

# Recognizable Facial Features in Patients with Alternating Hemiplegia of Childhood

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Alternating hemiplegia of childhood is an early onset neurodevelopmental disorder characterized by paroxysmic episodes of alternating hemiplegia, variable degrees of intellectual disability, and dystonic movements. The main causative gene, *ATPIA3*, is also responsible for other neurodevelopmental disorders. While the neurological profile of this condition is well defined, the question whether a recognizable pattern of physical anomalies does exist in this condition is still open. We performed a morphological evaluation of 30 patients at different ages. All patients were evaluated independently by each author and evaluation sheets were compared, discussed, and agreed afterwards. This study started before the identification of *ATPIA3* as the causative gene, and the patients were selected upon their neurological picture. Four of these 30 patients tested negative for *ATPIA3* mutations and were excluded from the present work. On physical ground, almost all patients shared a similar physical phenotype consisting of hypotonia, long face, thin eyebrows, strabismus, hypertelorism, long palpebral fissures, downturned mouth, and slender habitus. Such phenotype is sufficiently typical to generate a recognizable gestalt. We also evaluated patients photographs taken from the parents in early childhood (6–20 months) to delineate a clinical profile possibly recognizable before the neurological signs suggest the diagnosis. Our data suggest that the typical early gestalt is sufficient to advise the molecular analysis of *ATPIA3*, even in absence of the pathognomonic neurological signs. Finally, since a number of patients is now adult, some information can be drawn on the phenotypic evolution of the facial appearance of patients with alternating hemiplegia of childhood. © 2016 Wiley Periodicals, Inc.

**Key words:** phenotype; alternating hemiplegia of childhood

## INTRODUCTION

Alternating hemiplegia of childhood (AHC) is a rare, early onset neurodevelopmental disorder with a prevalence of 1:100,000 [Hoei-Hansen et al., 2014] characterized by paroxysmal manifestations of tonic, dystonic, and/or hemiplegic attacks, and oculomotor abnormalities. All these manifestations can be triggered by factors such as psychological or physical stress. Typically, these phenomena regress with transition from wakefulness to sleep. Epileptic seizures with a variable pattern have also been reported

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[Neville and Ninan, 2007]. Additional non-paroxysmal signs such as marked hypotonia, dystonia, tremor, ataxia, and intellectual disability (ID) of variable degree are also present.

Alternating hemiplegia of childhood usually manifests within 18 months of age, but in a large group of patients the first clinical signs occur even earlier, usually before 6 months [Panagiotakaki et al., 2015].

The classic neurologic diagnostic criteria include: (i) onset before 18 months of age; (ii) paroxysmal occurrence of tonic/dystonic spells, oculomotor alterations, and autonomic phenomena; (iii) repeated attacks of hemiplegia involving either side of the body; (iv) recovery from attacks upon sleeping; and (v) ID of variable degree [Bourgeois et al., 1993].

The course of the disease is variable ranging from mild psychomotor impairment to severe disability from early childhood. Sudden death has also been reported in a few patients.

In 2012, mutations in *ATPIA3* were identified as causative for AHC [Heinzen et al., 2012]. At that time, it was already known that another condition, rapid-onset dystonia-parkinsonism (RDP) was caused by alterations in the same gene, but at different sites. Another neurological phenotype, cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS)

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syndrome, was subsequently found to be caused by different mutations in this same gene [Sweney et al., 2015]. Rapid-onset dystonia-parkinsonism is characterized by acute or subacute onset of rapidly evolving dystonia and parkinsonism in adolescence or adulthood (variably between 9 months and 59 years) after a physical or psychological trigger. The CAPOS syndrome [Nicolaidis et al., 1996] manifests with early onset cerebellar ataxia, areflexia, pes cavus deformity, optic atrophy, and sensorineural hearing loss. Usually, an abrupt onset of neurological symptoms occurs, predominantly hypotonia and ataxia, triggered by stressors such as a fever, with onset from 9 to 16 months.

Whereas RDP is usually dominantly inherited, CAPOS syndrome and AHC appear sporadically, being due to *de novo* mutations in *ATPIA3*.

Mutations in the coding region of *ATPIA3* are detected in 75–90% of patients with a clinical diagnosis of AHC, indicating that additional causative genes, yet unknown, might exist. *ATPIA3* encodes the sodium-potassium (Na<sup>+</sup>/K<sup>+</sup>) ATPase alpha three subunit, whose assembly with other subunits results in a pump that plays a critical role in maintaining the electrochemical gradients of Na<sup>+</sup> and K<sup>+</sup> across the plasma membrane: upon ATP hydrolysis, three Na<sup>+</sup> ions are exchanged with two K<sup>+</sup> ions. Altogether there are four alpha subunits (1–4) and three of them (1–3) are expressed in the nervous system [McGrail et al., 1991]. After the discovery that AHC and RDP are allelic conditions, it has been observed that the mutational spectrum of these two conditions is distinct, suggesting that AHC-associated mutations have a more severe functional and clinical impact as compared to those associated with RDP. Exceptionally, a typical RDP mutation has been reported in one AHC patient [Boelman et al., 2014]. In both conditions, the biological mechanisms underlying stress intolerance in neurons with *ATPIA3* alterations are still unknown.

Although more than 30 *ATPIA3* mutations have been reported in patients with AHC, it is clear that a mutational clustering does exist, as more than 50% of patients have either one of two recurrent mutations, that is, p.Asp801Asn (c.2401G>A) or p.Glu815Lys (c.2443G>A). A third mutation, the p.Gly947Arg (c.2839G>A or c.2839G>C), is also quite frequent in Caucasian patients with AHC. The p.Glu815Lys mutation is clearly associated with the most severe neurological phenotype.

Whereas the neurological profile of patients with AHC has been extensively delineated, the question whether a recognizable pattern of physical anomalies exists in this condition is still open. In an attempt to identify a recognizable physical profile for AHC, we performed a morphological evaluation at different ages of 30 patients with a neurological diagnosis of AHC. The purpose of this report is to draw attention to some physical signs, common to AHC patients, detectable at different ages, but especially in early childhood, and to show the changes of this phenotype with age. The result of this analysis is the delineation of a typical physical phenotype that is recognizable upon morphological examination of the patient.

## METHODS

Each patient underwent a thorough morphological evaluation and photographs were taken upon written consent by parents. Parents also kindly provided photographs taken in early childhood.

Pre- and post-natal history was recorded. The study has been approved by the ethical board of the Italian Association for AHC (AISEA).

Three of the four authors (FG, FDT, and GN) evaluated each patient in person separately and reached a consensus. However, we determined that our conclusions be validated by an independent expert. Therefore, we submitted clinical reports and photographs to GZ who suggested that the description of the early age phenotype be separated from that seen at an older age. Indeed, the phenotype observed in early childhood bears significant differences with respect to that manifesting at an adult age. A final consensus was reached whose result is summarized in Tables I and II.

All patients were tested by Sanger sequencing of the coding region of *ATPIA3* and were previously reported [Heinzen et al., 2012]: the mutation synopsis is reported in the Tables. Four out of 30 (13%) individuals did not have identified mutations, but the diagnosis of AHC could be supported on the basis of the neurological manifestations. However, their physical descriptions were not included in this report.

Figure 1 is a compilation of the facial phenotypes in early infancy. Figure 2 reports the facial phenotype in childhood and Figure 3, the facial appearance in adulthood. For some patients, images at two different ages were available. Some patients were examined only in adult life.

## RESULTS

### Pre- and Peri-Natal Findings

Information on possible peri-conceptual exposures and on pregnancy were recorded in 24/30 patients. A total of 9/30 fathers were working in industries with a potential risk of exposure to genotoxic agents (such as polyurethane, tin, and xylol) in the peri-conceptual period. One third of these pregnancies was characterized by reduced fetal movements, fetal hiccups but normal fetal growth.

Half of the births were by caesarean delivery and marked hypotonia was recorded in all patients. Neurological issues, including abnormal eye movements, seizures, or paroxysmal episodes occurred between the first few days and 18 months.

By evaluating the pictures taken in early infancy a few findings appeared to be present in all patients (Fig. 1): a wide, prominent forehead, thin but well-defined eyebrows extending to the temporal side of the forehead, depressed nasal bridge, long philtrum, drooping cheeks, downturned corners of mouth, enhanced cupid's bow of the upper lip with everted lower lip vermilion (Table I).

As shown in Figure 2, the facial appearance became more striking with age. In most patients, the frontal bossing disappeared, but the eyebrows were even more typical in 20 out of 26 patients. With the persistence of hypotonia, the palpebral fissures may become down slanting with a full periorbital region. The philtrum appeared long, while the mouth was large and almost maintained the appearance observed in early infancy.

The degree of ID correlated with the type of *ATPIA3* alteration, being most severe in patients with p.Glu815Lys or slightly less in those with the p.Asp801Asn mutation. Motor impairment was a common finding and, especially in adult life, some patients had difficulties in ambulation, and a few were wheelchair-bound. The

TABLE I. Summary of Clinical and Molecular Findings in Young Patients With AHC

Patient no.	Prenatal	Delivery	Level of ID	Coding sequence	High front	Thin, horizontal eyebrows	Long or hypotonic face	Everted lower lip vermilion enhanced cupid's bow of upper lip	Long philtrum	Down slanting/long palpebral fissures	Other findings	ATP1A3
2	?	Vaginal	Moderate	n.a.	+	+	±	±	+	—	Polymicrogyria	Leu888Pro
5	?	?	Moderate	n.a.	+	+	±	±	+	—	Bilateral congenital hip luxation	Val919del
6	?	?	Moderate	n.a.	+	+	±	+	—	—	1 CLS/pectus excavatum	Asp801Asn Glu815Lys
7	?	?	Moderate/severe	n.a.	+	—	—	—	+	—	Pectus excavatum	Met806Arg
9	?	?	Mild	n.a.	+	+	±	+	+	—	Pectus excavatum	Glu815Lys Glu815Lys
10	?	?	Moderate/severe	n.a.	+	+	—	±	±	—	2 CLS	Glu815Lys Glu815Lys
11	Fetal hiccup Podalic presentation	CD	Severe	n.a.	+	—	±	±	±	—	Autistic behavior	Glu815Lys Glu815Lys
12	nl	Vaginal	Mild/moderate	n.a.	+	+	±	—	—	—	Large ears 1 CLS	Gly947Arg
15	nl	CD	Severe	n.a.	+	—	±	+	+	—	2 CLS	Glu815Lys
18	Identical twins	CD	Mild/moderate	n.a.	—	—	—	±	+	—	Achantosis nigricans hyrsutism	Asn733Ser
21	nl	Vaginal	Moderate	n.a.	+	+	±	+	+	—	2 CLS	Asp801Asn
22	nl	nl	Moderate	n.a.	±	—	+	+	+	—	2 CLS	Asp801Asn
23	Threat of abortion	CD	Mild/moderate	n.a.	+	—	+	+	+	—	2 CLS	Gly947Arg

CD, cesarean delivery; WT, wild-type; CLS, café-au-lait spots.

TABLE II. Summary of Clinical and Molecular Findings in AHC Patients of Young/Adult Age

Patient no.	Prenatal	Delivery	Level of ID	Slender habitus	High front	Facial features					Down slanting/long palpebral fissures	Other findings	ATP1A3 coding sequence
						Thin, horizontal eyebrows	Long, hypotonic face	Everted lower lip vermillion or large mouth	Long philtrum	Long, hypotonic face			
2	Reduced fetal movements	?	Moderate/severe		+	+	+	+	+	-	+	Polymicrogyria	Leu888Pro
3	Reduced fetal movements	?	Severe		±	+	-	-	+	+	±	Facial asymmetry	Glu815Lys
4	?	?	Mild/moderate		+	+	-	-	+	+	+	Bilateral congenital hip luxation	Asp801Asn Val919del
5	?	Vaginal	Moderate		-	+	+	+	+	+	+		
6	?	?	Moderate		+	±	+	±	±	-	-		Asp801Asn
7	?	?	Moderate/severe		+	±	+	-	+	+	+	1 CLS/pectus excavatum	Glu815Lys
8	nl	Vaginal	Moderate		+	+	+	+	+	+	+	Pectus excavatum	Cys333Phe Met806Arg
9	?	?	Mild		+	+	+	+	+	+	+		
10	?	?	Moderate/severe		+	±	+	±	+	-	+	2 CLS	Glu815Lys
11	Fetal hiccup podalic presentation	CD	Severe		+	-	+	+	+	-	-	Autistic behavior	Glu815Lys
12	nl	Vaginal	Mild/moderate		+	+	+	+	+	+	+	Large ears 1 CLS	Gly947Arg
13	nl	Vaginal	Moderate		±	+	+	+	+	+	+		Asp801Asn
14	nl	Vaginal	Mild		+	+	+	+	+	+	-		Gly947Arg
15	nl	CD	Severe		+	-	-	+	+	+	±	2 CLS	Glu815Lys
16	Reduced fetal movements/identical twin	CD	Severe		-	-	-	-	+	-	±	Coarseness of facial traits	Glu815Lys
17	nl	Vaginal	Severe		±	+	+	±	±	+	+	Hyperventilation achantosis nigricans	Ala955Asp Asn723Ser
18	Identical twins	CD	Mild/moderate		-	±	±	+	+	+	-	hyrurtism	
19	nl	Vaginal	Mild		+	+	+	+	+	-	+		Ala338Pro
21	nl	Vaginal	Moderate		+	+	+	+	+	+	+	2 CLS	Asp801Asn
22	nl	nl	Moderate		+	+	+	+	+	-	-		Asp801Asn
23	Threat of abortion	CD	Mild/moderate		+	+	+	±	±	-	-	Asymmetry	Gly947Arg
24	nl	Vaginal	Mild		±	-	+	+	+	-	+		Gly947Arg
26	nl	Vaginal	Moderate		+	+	+	+	+	-	+		Asp801Asn
27	Reduced fetal movements	CD	Moderate		-	-	-	+	+	-	±	Late-onset psychosis	Asp801Asn
28	nl	Vaginal	Moderate/severe		-	+	+	+	+	-	±	Hyrtism	Glu815Lys
29	nl	CD	Moderate		+	+	+	+	+	-	±		Asp801Asn

CD, cesarean delivery; WT, wild-type; CLS, café-au-lait spots.



**FIG. 1.** Facial appearance of patients with AHC in the first 18 months of life. Note the high forehead, thin eyebrows, full cheeks, and enhanced cupid's bow upper lip.

p.Ala955Asp (c.2864C>A) and p.Leu888Pro (c.2663T>C) mutations (patients 17 and 2, respectively) were also associated with a severe clinical presentation: patient 17 had severe epileptic encephalopathy, no self care skills, absence of expressive language, and episodes of hyperventilation. The patients who had alterations of milder effect, such as the p.Gly947Arg, p.Met806Arg (c.2417T>G) or p.Ala338Pro (c.1012G>C), appeared to have cognitive and motor disability, but developed expressive language, and motor skills. Patient 5, with the p.Val919del (c.2755\_2757delGTC) mutation, unique among all those reported so far, had apparent ID, and was able to author a book entitled "The Convoy of Trucks." However, it should be noted that also patient 4, who had the similarly severe mutation p.Asp801Asn, was still able to author an autobiographical book entitled "Andrea's Wonderful World."

With the exception of patients with severe neurodevelopmental impairment, we noticed a strong attitude toward socialization. Patient 24, when informed that he was a carrier of the p.Gly947Arg mutation, told us that he felt happy about this discovery, not for

himself, as he was already over 40, but for the younger patients who could benefit from a targeted therapy.

## DISCUSSION

Several conditions with epilepsy, encephalopathy, and developmental delay share clinical manifestations with AHC: among those, Angelman and Pitt–Hopkins syndromes [Margolis et al., 2015]. One patient of this cohort, patient 17, underwent molecular testing for *TCF4*, because he also had episodes of hyperventilation; only when a hemiplegic attack was recorded did he receive a diagnosis of AHC, confirmed by mutational analysis of *ATPIA3*. He also had molecular testing for Angelman syndrome as did many other patients in the study. Clearly, the phenotypic overlap between these conditions is limited to the clinical presentation of the most severe *ATPIA3* mutations, such as p.Glu815Lys and p.Ala955Asp. With respect to Angelman syndrome, it should be noted that the typical prominent





**FIG. 2.** Facial appearance of patients with AHC in middle childhood. Note the high forehead, thin eyebrows, hypotonic face, and everted lower lip vermilion.

mandibular bone is not present in patients with AHC, who also lack the inappropriate laughing episodes and the typical EEG pattern. Also, even in those patients with the p.Glu815Lys variant, it is possible to observe some language development. The occurrence of hyperventilation episodes among other autonomic dysfunctions may lead to suspect a diagnosis of Pitt–Hopkins syndrome, again in patients with severe AHC. Aside from the different gestaltic appearance, the neurological involvement in AHC is characterized by more specific manifestations (recurrent hemiplegic attacks and dystonia) than in Pitt–Hopkins syndrome. Furthermore, there are usually no brain alterations or microcephaly in patients with AHC whereas these findings can be present in those with Pitt–Hopkins syndrome [Tan et al., 2014]. Other severe early onset epileptic encephalopathies in need of differential diagnosis include Dravet and Ohtahara syndromes [Nakamura et al., 2013], caused by alterations in *SCN1A* or *SCN2A*, respectively. In these conditions, the differential diagnosis can be difficult. However, the untractable epilepsy is more typical of *SCN2A* mutations. Obviously, the occurrence of episodic hemiplegia, which can be difficult to observe, clearly distinguishes AHC from all these conditions. The clinical picture caused by milder *ATPIA3* alterations may overlap with that of hemiplegic migraine and other channelopathies. Usually, in the case of hemiplegic migraine, the family history is positive, and no developmental disabilities or seizures are evident.

Although AHC is usually considered a purely neurodevelopmental condition, we found that almost 22 of 26 patients with a confirmed molecular alteration in *ATPIA3* shared a similar physical phenotype consisting of generalized hypotonia, long face, thin and well-defined eyebrows, strabismus, widely spaced eyes, long palpebral fissures, downturned mouth, and slender habitus. We consider this phenotype sufficiently typical to delineate a recognizable gestalt. These physical findings, together with the neurological manifestations, even in the absence of the typical episodic hemiplegia, should prompt the diagnostic suspicion of AHC and induce the genetic testing. To ensure full diagnostic coverage for AHC, it is advisable to include *ATPIA3* in genetic testing panels including other genes responsible for epileptic encephalopathies.

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**FIG. 3.** Facial appearance of adults with AHC. Note the change in facial appearance. In some patients, there is persistence of hypotonia, thin eyebrows, and downturned mouth corners.

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## DEDICATION

This article is dedicated to John Carey, longtime friend and highly esteemed colleague, in recognition of his commitment to excellence in the fields where he is a recognized world leader: patient care, clinical genetics and pediatrics, and science writing. He has been and continues to be a source of inspiration for colleagues of all ages, ourselves included. Thank you John. We wish you all the best for your future endeavors.

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