardi J. Alternating hemiplegia in infants: report of five cases. Dev Med Child Neurol 1980; 22: 784-791.
4. Mikati MA, Panagiotakaki E, Arzimanoglou A. Revision of the diagnostic criteria of alternating hemiplegia of childhood. Eur J Paediatr Neurol 2021; 32: A4-A5.
5. Swoboda KJ, Kanavakis E, Xaidara A, et al. Alternating hemiplegia of childhood or familial hemiplegic migraine? A novel ATP1A2 mutation. Ann Neurol 2004; 55: 884-887.
6. Wilbur C, Buerki SE, Guella I, et al. An Infant with epilepsy and recurrent hemiplegia due to compound heterozygous variants in ATP1A2. Pediatr Neurol 2017; 75: 87-90.
7. Huang D, Liu M, Wang H, et al. De novo ATP1A2 variants in two Chinese children with alternating hemiplegia of childhood upgraded the gene–disease relationship and variant classification: a case report. BMC Med Genomics 2021; 14: 95.
8. Calame DG, Houck K, Lotze T, Emrick L, Parnes M. A novel ATP1A2 variant associated with severe stepwise regression, hemiplegia, epilepsy and movement disorders in two unrelated patients. Eur J Paediatr Neurol 2021; 31: 21-26.
9. Roid GH, Sajewicz-Radtke U, Radtke BM, Lipowska M. Skale inteligencji Stanford-Binet (ed. 5). Pracownia Testów Psychologicznych i Pedagogicznych, Gdańsk 2017.
10. Sweadner KJ, Arystarkhova E, Penniston J, Swoboda K. Genotype-structure-phenotype relationships diverge in paralogs ATP1A1, ATP1A2, and ATP1A3. Neurol Genet 2019; 5: e303.
11. Li Y, Tang W, Kang L, et al. Functional correlation of ATP1A2 mutations with phenotypic spectrum: from pure hemiplegic migraine to its variant forms. J Headache Pain. 2021; 22: 92.
12. Todt U, Dichgans M, Jurkat-Rott K, et al. Rare missense variants in ATP1A2 in families with clustering of common forms of migraine. Hum Mutat 2005; 26: 315-321.
13. Masoud M, Prange L, Wuchich J, Hunanyan A, Mikati MA. Diagnosis and treatment of alternating hemiplegia of childhood. Curr Treat Options Neurol 2017; 19: 8.
14. Vetro A, Nielsen HN, Holm R, et al. ATP1A2- and ATP1A3-associated early profound epileptic encephalopathy and polymicrogyria. Brain 2021; 144: 1435-1450.