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RESEARCH SUBMISSIONS

Familial hemiplegic migraine in pediatric patients: A genetic, clinical, and follow-up study

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Abstract

Objective: The aim of this study was to describe a cohort of pediatric patients with genetically confirmed familial hemiplegic migraine (FHM). The knowledge of genotype–phenotype correlations may suggest prognostic factors associated with severe phenotypes.

Background: Hemiplegic migraine is a rare disease and data concerning the pediatric population are even more rare as they are often extrapolated from mixed cohorts.

Methods: We selected patients who met International Classification of Headache Disorders, third edition criteria for FHM, who had a molecular diagnosis, and whose first attack occurred under the age of 18 years.

Results: We enrolled nine patients (seven males and two females) first referred to our three centers. Three of the nine (33%) patients had calcium voltage-gated channel subunit alpha1 A (*CACNA1A*) mutations, five (55%) had ATPase Na+/K+ transporting subunit alpha 2 (*ATP1A2*) mutations, and one had both genetic mutations. The patients experienced at least one aura feature other than hemiplegia during the first attack. The mean (SD) duration of HM attacks in the sample was 11.3 (17.1) h; 3.8 (6.1) h in the *ATP1A2* group, and 24.3 (23.5) h in the *CACNA1A* group. The mean (SD, range) duration of follow-up was 7.4 (2.2, 3–10) years. During the first year from the disorder's onset, only four patients had additional attacks. Over the course of follow-up, the attack frequency overall was 0.4 attacks/year without a difference between the two groups (*CACNA1A* and *ATP1A2*).

Conclusion: The study data show that most of our patients with early-onset FHM experienced infrequent and non-severe attacks, which improved over time. Furthermore, the clinical course revealed neither the appearance of novel neurological disorders or a deterioration of basic neurological or cognitive functioning.

KEYWORDS
ATP1A2, *CACNA1A*, *CACNA1E*, familial hemiplegic migraine, hemiplegic migraine, migraine

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INTRODUCTION

Hemiplegic migraine (HM), a subtype of migraine with aura, is characterized by headache attacks and motor alterations, specifically unilateral reversible weakness.[1] HM is a rare disease and data on the pediatric population are even more rare, often extrapolated from mixed samples. A sporadic (SHM) and a familial (FHM) subtype of HM have been identified. Advances in migraine genetics demonstrate that FHM is an autosomal dominant inherited disorder mostly caused by three genes: *CACNA1A*, *ATP1A2*, and *SCN1A* coding for the α1 pore-forming subunit of the voltage-gated calcium channel P/Q type ($Ca_v2.1$), the alpha 2 isoform of the Na(+), K(+)-ATPase, and alpha 1 subunit of the voltage-gated sodium channel ($Na_v1.1$), respectively.[2] At least a quarter of individuals with FHM and most cases with SHM do not have mutations in these three aforementioned genes.[2] It has been reported that the onset of HM usually occurs in the second decade of life, but the disorder can also arise between the ages of 1 and 45 years.[2,3] The aim of our study was to longitudinally follow a sample of children with genetically confirmed FHM, and better understand how clinical features, clinical course, and prognosis relate to their specific genetic variant in order to build well-defined phenotypes.

METHODS

This is a retrospective observational case series of pediatric patients with genetically confirmed FHM first seen at our three centers. The study is a secondary analysis of previously collected data from eight unpublished patients and one previously published patient.[4] The sample size was based on the available data and no statistical power calculation was conducted before the study. We performed a post hoc analysis of the clinical course reviewing all available clinical, laboratory, and imaging data reported in the patients' medical records. The enrolled patients met the following criteria:

- Clinical data consistent with the International Classification of Headache Disorders, third edition (ICHD-3) for FHM.
- Documented genetic tests (Table 1).
- First attack at <18 years of age.

Written informed consent was obtained from the parents of patients aged <18 years and from all individuals aged ≥18 years. According to local ethical policies, the study was deemed exempt from formal approval by the hospital ethics committee.

Clinical data

The clinical information included: personal data, family history of HM or other types of headache, personal history of headache and/or epilepsy, the association of other current or past diseases such as cardiovascular or hematological diseases, and any developmental delay. Collected data included details of the first attack (duration of the attack and pain, side of the hemiparesis, speech and/or consciousness impairment, associated other typical symptoms of migraine aura, allodynia, attack sequence), recurrence of attacks during the ensuing years, time of the last attack, genetic tests, blood analysis, neurological examinations, neuroimaging investigations (computed tomography during attack, magnetic resonance imaging [MRI] post-attack), and use of symptomatic/prophylactic therapy.

Statistical analysis

Normality assumptions were checked using a quantile–quantile plot documenting a normal distribution for all data. A descriptive analysis of the demographic and clinical characteristics of the sample was reported. We calculated the mean, standard deviation (SD), minimum value, and maximum value of continuous variables, and frequency counts for categorical variables. All analyses were run using the Statistical Package for the Social Sciences (SPSS) Statistics 23 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. IBM Corp., Armonk, NY, USA).

RESULTS

General characteristics

There were nine patients with FHM, seven males and two females, with a mean (SD, range) age of HM attack onset of 9.1 (4.1, 3.9–15) years. Genetic tests, performed in trios (proband, father, and mother), showed that three of the nine (33%) patients had *CACNA1A* mutations, five (55%) had *ATP1A2* mutations, and one had both aforementioned genetic mutations (Table 1). Of these, 67% (six of the nine) were recurrent mutations. Two different missense *CACNA1A* variants (recurrent p.Thr666Met and novel p.Arg1421Gln) detected in three patients involve highly conserved residues located in the pore loop connecting S5 and S6 (D II and D III domain). Five different *ATP1A2* variants including four missense and one splice site (three recurrent: p.Tyr9Asn, p.Gly615Arg, p.Gly758Ala; and two novel: p.Pro798Leu, c.2942+4A>G-) were referred. One patient had a double missense mutation: a recurrent *CACNA1A* (p.Arg192Gln) and a novel *ATP1A2* (p. Gly254Asp). The functional studies of mutant Ca^{2+} channels show that FHM1 mutations, including the *CACNA1A* (p.Thr666Met, p.Arg192Gln), result in gain of function (GoF) of human neuronal $Ca_v2.1$channels.[5] We do not know whether the p.Arg1421Gln variant results in a GoF or a loss of function (LoF) of the $Ca_v2.1$ channel because, being a novel variant, functional studies are lacking. This variant entails the replacement of a positively charged arginine with a neutral not polar glutamine and involves a highly conserved residue located in the extracellular pore loop connecting S5 and S6, likely altering the calcium channel structure at this functionally critical region for calcium influx; however, the variant, located very close to the exon–intron boundary, could lead to

abnormal splicing resulting in aberrant transcripts (Alamut visual ese predictions: Splicing predictions at nearest natural junction predicted a change at donor site 1 bps downstream: −64.2% MaxEnt: −81.2%, NNSPLICE: −98.9%, HSF: −12.6%). Functional studies of all investigated FHM2 mutations, including the p.Gly615Arg, usually result in partial or complete loss of activity of the α2 Na^+/K^+ ATPase.[6] The p.Gly758Ala, found in a 15-year-old girl with SHM, has not been investigated with functional studies[7] to date, as well as the two novel missense (p.Gly254Asp, p.Pro798Leu) mutations and the novel splicing variant (c.2942+4A>G) having only in silico prediction data. The p.Tyr9Asn, located in the N-terminal of ATPase alpha 2 subunit, is a variant with conflicting pathogenic verdicts by prediction tools. All nine patients had a parent/relative with the same genetic mutation. Of note, two individuals with *CACNA1A* mutation (p.Thr666Met) included in the study were brothers and were both aged <18 years at onset of the attacks.

All patients had at least one parent/relative with a history of migraine with or without aura. In all nine of the patients' parents/relatives, the same genetic mutation was documented with clinical features similar to probands (two of them were siblings and carriers of the same pathogenic mutation in *CACNA1A*). Among them, only a parent with missense variant *CACNA1A* (p.Arg1421Gln) had an allelic disorder (episodic ataxia type 2 [EA2]) in early youth without migraine.

Characteristics of migraine

Among the triggers of FHM, we found that three of the nine patients (two *CACNA1A* and one *ATP1A2*) reported head trauma as the cause of both the first attack of HM and its recurrence.

Non-motor aura

All but one patient had at least one non-motor aura associated with HM attacks. The most common aura was a sensory symptom; five of the nine patients had paresthesia in the upper and/or lower limbs. Five of the nine patients had transient language deficits, some patients showed brainstem-related symptoms (confusional state, drowsiness or cognitive impairment, and dysarthria), and one reported visual aura. Two of the nine patents had two non-motor symptoms, while four of the nine patients presented at least three of these non-motor symptoms at the same time.

Duration of HM attack

The mean (SD, range) duration of the first HM attacks, including the duration of the aura symptoms and the headache phase, available in only seven of the nine patients, was 11.3 (17.1, 0.5–48) h; notably, the duration of the attacks was ≤1 h in one of the seven patients, between 1 and 2 h in three, and >12 h in three. In the *ATP1A2* group, the mean (SD, range) duration of attacks was 3.8 (6.1, 0.5–13) h; the *CACNA1A* group had a mean (SD, range) attack duration of 24.3 (23.5, 1–48) h.

Associated signs and symptoms

All patients complained of moderate/severe pulsating pain during or after the motor aura; four of the nine patients had pallor, six experienced emesis, and one had irritability and motor agitation. Four of the nine patients had a history of headache with migraine characteristics and one complained of tension-type headache attacks. One patient was on valproic acid for behavioral problems, one had a learning disability, and one had an intellectual disability.

Other investigations

Neuroimaging showed decreased left transversus venous sinus flow in two of the patients with *ATP1A2*. One patient with *CACNA1A* had a retrocerebellar cyst. Interictal electroencephalograms showed asymmetrical slow-wave activity, contralateral to motor weakness in six of the nine patients, and recurrent generalized 3 Hz regular spike-wave complex discharges in one.

Follow-up

The mean (SD, range) follow-up was 7.4 (2.2, 3–10) years. During follow-up, two of the nine patients had only the initial attack until the last evaluation 6–8 years later. During the first year after onset, four of the nine patients had another attack, while six of the nine patients further experienced one or two new attacks between the second and third years. Three of the nine patients experienced a new attack at >3 years after onset. Overall, the attack frequency during follow-up was 0.4 attacks/year without a difference between the two groups (*CACNA1A*/*ATP1A2*). Neurological examination was normal at baseline and during follow-up in all patients. Two patients with neurodevelopmental disorders did not show a deterioration of cognitive functions during follow-up. Prophylactic therapy with acetylsalicylic acid and topiramate was used in one patient. Paracetamol and ibuprofen, the main acute treatments during attacks, were effective in relieving pain. There were no relevant differences between the features of the first attacks and the following ones. Overall, our sample did not show different clinical features between the main subgroups as well as the patient with double mutation (CACNA1A+ ATP1A2). Detailed demographic, genetic, and clinical data of the sample are reported in Table 1, and summary data in Table 2.

We thought it useful to report separately a 10th pediatric patient who had HM, although not definitively FHM, associated with *CACNA1E* (p.Asn1691Ser) variant. The patient's first attack lasted 2 h and recurred at a rate of 1.3 attacks/year over the following 2 years. The attacks also included non-motor aura symptoms such

TABLE 1 Detailed demographic, genetic, and clinical data of the sample.

Pts	First attack age, years	Follow-up, years	Gene (NM_)/genetic variant	Variant characteristics and in silico prediction	Visual aura	Sensory aura	Transient language deficit	Confusional state	Vigilance loss/ drowsiness	Nausea
1	10	8.2	*ATP1A2* (NM_000702.4) c.1843G>A (p.Gly615Arg)	Recurrent missense, IC, large loop S4-S5; ClinVar: likely pathogenic; Mutation tasting: disease causing; Poliphen2: probably damaging; SIFT: damaging; VarSome: likely pathogenic	–	–	+	+	+	?
2	5.9	9.2	*ATP1A2* NM_000702.4) c.25T>A (p.Tyr9Asn)	Recurrent missense, IC, N-terminal. ClinVar: conflicting, Mutation tasting: disease causing. Poliphen2: benign; SIFT: tolerated; VarSome: likely benign	–	–	–	–	–	–
3	15	4.5	*ATP1A2* (NM_000702.4) c.2273G>C (p.Gly758AIa)	Recurrent missense, IC, large loop S4-S5. ClinVar: conflicting; Mutation tasting: disease causing; Poliphen2: benign; SIFT: damaging; VarSome: pathogenicity scores: 10/17	–	Paresthesia		–	–	+
4	12.5	10.1	*ATP1A2* (NM_000702.4) c.2942+4A>G	Novel splicing site, VarSome: pathogenicity scores 1/2	Right hemianopsia	Right hand/facial hypoesthesia	+	+	–	+
5	13.7	8.4	*ATP1A2* (NM_000702.4) c.2393C>T p.Pro798Leu)	Novel missense, EC S5-S6. Mutation tasting: disease causing; Poliphen2: probably damaging; SIFT: damaging; VarSome: pathogenicity scores	–	Paresthesia	+	+	–	–
6	12	5.1	*ATP1A2* (NM_000702.4) c.761G>A (p.Gly254Asp)	Novel missense, IC M2-M3 linker. Mutation tasting: disease causing; Poliphen2: probably damaging; VarSome: likely pathogenic	–	Paresthesia	+	–	–	–
			CACNA1A (NM_023035.2) c.575G>A (p.Arg192Gln)	Recurrent missense, TM, D-I S4. ClinVar: pathogenic; Mutation tasting: disease causing; Poliphen2: probably damaging; SIFT: damaging; VarSome: pathogenicity scores7/19						
7	3.9	7.2	*CACNA1A* (NM_023035.2) c.1997C>T (p.Thr666Met)	Recurrent missense, pore region (D-II S5-S6 region). ClinVar: pathogenic; Mutation tasting: disease causing; Poliphen2: probably damaging; SIFT: damaging; VarSome: pathogenic scores14/18	–	–		+	+	+

Vomit	Trigger	Attack frequency, attacks/year	Attack duration, h	Associated disorders	Interictal EEG	MRI/MRA/CT	Prophylactic therapy	Symptomatic treatment
+		0.24	NA		Left central high-voltage slow-wave sequences	Interictal MRI: images of slight swelling of the left occipito-parietal and posterior temporal cortex and parahippocampal, with slight hyperintensity on T2 sequences without evident contrast-enhancement		Ibuprofen
–		0.08	0.5	Tension-type headache, diabetes mellitus	Right fronto-central slow-wave discharges	Interictal MRI: normal		Ibuprofen
+		0.66	1	Migraine	Alternant hemispheric slow waves	Ictal CT: normal		Paracetamol / ibuprofen
+		0.79	13		NA	Interictal MRA: asymmetry of the transverse sinuses (R > L)		Paracetamol
+	Head trauma	0.59	1	Migraine	Normal	Interictal MRA: flow decrease of the left main venous sinuses, but pervious to contrastographic balance. Ictal CT: left punctiform nucleocapsular hyperdensity, mild flattening of the pericerebral grooves, mild narrow ventricular system	Topiramate, omeprazole, acetylsalicylic acid	
–	–	0.58	NA		Left temporo-occipital slow wave; hemispheric asymmetry of background activity	Interictal MRI: negative; ictal basal CT and CT angiography: negative		
+	Head trauma	0.14	24	Learning disability, migraine	Bilateral (left>right) centro-posterior delta theta activity	Ictal CT: small left occipital hyperdensity, right punctiform cerebellar calcification		

(Continues)

TABLE 1 (Continued)

Pts	First attack age, years	Follow-up, years	Gene (NM_)/genetic variant	Variant characteristics and in silico prediction	Visual aura	Sensory aura	Transient language deficit	Confusional state	Vigilance loss/ drowsiness	Nausea
8	6.3	9.2	*CACNA1A* (NM_023035.2) c.1997C>T (p.Thr666Met)	Recurrent missense, pore region (D-II S5-S6 region). ClinVar: pathogenic; Mutation tasting: disease causing; Poliphen2: probably damaging; SIFT: damaging; VarSome: pathogenic scores 14/18	–	–	+	+	+	–
9	3.9	5.6	*CACNA1A* (NM_023035.2) c.4262G>A (p.Arg1421Gln)	Novel missense, EC pore loop (D-III S5-S6). ClinVar: conflicting; Mutation taster: disease causing; Poliphen2: possibly damaging; SIFT: tolerated; VarSome: pathogenicity scores 4/19	–	Paresthesia	–	–	–	+
10	9.10	3.1	*CACNA1E* (NM_000721.4) c.5072A>G (p.Asn1691Ser)	De novo?, recurrent missense, EC. D-IV S6. Clin Var: uncertain significance 0/3/15; Mutation taster: polymorphism; Poliphen2: benign; SIFT: tolerated; VarSome: likely benign	Left hemianopsia	Paresthesia	–	–	–	–

Abbreviations: CT, computed tomography; EC, extracellular domain; EEG, electroencephalography; IC, intracellular domain; ictal, during attack; interictal, post attack; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NA, not available; SIFT, Sorting Intolerant From Tolerant; S-W, spike wave; TM, transmembrane location.

as paresthesias and left hemianopsia and were triggered by physical effort. The patient also had childhood occipital epilepsy with left occipital spike-wave discharges on electroencephalography, successfully treated with valproic acid. Neurological and intellectual examinations were normal at baseline and during the follow-up.

DISCUSSION

This case series of pediatric patients with FHM helps to understand the phenotypes of early-onset FHM. Notably, we described the duration of the first attack, non-motor aura symptoms, their eventual recurrence, associated disorders, and finally, the clinical course of the attacks and associated disorders, and related genetic mutations (Table 1).

Although several studies on HM have been published in the last 15 years, current knowledge on this topic is partial and mainly based on extrapolations from mixed cohort studies; therefore, the challenge to identify an early-onset phenotype is still ongoing.

Riant et al.,[8] in a sample of 25 patients with early-onset SHM (aged <16 years), found that the duration of attacks was variable, ranging from 10 min to 3 weeks, as well as the number of attacks, ranging from one in a lifetime to three per month, and attacks were triggered by benign head injury, stress, and fatigue. In addition, 23/25 individuals were carriers of the FHM gene mutations (*CACNA1A* or *ATP1A2)* mainly when they were associated with neurological symptoms including cerebellar ataxia, epileptic seizures, or various degrees of intellectual disability.[8]

The review by Russell and Ducros,[2] based on a detailed analysis of the clinical features of previously reported 300–400 families with HM (SHM and FHM), was an important milestone for the subsequent studies on the topic. They did not point out relevant clinical differences in the motor aura and other clinical features between the two groups. Notably, the study reported that clinical features of SHM and FHM with identified genetic mutations ranged from short-lived attacks of hemiparesis to severe early-onset forms with long-lasting hemiparesis associated with persistent cerebellar ataxia, epilepsy, transient blindness, or intellectual disability. The mean age of onset in the three pure genetic subtypes, FHM1, FHM2, and FHM3, was 12, 11, and 13 years, respectively, but with a wide range. The mean frequency of attacks was low (3 attacks/year) with a wide range whose lowest extreme was characterized by few attacks in the lifetime. Furthermore, their frequency and severity often decreased in adulthood, and long intervals without attacks can occur. Minor

Vomit	Trigger	Attack frequency, attacks/year	Attack duration, h	Associated disorders	Interictal EEG	MRI/MRA/CT	Prophylactic therapy	Symptomatic treatment
–	Head trauma	0.32	48	Migraine	Left hemisphere high-voltage delta activity	Interictal MRI: tiny epiphysis cyst		
+	–	0.71	1	Intellectual disability; behavior dysregulation	Generalized 3 Hz S-W discharges	Interictal MRI: normal		Valproic acid
–	Physical effort	1.3	2	Childhood occipital epilepsy	Left occipital S-W discharges	NA		Valproic acid

head trauma, fatigue, and emotional distress were the most common triggers.[2]

The Pelzer et al.[9] study, carried out on a large sample of 208 patients with HM (nine SHM and 199 FHM), detected a poorer prognosis in severity and frequency of attacks, and associated neurological dysfunctions in patients carrying *CACNA1A*, *ATP1A2*, or *SCN1A* mutations. A recent review found that the age of onset of HM ranged between 12 and 17 years but did not focus attention on pediatric-onset and prognosis in the early years.[3] A recent follow-up study, focusing on clinical course and treatment in eight patients with early-onset FHM1 from a family carrying a *CACNA1A* p.T666M mutation, reported that seven had additional non-progressive cerebellar signs and cerebellar atrophy on MRI. Furthermore, clinical course can be biphasic with improvement in frequency and severity of attacks after adolescence (six patients) and eventual recurrence of migraine with prolonged aura later in adulthood (three), while neurological signs and cognitive deficits displayed a relatively steady course.[10]

To date, the study of Toldo et al.[11] is the only one that reported short-term follow-up data on a sample of 46 patients with SHM (32/46) and FHM (14/46) with early onset. The present study shows that some data are similar to those reported by Toldo et al.,[11] in particular, the duration of follow-up (mean 7.4 vs. 4.4 years) and sample size (10 vs. 14 patients) but with some additional details regarding genetic variants. Both studies, although carried out on small samples, are selectively focused on childhood and youth onset. Toldo et al.[11] agreed there are no relevant clinical differences between patients with SHM and FHM. Nevertheless, their data were not related to a specific gene involved in the FHM subgroup which, further, is smaller than the SHM one;[11] however, we believe that a clear distinction between the two subtypes is not always useful as patients with SHM may through time migrate to the FHM subtype due to the onset of the disorder in a relative and, furthermore, some of them carry genetic variants associated with the subtype FHM.[12] Noteworthy, the variant *CACNA1A* (p.Arg1421Gln) resulted in two different allelic disorders in the same family (mother with EA2 and son with HM).[4] Overlapping features, including typical and uncommon symptoms of mentioned disorders, have been reported among members of the same family.[13–17] In addition, it has been suggested that mutations involving the splice site regions are often associated with higher variability of the phenotype and with the overlap of the common symptoms of the allelic disorders FHM1, EA2, and spinocerebellar ataxia type 6.[18] Moreover, most studies concluded that other unknown individual modifier genes and/or environmental

TABLE 2 Summary data.

Variable	Value
Sex, *n*, female/male	2/7
Age at onset of first attack, years, mean (SD, range)	9.1 (4.1, 3.9–15)
Follow-up, years, mean (SD, range)	7.4 (2.2, 3–10)
Attack duration, h	
Mean (SD, range)	11.3 (17.1, 0.5–48)
<1, *n/N*	1/7
>1h–<2, *n/N*	3/7
>12, *n/N*	3/7
Other non-motor aura, *n/N*	
Visual	1/9
Sensory	5/9
Language	5/9
Confusional state	4/9
Drowsiness	4/9
Migraine	4/9
Tension-type headache, *n/N*	1/9
Psychomotor retardation/intellectual disability, *n/N*	1/9
Learning disability, *n/N*	1/9
Triggers, *n/N*	
Head trauma	3/9
Frequency of attacks, attacks/year	0.4

factors might play a regulatory role in phenotypic variability.[13–17] The p.Tyr9Asn has been reported in a 50-year-old woman with SHM with mild symptoms and low functional difference v/s *wt*.[19–21] The low evolutionary conservation of the residue p.Tyr9Asn in the N-terminal of ATPase alpha 2 subunit, important for inter-domain interactions, and its weak interference with targeting, make it questionable whether to classify it as a rare missense variant without pathogenic effects. Therefore, it could be assumed that the mutation of our patient, inherited from the affected father with a typical FHM2 phenotype, although rare and of uncertain pathogenicity, may have been interfered in vivo with by other unknown individual modifier genes, with a regulatory role, to result in the clinical consequences. This further occurrence of the *ATP1A2* p.Tyr9Asn variant in our study enhances the pathogenicity verdict compared to those previously assessed by prediction tools.

Pediatric migraine usually has a favorable outcome with a reduction of attacks in short–medium term follow-up.[22–24] The results of the present study and that of the Toldo et al.[11] suggest that pediatric patients with HM generally have a favorable overall prognosis and trend in attack frequency. Our sample had a lower frequency of attacks in the first year than the Toldo et al.[11] study, which reported a frequency of attacks of 2.2 attacks/year; however, the latter reported a decreased attack frequency in subsequent years (~70% of patients had <1 attack or no attacks per year) and only 21% had >1 attack/year, which also appeared to be milder.

The main clinical features of the first attack and the frequency of attacks in short-term follow-up in both samples were similar (mean duration of 7.4 years in this study vs. mean duration of 4.4 years in the Toldo et al.[11] study). Furthermore, we did not detect a different distribution of clinical features among the genetic subtypes of our patients. The duration of the first attacks was similar in the two samples (ours and the Toldo et al.[11] study); however, we found a difference between the *CACNA1A* and *ATP1A2* groups, with initial attacks being longer in the *CACNA1A* group. In the following few attacks, no substantial clinical differences from the first attack were observed. Preventive therapy was not warranted in almost all cases given the low attack frequency.[8,24–26]

It is noteworthy that Toldo et al.[11] reported that some symptoms such as isolated seizures, long-lasting aphasia during fever, and prolonged clumsiness following minor head trauma preceded, even by a long while, the first episode of HM.

The above paroxysmal events were found in 15% of the patients but their relationship with HM remains uncertain and should be further investigated.[11] In our sample, only one of the nine (11%) patients had visual aura associated with motor aura, while in the Toldo et al.[11] sample, visual aura was found in six of 12 (50%) patients with FHM and eight of 28 (29%) with SHM. Also, in the Toldo et al.[11] study, sensory aura was the predominant non-motor aura compared to the prevalent visual aura reported in population studies of migraine with aura.[27] In agreement with the Toldo et al.[11] study, cognitive and/or neurological disorders were not among the predominantly associated symptoms in our patients. During follow-up, none of our patients experienced ataxia or other cerebellar signs or cognitive impairment. A head injury may have triggered the attacks in three patients. Only one patient took prophylactic therapy. Our study highlights that the clinical onset of pediatric FHM has several features beyond motor aura, and the overall neurological outcome until the last evaluation is favorable in most patients. Furthermore, although the *CACNA1E* missense variant (p.Asn1691Ser) is considered partially tolerant by bioinformatics tools (gnomAD v2.1.1 https://gnomad.broadinstitute.org/), recently, de novo *CACNA1E* variants have been identified in 30 individuals with severe developmental and epileptic encephalopathies.[28] Notably, three of them with the LoF variants had milder phenotypes suggesting that LoF of the *CACNA1E* variants may be associated with a milder phenotype also without or less severe epilepsy.[28] Further, seven unrelated patients with intellectual disability, developmental regression, and autism spectrum disorder-like behavioral profile, without epilepsy, were reported in association with de novo heterozygous *CACNA1E* variants.[29] Finally, it has been reported that a polymorphism in the *CACNA1E* gene (Asp859Glu–rs35737760) is overrepresented in patients with complex migraine, notably, with brainstem and hemiplegic aura but, unfortunately, the functional consequences of this substitution are not yet known.[30] In conclusion, the data from this short-term follow-up study showed that most of our patients with early-onset FHM experienced infrequent and non-severe attacks which, usually, did not require preventive treatment.[25]

We are aware that, as the channel's structural abnormality is persistent, we cannot predict the functional consequences on the excitation/inhibition machinery over the long term. It is conceivable that during brain maturation, the dysfunction of the channel can be gradually counterweighted by other arising brain functions, thus converting into a simple condition of susceptibility. At any time in life, other detrimental events could break down the unsteady balance of channel function and cause the recurrence of previous or novel clinical symptoms.

Our study has some limitations. The collection of the retrospective phenotypic characteristics, based on available data, often lacked details. Notably, the subjectivity of some clinical findings, such as the low intensity of symptoms, the characteristics of some visual and sensory auras, the perception of the duration of the motor aura, and the grading of paresis of the first attack can sometimes lead to an inaccurate reporting of the symptoms up to complete omission. Sometimes these difficulties are due to the age-dependent inability to recall the events and/or to the peculiarity that these data are usually collected in the emergency room. Another limitation is the small number of cases did not allow us to statistically compare the characteristics of our subgroups or the frequency of signs and symptoms of our patients with those of other studies. Finally, the results suggest that a better understanding of the genotype–phenotype correlation could reveal the prognostic factors associated with severe phenotypes for which common or targeted prophylactic treatment may be indicated.

AUTHOR CONTRIBUTIONS

Study concept and design: Giuseppe Donato Mangano, Vincenzo Raieli. *Acquisition of data*: Maria Rita Capizzi, Elide Mantuano, Liana Veneziano, Giuseppe Quatrosi, Rosaria Nardello. *Analysis and interpretation of data*: Vincenzo Raieli, Elide Mantuano, Liana Veneziano, Giuseppe Donato Mangano. *Drafting of the manuscript*: Giuseppe Donato Mangano, Maria Rita Capizzi, Vincenzo Raieli. *Revising it for intellectual content*: Giuseppe Santangelo, Rosaria Nardello, Vincenzo Raieli. *Final approval of the completed manuscript*: Giuseppe Donato Mangano, Vincenzo Raieli, Maria Rita Capizzi, Elide Mantuano, Liana Veneziano, Rosaria Nardello, Giuseppe Santangelo.

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CONFLICT OF INTEREST STATEMENT

Giuseppe Donato Mangano, **Maria Rita Capizzi**, **Elide Mantuano**, **Liana Veneziano**, **Giuseppe Santangelo**, **Giuseppe Quatrosi**, **Rosaria Nardello**, and **Vincenzo Raieli** declare no conflicts of interest.

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