CACNA1A-Related Channelopathies: Clinical Manifestations and Treatment Options

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Abstract

In the last decade, variants in the Ca^{2+} channel gene *CACNA1A* emerged as a frequent aetiology of rare neurological phenotypes sharing a common denominator of variable paroxysmal manifestations and chronic cerebellar dysfunction.

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Handbook of Experimental Pharmacology, https://doi.org/10.1007/164_2022_625

The spectrum of paroxysmal manifestations encompasses migraine with hemiplegic aura, episodic ataxia, epilepsy and paroxysmal non-epileptic movement disorders. Additional chronic neurological symptoms range from severe developmental phenotypes in early-onset cases to neurobehavioural disorders and chronic cerebellar ataxia in older children and adults.

In the present review we systematically approach the clinical manifestations of *CACNA1A* variants, delineate genotype–phenotype correlations and elaborate on the emerging concept of an age-dependent phenotypic spectrum in *CACNA1A* disease. We furthermore reflect on different therapy options available for paroxysmal symptoms in *CACNA1A* and address open issues to prioritize in the future clinical research.

Keywords

Acetazolamide · *CACNA1A* · Cerebellar ataxia · Developmental delay · Epilepsy · Episodic ataxia · Familial hemiplegic migraine · Genetic testing · Therapy

1 Introduction

The advent of the genetic era unveiled the critical role of ion channel dysfunction as substrate of rare neurological disorders with paroxysmal manifestations (Graves and Hanna 2005). Variants in the Ca^{2+} channel gene *CACNA1A* emerged as a particularly frequent aetiology of such rare phenotypes (Indelicato and Boesch 2021).

The *CACNA1A* gene encodes the pore-forming subunit α1 of the neuronal voltage-gated Ca^{2+} channel P/Q. In the central nervous system (CNS), P/Q channels are ubiquitously expressed and particularly abundant in cerebellum granules and Purkinje cells. At the presynaptic terminal, P/Q channels activation upon depolarization results in a Ca^{2+} inflow which in turn triggers the vesicular neurotransmitter release (Catterall 2011). Beyond the regulation of synaptic transmission and related plasticity processes, P/Q Ca^{2+} currents influence the gating of K^+ channels, transcriptional activity as well as intracellular signalling pathways (Zamponi et al. 2015).

The first association between *CACNA1A* and human diseases dates to 1996, as its mutations were linked to two autosomal dominant neurological disorders: familial hemiplegic migraine type 1 (FHM1) and episodic ataxia type 2 (EA2) (Ophoff et al. 1996). FHM1 and EA2 are classical channelopathies featuring peculiar recurring neurological symptoms, such as migraine with motor aura and attacks of paroxysmal vertigo and ataxia. Shortly after, a third autosomal dominant disorder, the spinocerebellar ataxia type 6 (SCA6), was mapped at *CACNA1A* locus (Zhuchenko et al. 1997). SCA6 may present with paroxysmal vertigo as inaugural symptom, but primarily features a late-onset progressive ataxic syndrome, which does not fit with the phenotype of a classical channelopathy.

In the last decade, cumulative reports delineated an even broader spectrum of clinical manifestations of *CACNA1A* variants, which in children can predate the classical hemiplegic migraine/episodic ataxia. On the one hand, the episodic

manifestations expanded to epilepsy as well as to additional paroxysmal non-epileptic movement disorders (Indelicato and Boesch 2021). On the other hand, a role of *CACNA1A* in determining early-onset, severe neurodevelopmental and neuropsychiatric phenotypes is emerging (Indelicato and Boesch 2021).

The paradigm change from three defined allelic disorders FHM1, EA2 and SCA6, to an evolving age-dependent spectrum in non-polyglutamine *CACNA1A* mutations is slowing getting its way across the scientific community. Though, the pathophysiological basis of this clinical variability and evolution is still largely unexplored.

Herein, we aim at offering an exhaustive, updated overview on the clinical spectrum of *CACNA1A* mutations, highlighting genotype–phenotype correlations, and focusing on age-dependent clinical features as well as on established and emerging therapeutic concepts.

2 Molecular Genetics of *CACNA1A* Disorders: Brief Overview

The *CACNA1A* locus resides on chromosome 19. The gene contains 47 exons and can through alternative splicing be translated in myriad isoforms with different regional distribution and kinetic properties (Lipscombe et al. 2013). The final structure of the α1 subunit recapitulates the canonical organization shared by several ion channels as illustrated in Fig. 1. Six transmembrane domains (S1–S6) are expressed in a repeated fashion and organized in a tertiary structure in which the domain S4, the voltage sensor, lines the pore opening (Catterall 2011). The S4 domain is enriched of positively charged amino acids. Several disease-associated missense variants lead to substitution of positively charged arginine in this segment (Indelicato and Boesch 2021).

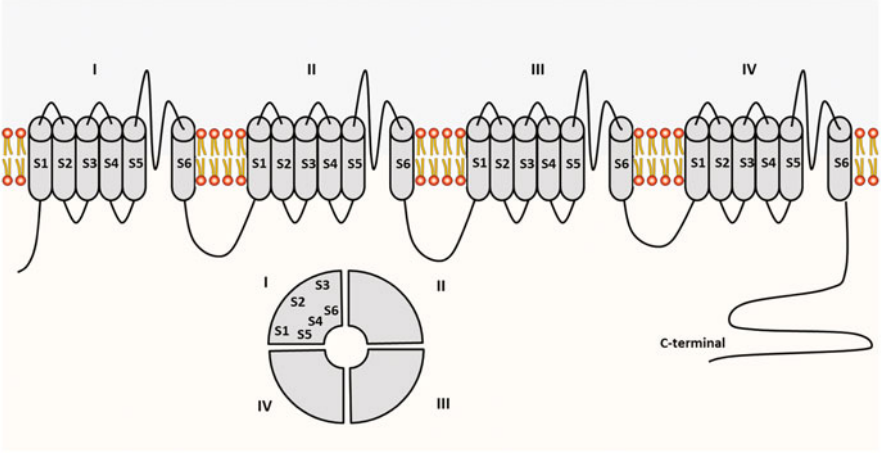

Fig. 1 Schematic representation of the α1 subunit of the voltage-gated Ca^{2+} channel P/Q

CACNA1A scores among the 2% most "intolerant" genes (Petrovski et al. 2013), a notion that underlines the need of a careful interpretation of new variants of – currently – unknown significance. Disease-associated genotypes span from missense mutations, usually with gain-of-function net effect, to loss-of-function truncating mutations and small deletions. The expansion of a CAG repeat coding for polyglutamine in the C-terminus of the gene represents a further disease genotype as we will address later.

Irrespective of the type of mutation, classical *CACNA1A* disorders feature an autosomal dominant pattern of inheritance. Few reports described exceptional cases of biallelic pathogenic *CACNA1A* variants. Individuals bearing biallelic pathogenic variants display an early-onset and a growing severity of phenotype from biallelic missense mutation (Ko et al. 2021) to one missense plus one truncating (Reinson et al. 2016) to a biallelic truncating mutation (Arteche-Lopez et al. 2021) which led to death few months after birth. Additional dysmorphic features as well as cerebral malformations may be evident in these cases.

3 One Side of the Clinical Phenotype: Paroxysmal Features

3.1 Hemiplegic Migraine

Migraine is a well-known episodic feature of *CACNA1A* disorders and migraine with hemiplegic aura represents the key feature of FHM1 (OMIM # 141500), the first genetically framed form of migraine with aura (Ophoff et al. 1996). Up to date, three further monogenic forms of familial hemiplegic migraine have been identified (Riant et al. 2022; Russell and Ducros 2011).

Migraine spells in FHM1 usually start in the first two decades and display a variety of positive and negative symptoms during the aura. These include positive visual phenomena, hemianopsia, tingling/numbness of the extremities, dysphasia, and various degree of motor deficits, from hemi- to tetraparesis (Battistini et al. 1999; Beauvais et al. 2004; Bhatia et al. 2008; Carreno et al. 2011; de Vries et al. 2008; Debiais et al. 2009; Ducros et al. 2001; Freilinger et al. 2011; Indelicato et al. 2017; Indelicato and Boesch 2021; Kinder et al. 2015; Pelzer et al. 2013, 2018a; Romaniello et al. 2010; Russell and Ducros 2011; Wada et al. 2002; Yamazaki et al. 2011). Aura can also display the features of a basilar-type migraine with diplopia, dysarthria, vertigo, tinnitus, hearing impairment, ataxia, and decreased level of consciousness (Cleves et al. 2010; Ducros et al. 2001; Haan et al. 1995). Accompanying vegetative symptoms range from the typical nausea and vomiting to severe blood pressure derangements, fever, and urticarious skin rash (Indelicato et al. 2017). Psychosis may occur during the aura (Liguori et al. 2013; Spranger et al. 1999; Topakian et al. 2014). Distinctive of FHM1, comparing to sporadic migraine forms, is the severity and prolonged character of the aura, which can span over several hours or even days (Battistini et al. 1999; Indelicato et al. 2017; Vahedi et al. 2000) and largely outlasts the burden of the subsequent headache. Co-occurring disturbance of consciousness is especially disabling and may range from

somnolence to coma (Curtain et al. 2006; Debiais et al. 2009; Ducros et al. 2001; Echenne et al. 1999; Fitzsimons and Wolfenden 1985; Kors et al. 2001; Malpas et al. 2010; Stam et al. 2009; Vahedi et al. 2000; Wada et al. 2002). Cumulative reports highlighted that severe migraine attacks may present as encephalitic state with additional fever and seizures, as well as severe hemiplegia (Battistini et al. 1999; Chan et al. 2008; Stam et al. 2009; Yamazaki et al. 2011). Although these dramatic clinical pictures may resolve without sequelae, in the setting of specific mutations, of which the S218L is the prototype, arising complications may be lethal (Debiais et al. 2009; Fitzsimons and Wolfenden 1985; Kors et al. 2001; Malpas et al. 2010; Stam et al. 2009).

Classical migraine triggers such as stress may be reported also by FHM1 patients. Peculiar triggers in FHM1 are represented by cerebral angiography (Ducros et al. 2001; Indelicato et al. 2017), as well as by bagatelle trauma in the setting of specific mutations, such as S218L (Curtain et al. 2006; Kors et al. 2001; Stam et al. 2009). In this setting, a progressive cerebral oedema may develop and lead to the above-mentioned severe attacks.

Hemiplegic migraine results in various degrees of slowing on routine scalp EEG, which can be visualized also several days after resolution of the symptoms (Indelicato et al. 2017, 2021b).

The frequency and course of hemiplegic migraine may be highly variable. Attack frequency spans from 1 to 2 spells in a lifespan to several episodes per month. In several cases in the literature and in our clinical experience, hemiplegic migraine shows a biphasic course (Indelicato et al. 2017). Indeed, a florid phase with recurring spells in the youth may transit in a long-lasting symptom-free interval (Ducros et al. 2001), which is eventually followed by flaring up at the end of 40s/beginning of 50s. Notably, patients may not recall their migraine attack (Indelicato et al. 2017; Stam et al. 2011).

FHM1 patients may suffer also from attacks of "common" migraine without hemiplegia.

FHM1 is typically caused by missense mutations with gain-of-function effect on Ca^{2+} currents, which are believed to facilitate a cascade of events that results in cortical spreading depression classically seen in migraine aura (de Vries et al. 2009; Rajakulendran et al. 2012; Striessnig 2020; van den Maagdenberg et al. 2010). Malignant mutations such as S218L display a particularly accentuated effect on the channel kinetics (Loonen et al. 2019; van den Maagdenberg et al. 2010).

3.2 Episodic Ataxia

Recurring spells of dysarthria, vertigo and coordination disturbances, a spectrum of symptoms defined as "episodic ataxia", represent the cardinal feature of EA2 (OMIM #108500). As for hemiplegic migraine, the genetic background of episodic ataxia is manifold, but the subtype due to *CACNA1A* mutations is the most frequent (Jen et al. 2007).

Episodic ataxia spells usually start in the first two life decades (Jen et al. 2004, 2007; Nachbauer et al. 2014; Subramony et al. 2003), but late-onset cases have been described (Imbrici et al. 2005). Reported symptoms include diplopia, blurred vision, tinnitus, dysarthria, coordination problems including marked balance disturbances and nausea. Cervical dystonia occasionally occurs as further ictal symptom (Hu et al. 2013; Spacey et al. 2005). Headache may also accompany ataxia spells (Nachbauer et al. 2014). Furthermore, EA2 patients may suffer from migraine occurring independently from spells of episodic ataxia (Jen et al. 2004; Subramony et al. 2003; Verriello et al. 2021).

Typically, episodic ataxia spells are shorter than migraine episodes, may even last few minutes, but are more frequent, recurring also several times per day. Physical and emotional stress are typical triggers (Jen et al. 2004). Furthermore, phenytoin, alcohol and caffeine consumption may precipitate the attacks (Kipfer and Strupp 2014; Nachbauer et al. 2014).

EA2 is typically associated with loss-of-function variants, usually mutations which interrupt the reading frame (deletion, in-frame insertion, truncating mutations) (Imbrici et al. 2005; Jen et al. 2004, 2007; Nachbauer et al. 2014; Ophoff et al. 1996; Riant et al. 2010).

3.3 Epilepsy

Shortly after the genetic allocation of FHM1 and EA2, several reports described epilepsy as additional features in *CACNA1A* families (Imbrici et al. 2004; Jouvenceau et al. 2001; Kors et al. 2004; Rajakulendran et al. 2010; Stam et al. 2008). Since *CACNA1A* diseases are channelopathies, this finding is not surprising, though the clinical picture and the underlying pathophysiological mechanisms are manifold and still unclear.

Three main patterns of epileptic comorbidities may be delineated (Brunklaus 2021; Indelicato and Boesch 2021):

- In FHM1 families, seizures mostly occur concomitantly with severe migraine attacks accompanied by fever and coma state. Particularly frequent is the description of seizures following trivial head trauma in patients bearing the S218L mutations (Stam et al. 2009; Yamazaki et al. 2011). Additional mutations recurrently associated with epileptic seizures are the R1349Q (Malpas et al. 2010; Sanchez-Albisua et al. 2013; Tantsis et al. 2016), and Y1385C (Ducros et al. 2001; Vahedi et al. 2000). Epileptic seizures in the interval are rare. All in all, seizures in FHM1 are considered "symptomatic", thus comparable to seizures caused by various non-specific major brain insults.
- Conversely, in EA2 families epilepsy is frequently described as "independent" manifestation usually occurring in children before the onset of paroxysmal ataxia (Choi et al. 2013; Damaj et al. 2015; Indelicato and Boesch 2021; Indelicato et al. 2021a, b; Riant et al. 2010; Strupp et al. 2005). Absence epilepsy and its correlating EEG changes (3 Hz spike-waves complexes) are the most common

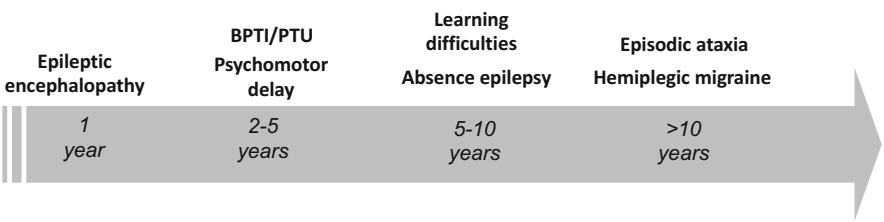

Fig. 2 The age-dependent phenotype of *CACNA1A* disorders (From Indelicato and Boesch 2021)

findings (Imbrici et al. 2004; Indelicato et al. 2021a, b; Jung et al. 2010; Labrum et al. 2009; Mantuano et al. 2010; Rajakulendran et al. 2010; Stendel et al. 2020), suggesting ~~a~~ susceptibility mechanism for generalized seizures in the setting of loss-of-function state of P/Q channels (Indelicato et al 2021b; Llinas et al. 2007). Description of epilepsy/seizure in adults with EA2 phenotypes is rare. In adults focal seizures as well as well-defined localized EEG foci have been described (Cuenca-Leon et al. 2009; Verriello et al. 2021).

- A third pattern emerged with the advent of whole exome sequencing studies in large paediatric cohorts affected by severe, therapy-resistant seizures accompanied by developmental delay/regression. These studies unravelled that de novo missense *CACNA1A* mutations recurrently cause severe early-onset epilepsy which phenotypically may present as classical developmental-epileptic encephalopathies such as Dravet syndrome, Lennox-Gastaut syndrome and epilepsy of infancy with migrating focal seizures (Epi et al. 2013; Epi 2016; Le Roux et al. 2021; Mitta et al. 2020). The term "developmental and epileptic encephalopathy-42" (DEE42) (OMIM #601011) has been coined to describe such new disease entities. Carriers of de novo missense mutations often present with early episodes of status epilepticus, especially triggered by fever (Guerin et al. 2008; Le Roux et al. 2021; Niu et al. 2022). Together with novel missense mutations, other well-known *CACNA1A* variants have been associated with these severe phenotypes, first of all the S218L (Epi 2016). In some children both severe epilepsy and episodes of flaccid hemiparesis can be noticed (Le Roux et al. 2021), a phenotype that overlaps with earlier reports of FHM1 families with a particularly severe disease in the offspring.

Taken together older and newer reports on carriers of *CACNA1A* mutations suggest that the nature and severity of symptoms may be at least partially age-dependent, an aspect overlooked by a majority because of its transient nature and absence later in life (see Fig. 2 as well as Indelicato and Boesch (2021); Indelicato et al. (2021b)).

3.4 Paroxysmal Non-epileptic Events

Observations from the kindred of FHM1 and EA2 families recently highlighted further paroxysmal, non-epileptic manifestation that in young children predate migraine and episodic ataxia (Gur-Hartman et al. 2020; Indelicato et al. 2017). The best characterized phenomenon is the "benign paroxysmal torticollis of the infancy" (BPTI) (Cuenca-Leon et al. 2008; Roubertie et al. 2008). This term indicated a form of paroxysmal cervical dystonia accompanied by pallor, nausea and malaise (Rosman et al. 2009). The strong association between BPTI and later onset of migraine in the general population contributed to the inclusion of this condition in the list of the "periodic syndromes" considered as precursors of migraine (Headache Classification Committee of the International Headache, S. 2013). While BPTI occurs isolated in other children (Danielsson et al. 2018), in *CACNA1A* mutation carriers, further subtle or overt neurological signs are usually detected at the examination (Gur-Hartman et al. 2020; Humbertclaude et al. 2020; Mantuano et al. 2010).

Similar to BPTI, the so-called paroxysmal tonic upward gaze (PTU) describes a condition of sudden tonic upwards deviation of the bulbi which is slowly emerging as a frequent manifestation in young children with *CACNA1A* mutations. As BPTI, the PTU spells predate the classical paroxysmal motor phenotypes (Blumkin et al. 2010; Chang et al. 2021; Gur-Hartman et al. 2020; Humbertclaude et al. 2020; Quade et al. 2020; Tantsis et al. 2016; Zhang et al. 2021).

4 The Other Side of the Clinical Phenotype: Chronic Neurological Manifestations

4.1 Cerebellar Ataxia and Further Chronic Motor Signs

Although some FHM1 and EA2 families present with an exquisite paroxysmal disorder, the majority of patients eventually develop some degree of chronic cerebellar signs in the course of their disease (Ducros et al. 2001; Indelicato and Boesch 2021; Jen et al. 2007).

Cerebellar features in FHM1 and EA2 patients are usually mild. The most frequent interictal sign is nystagmus, which frequently shows a major down-beat component (Indelicato et al. 2019, 2021a; Marti et al. 2008; Strupp et al. 2007; Yabe et al. 2008). The second most common chronic feature is gait ataxia. In our experience and as it has been shown through objective gait analysis (Indelicato et al. 2021a), the gait in *CACNA1A* patient is not constantly broadened as in other ataxic disorders, though instability upon external perturbances may be prominent and falls occur early in disease course (Indelicato et al. 2021a). Conversely, dysmetria of the extremities is usually mild, if present at all. Chronic cerebellar signs usually do not display a relevant progression, but exceptions are also encountered. Indeed, in some cases paroxysmal symptoms soon abate and a rather fast progressive gait ataxia dominates the clinical picture. An isolated "SCA6-like" chronic progressive cerebellar syndrome may also be the only presentation (Coutelier et al. 2017; Marti et al.

2008; Nikonishyna et al. 2022) in carriers of conventional, non-polyglutamine, *CACNA1A* mutations. In severe cases, further motor signs such as spasticity and positive Babinski signs may be evident. Additional dystonic features, especially cervical dystonia, are recurrently reported (Cuenca-Leon et al. 2009; Fuerte-Hortigon et al. 2020; Spacey et al. 2005).

The time of onset of chronic cerebellar signs is highly variable. In young children, cerebellar ataxia is not easy to diagnose. Indeed, the typical signs of a cerebellar syndrome may not be evident before the second-third year of life (Bertini et al. 2018). Unspecific signs such as generalized hypotonia or delay in the acquisition of motor milestones offer a clinical clue (Izquierdo-Serra et al. 2020) and can be later recalled by the parents of young adults upon clinical interview (Indelicato et al. 2019). Severe motor features in infants usually frame within a general developmental delay phenotype as described in the following paragraph. Mild cerebellar signs can be noticed for the first time in young adults during an acute referral because of a migraine or episodic ataxia spell.

4.2 Developmental Delay, Cognitive and Behavioural Features

The parents of young adults with FHM1 and EA2 can often recall some delay in the acquisition of early milestones, described as a slight delay in walking or speaking (Indelicato et al. 2019). Later, learning problems may become evident and lead to the inclusion in special education programs (Indelicato et al. 2019). In schoolchildren, prominent behavioural problems may arise, compatible with attention-deficit hyperactivity disorder or autistic spectrum disorders (Damaj et al. 2015; Indelicato et al. 2019; Nardello et al. 2020; Tantsis et al. 2016). In the literature, reports of such prominent neurobehavioural features are limited to children. This observation, along with our clinical experience, suggests that in children arising from FHM1 and EA2 families behavioural abnormalities may ameliorate spontaneously (Indelicato et al. 2017). Though, subtle cognitive dysfunction may be detectable in later life (Indelicato et al. 2019; Karner et al. 2010, 2012). Several authors reported that adult patients are mostly employed in unskilled labour, have poor education level and often psychiatric comorbidities, as well as impulsive/sociopathic behaviour (Freilinger et al. 2008; Indelicato et al. 2019; Nachbauer et al. 2014). Few studies applied formal neuropsychological testing in adults with genetically confirmed *CACNA1A* disease (Indelicato et al. 2019; Karner et al. 2010, 2012). These works revealed deficits in several cognitive domains, first of all in executive functions, figural memory and visuo-constructive abilities. Late-onset progressive cognitive decline consistent with dementia is rare (Freilinger et al. 2011).

Cumulative reports highlighted that a severe neurodevelopmental phenotype, isolated or along with severe epilepsy can dominate the clinical picture in infants with de novo *CACNA1A* mutations (Gur-Hartman et al. 2020; Humbertclaude et al. 2020; Luo et al. 2017; Ohba et al. 2013; Weyhrauch et al. 2016). A developmental regression after the normal milestones acquisition has also been reported (Guerin et al. 2008), often following severe hemiplegic attacks with encephalitic features, a

clinical picture which can overlap with that of mitochondrial diseases such as MELAS (Knierim et al. 2011).

4.3 Imaging Findings

The typical imaging findings in FHM1 and EA2 are represented by an isolated cerebellar atrophy with solely – or prevalent – involvement of the vermis (Indelicato et al. 2019). The degree of atrophy is usually mild. Parallel to the variable clinical manifestations, more severe atrophy pattern may appear. Cerebellar atrophy may not be evident in infants, but eventually developed in a majority of cases later in the disease course (Gur-Hartman et al. 2020). Further findings in early-onset severe cases encompass cerebral undersulcation, mild cerebral atrophy and thinning of the corpus callosum (Ko et al. 2021; Reinson et al. 2016; Weyhrauch et al. 2016). During severe hemiplegic migraine attacks, imaging techniques can capture a hypermetabolism or oedema in the hemisphere contralateral to the aura symptoms which can later evolve in a hemicerebral atrophy (Indelicato et al. 2017; Pelzer et al. 2018b; Tashiro et al. 2014).

5 Spinocerebellar Ataxia Type 6: A Polyglutamine *CACNA1A* Disorder

SCA6 is caused by a pathologically expanded CAG repeat, coding for a polyglutamine stretch, at the C-terminus of *CACNA1A* (Zhuchenko et al. 1997). Normal alleles host up to 18 repeats, while disease causing alleles contain >19 repeats (19–33 repeats). As in other polyglutamine disorders, the length of the pathologically expanded allele is inversely correlated to the age at onset and the disease severity (Geschwind et al. 1997; Schols et al. 1998; Stevanin et al. 1997). Phenotypically, SCA6 resembles other polyglutamine-related spinocerebellar ataxias, by featuring a chronic progressive cerebellar syndrome with adult onset (Geschwind et al. 1997; Schols et al. 1998; Stevanin et al. 1997). Somehow differently from other SCAs, it presents with a pure cerebellar phenotype, without major features of brainstem or cerebral involvement, and it usually manifests later in life, in the fifth to sixth decade. Generally, the phenotype of SCA6 is milder than that of other SCAs, which usually also bear longer CAG-repeats. Natural history data revealed that the lifespan in SCA6 is not shortened (Jacobi et al. 2015). Differently from other SCAs and in line with its allelic disorders, SCA6 patients may display some marked clinical fluctuations at the beginning of disease, which sometimes resemble the paroxysmal ataxia episodes of EA2 (Jen et al. 1998).

From a pathophysiological point of view, SCA6 is not primary a channelopathy. Indeed, α1-subunits bearing expanded CAG do not seem to affect calcium currents (Giunti et al. 2015). Ten years ago, the research group of Gomez et al. discovered a novel internal ribosomal entry site at *CACNA1A* locus, implicating that gene encodes not only the α1-subunit, but also a second shorter protein, carrying the

CAG-expansion (Du et al. 2013). The newly described peptide α1ACT translocates in the nucleus, where it acts as transcription factor, regulating the expression of several genes with a pivotal role in neuronal growth (Du et al. 2019). Dysfunction of the polyglutamine-bearing α1ACT protein is thus believed to be the main driver of SCA6 pathophysiology.

6 Treatment Options in *CACNA1A* Disorders

The availability of effective pharmacological treatments makes *CACNA1A* disorders a not-to-be-missed diagnosis in the genetic work-up of suggestive clinical phenotypes. Despite the lack of controlled trials, cumulative reports and the clinical experience undoubtedly proved the effectiveness of several therapeutics in the prevention of disabling paroxysmal manifestations in FHM1 and EA2. Acetazolamide, aminopyridines, flunarizine and topiramate are drugs with an established effect as interval prophylaxis (Indelicato and Boesch 2021; Pelzer et al. 2013; Strupp et al. 2007). Up to date, no clear recommendations are available concerning the treatment of *CACNA1A* related epilepsy. Since seizures are also paroxysmal manifestations, an effect of the established effective prophylaxes could be assumed.

Over the time, paroxysmal manifestations subside, spontaneously or upon medical treatment, and chronic neurological symptoms, first of all gait ataxia, become the major burden of disease. Although the interval therapy does not have major impact on chronic balance disorder, it may still result in some stabilization, by smoothening clinical fluctuations. In this setting, rehabilitation represents the main long-term therapy. Neurodevelopmental and neuropsychiatric issues similarly await a targeted pharmacological treatment.

In the following paragraphs, we summarize the evidence supporting the application of several pharmacological treatments in *CACNA1A* disorders, address open issues and priorities for future clinical research.

6.1 Acetazolamide: A Serendipitous Discovery

In 1978, Griggs and colleagues reported on a large family with autosomal dominant inherited paroxysmal ataxia which displayed a dramatic response to a serendipitous trial of acetazolamide (Griggs et al. 1978). The confirmation of the dramatic effect of acetazolamide in following reports contributed to delineate the disease entity "acetazolamide-responsive paroxysmal ataxia" (Neufeld et al. 1996). This clinically defined disorder received its genetic allocation as EA2 after the description of *CACNA1A* mutations by Ophoff and colleagues.

Acetazolamide is a carbonic anhydrase inhibitor. Carbonic anhydrase catalyses the interconversion between water and carbon dioxide to carbonic acid, which in the body fluids solubilizes as hydrogen and bicarbonate ions. The inhibition of carbonic anhydrase in the kidney hampers the reabsorption of bicarbonate as well as of sodium and chloride, which goes along with excretion of water along with ions

resulting in a diuretic effect (2012). The consequence at a systemic level is a decrease in blood pressure, intracranial and intraocular pressures. Furthermore, bicarbonate excretion increases the pH of the blood as well as of the cerebrospinal fluid.

The clinical application of acetazolamide spans from the altitude sickness to glaucoma, intracranial hypertension to epilepsy (Van Berkel and Elefritz 2018). Up to date, the beneficial effect of acetazolamide in *CACNA1A* disorders is believed to directly derive from the pH alterations elicited by the drug. Earlier studies applying phosphorous magnetic resonance spectroscopy in small non-genetically confirmed cohorts revealed that pH in the cerebellum is higher in patients compared to controls and normalizes upon treatment with acetazolamide (Bain et al. 1992; Sappey-Marinier et al. 1999). Changes in extra- and intracellular pH influence the potassium currents as well as the opening of sodium and calcium channels and may thus mitigate the effect of an abnormal opening kinetics in the setting of *CACNA1A* mutations (Strupp et al. 2007). This positive effect is not restricted to P/Q channel mutations, as acetazolamide improves the manifestations of further ion channel disorders, such as hypokalemic periodic paralysis. Notably, the influence of pH fluctuations induced by acetazolamide may be more marked in the setting of a mutated ion channel than in the wild-type (Strupp et al. 2007).

Acetazolamide was primarily applied in EA2, but it has been also proven effective in the prevention of hemiplegic migraine (Battistini et al. 1999; Indelicato et al. 2017), as well as in the treatment of paroxysmal dizziness that predates chronic ataxia in SCA6 (Jen et al. 1998). Sparse reports suggested that acetazolamide may also mitigate some chronic features. Our recommendation is a trial of acetazolamide also in primary chronic courses, as a positive effect on fluctuations may also contribute to disease stabilization. In our clinical experience, acetazolamide contributed also to the stabilization of psychopathological status in *CACNA1A* patients with concomitant schizophrenia (Mechtcheriakov et al. 2003).

Several side effects limit the application of acetazolamide. The most frequent is represented by distal paraesthesia, a non-dangerous symptom that may however be bothersome for patients and lead to early withdrawal. In our clinical experience, paraesthesias are both an indicator of therapy compliance and of expected clinical benefit. Further side effects, probably induced by the metabolic acidosis, are fatigue, muscle stiffness, gastrointestinal disturbances as well as nephrolithiasis (Strupp et al. 2007). Shifts in blood electrolytes represent a caveat for treatment in older patients or in the setting of impaired renal function. Blood count alterations may also occur.

Up to very recent time, no randomized trials investigated the effect of acetazolamide in *CACNA1A* disorders. Despite this and the moderate tolerability, acetazolamide represents the first line therapy in the setting of paroxysmal symptoms due to *CACNA1A* mutations. The usual daily dosage ranges from 250 to 1,000 mg. In the clinical routine, a trial of acetazolamide is always performed in absence of contraindications. Clinical experience (personal observation as well as of Strupp et al. (2007)) shows that in some patients acetazolamide may lose efficacy over the time. In this case or in the setting of adverse events/contraindication, further pharmacological interventions are available (see Table 1).

Table 1 Established therapeutic compounds and their applications in *CACNA1A* disorder

Compound	Dosage	Mechanisms of action	Application
Acetazolamide	250–1,000 mg/daily	Carbon anhydrase inhibition	First line therapy for EA2, as well as prevention of paroxysmal manifestation in FHM1
4-aminopyridine	10–15 mg/daily	K^+ channel blocker	EA2, interictal nystagmus, episodic ataxia in other settings (e.g. SCA6)
Fampridine	20 mg/daily	K^+ channel blocker (prolonged-release form of 4-AP)	As 4-AP
Flunarizine	5–10 mg/daily	Ca^{2+} channel blocker	First line migraine prophylaxis in FHM1
Topiramate	50–100 mg/daily	Na^+ channel blocker, AMPA inhibition, GABA enhancer, weak carbonic anhydrase inhibition	Overlap phenotypes episodic ataxia/hemiplegic migraine as well as overlap with epileptic manifestations

6.2 Aminopyridines in the Treatment of Episodic Ataxia

Aminopyridines are potassium channel blockers which have been originally applied in the treatment of down-beat nystagmus (Strupp et al. 2003). The beneficial effect on nystagmus may derive from an increasing inhibitory firing of the Purkinje cells. An earlier report described a beneficial effect of 4-aminopyridines in two patients with EA2 who no longer responded to acetazolamide (Strupp et al. 2004). This observation was corroborated in an observational study (Strupp et al. 2004) as well as in a randomized, double-blind, placebo-controlled, crossover trial, comparing 4-aminopyridine with placebo (Strupp et al. 2011). Based on these data, a treatment with 4-aminopyridine 15 mg/die is recommended in patients with EA2. However, 4-aminopyridine is not licensed for other indications and its availability may be limited. Instead, the prolonged-release form fampridine (Fampyra, Biogen) holds an approval for the symptomatic treatment of gait disturbances in multiple sclerosis and has been recently investigated in a crossover trial versus acetazolamide and placebo in a group of patients with episodic ataxia with and without confirmed *CACNA1A* mutation (Muth et al. 2021). Fampridine was effective in reducing the number of attacks to 63% compared to placebo. In comparison, acetazolamide appeared to be likely more effective (reduction of attacks to 52%), though it was, as expected, far less well tolerated. Aminopyridines can be applied also to treat the interictal nystagmus, which in both EA2 and SCA6 patients may be highly disabling and contribute to balance disorder.

Concerning safety issues, aminopyridines may increase seizure risk and are contraindicated in the setting of prolonged QT interval as well as in renal insufficiency.

6.3 Migraine Prophylaxis in FHM1: Flunarizine, Topiramate and Other Compounds

FHM1 patients may experience severe migraine attacks. Especially in the setting of disorders of consciousness, the establishment of an effective prophylaxis is mandatory since there is no treatment available to arrest the aura.

The best characterized migraine prophylaxis in FHM1 is flunarizine (Karsan et al. 2018; Peer Mohamed et al. 2012). Flunarizine is a non-selective Ca^{2+} channel blocker which is approved also in the treatment of common migraine and has been proven to be safe and effective in children (Peer Mohamed et al. 2012). Experimental evidence suggests that blocking of Ca^{2+} and Na^{+} currents induced by flunarizine raises the threshold for the cortical spreading depression phenomenon underlying migraine (Eikermann-Haerter et al. 2012; Ye et al. 2011). Flunarizine may be particularly beneficial in the treatment of migraine with aura and several reports confirmed its effectiveness in FHM1 (Pelzer et al. 2013). The usual dosage is 10 mg daily. Common side effects include sedation as well as depressive mood and weight gain. Flunarizine also increases the risk of developing a pharmacologically induced parkinsonism after long-term use (Karsan et al. 2018). Considering this risk profile, evening schedule in the administration as well as caution in the treatment of specific patient group (elderly, known depression) should be paid.

Sparse reports highlight a relevant effect of the Ca^{2+} channel blocker verapamil in migraine with hemiplegic aura (Yu and Horowitz 2001; Yu and Horowitz 2003). Though, to the best of our knowledge, only one genetically confirmed FHM1 case with good response to verapamil is reported, notably with severe attacks induced by trivial trauma within an R1349Q mutation (Knierim et al. 2011).

As previously mentioned, acetazolamide is effective also in the prevention of migraine in FHM1 while this effect cannot be generalized to other forms of migraine (Vahedi et al. 2002). Interestingly, topiramate is also an established migraine prophylaxis which bears carbon anhydrase inhibition properties and has been reported to be effective in sparse reports in both FHM1 and EA2 (Gonzalez-Mingot et al. 2022; Indelicato et al. 2017). In the clinical experience of ours and others (Pelzer et al. 2013) topiramate is generally better tolerated in *CACNA1A* patients as in common migraineurs. Side effects of topiramate partly overlap with those of acetazolamide, due to clear overlapping mechanisms. Furthermore, topiramate may have central side effects such as impaired concentration, speech disorders and cognitive disturbances which are reversible upon drug withdrawal. Topiramate and to less extent acetazolamide also have an anorexiant effect which may be advantageous in the clinical practice.

Controversially, poor evidence is available for other classical migraine prophylaxes such as beta blockers (propranolol, metoprolol) (Pelzer et al. 2013). We personally used metoprolol with benefit as add-on prophylaxis in a patient experiencing severe hypertensive crisis concomitant to hemiplegic attacks (Indelicato et al. 2017). Reports from migraine with aura suggest a possible beneficial effect of valproate and lamotrigine (Pelzer et al. 2013), which could be used as reserve treatments in the setting of specific comorbidities such as epilepsy.

6.4 The Treatment of *CACNA1A* Related Epilepsy: Where Do We Stand?

Data on therapy of *CACNA1A* related epilepsy are controversial and systematic analysis are lacking. Generally, early-onset severe phenotypes present with the stigmata of a therapy refractory epilepsy, while later onset epileptic syndromes appear to be prone to a good seizure control upon classical antiepileptic drugs (AED) (Le Roux et al. 2021; Niu et al. 2022; Verriello et al. 2021).

Interestingly, acetazolamide bears also anticonvulsive properties and in the past it was applied in the treatment of catamenial aggravation of epilepsy (Lim et al. 2001). The pharmacodynamically related drug topiramate is an approved AED. Interestingly, recent findings point towards a favourable response to topiramate in *CACNA1A* related epilepsy (Le Roux et al. 2021). Zhang et al. reported three seizure free children after adding up topiramate to AED polytherapy (Zhang et al. 2020). Le Roux et al. similarly reported that add-on therapy with topiramate reduced seizure frequency in eight out of nine patients (one patient seizure free after topiramate) (Le Roux et al. 2021). In the latter study, acetazolamide was less effective than topiramate in seizure control. Contrasting findings have been reported for levetiracetam (Le Roux et al. 2021). Finally, additional therapy with valproate has been described to be beneficial both in epilepsy and migraine (Niu et al. 2022; Pelzer et al. 2013; Zhang et al. 2020). In the same report of Le Roux (Le Roux et al. 2021), ketogenic diet resulted in clinical improvement in one out of four patients; vagus nerve stimulation yielded no benefit in four implanted patients. The singular description of a "dramatic" improvement of therapy resistant absence seizure to pyridoxine in one child (Du et al. 2017) was not replied up to now in further reports. Finally, cumulative literature suggest that seizure may spontaneously improve over the time independently from AED administration (Indelicato et al. 2021b).

6.5 Acute Treatment of EA2 and FHM1 Spells

Up to date, no specific treatment is available which effectively abates ataxia or hemiplegic migraine spells. One single report described abating aura manifestations upon administration of intranasal ketamine (Kaube et al. 2000). The mechanism of action is unclear and this finding has not been replicated. Therefore, and considering the safety profile of ketamine, its application is not recommended. In the acute treatment of severe hemiplegic attacks with brain oedema, an empirical symptomatic management with corticosteroid or hypertonic saline should be considered. The treatment of the migraine related headache relies on the same therapeutics available for common migraine, with a controversial caveat for triptans. Since triptans are powerful vasoconstricting agents, their application in FHM was believed to possibly aggravate neurological deficits and leading to migrainous strokes. Currently, the US Food and Drug Administration approved package labelling states that triptans are

contraindicated in patients with hemiplegic migraine. Some retrospective case series showed a safe profile for triptans in the treatment of hemiplegic migraine (Artto et al. 2007; Mathew et al. 2016). In our clinical practice, we do not apply triptans in FHM1.

7 Conclusion and Future Directions

Advancements in clinical research in *CACNA1A* disorders are gaining a faster pace. The recent creation of consortia of clinicians and patients advocacy representatives in Europe and North America is further contributing to these developments. These advancements bring along relevant implications for the clinical routine and set priorities for the future lines of research.

In the clinical routine, the achievement of a genetic diagnosis in case of paroxysmal or hemiplegic manifestation should become mandatory to stratify carriers with severe mutations, rule out differential diagnosis (such as *PRRT2*, *ATP1A2*, etc.) and guide the choice of an interval prophylaxis. Furthermore, we recommend the introduction of regular cognitive and behavioural testing with standardized instruments to detect and address the often neglected non-motor symptoms of *CACNA1A* disorders.

CACNA1A disease spectrum is manifold and evolves over the time. Paediatricians and adult neurologists deal only with a limited side of it. Efforts should be made to develop clinical registers for the collection of longitudinal data to guide rigorous clinical and treatment follow-up and establish valid diagnostic and therapeutic algorithms. In turn, this will translate in an optimized management transition from child to adult neurology. Natural history studies will also help us understanding the response of further symptoms, such as epilepsy, to available pharmacological therapy as well as elucidating their impact on cognitive and motor development.

Understanding how the phenotype evolves across life will be pivotal in directing basic research in the quest for underlying pathophysiological mechanisms. Longstanding efforts in the SCA6 research culminated in the seminal discovery of the bicistronic nature of *CACNA1A* and set the target for the development of oriented therapeutic intervention (Pastor et al. 2018). Such a key mechanism is still to be unveiled in paroxysmal *CACNA1A* disorders. The definition of suitable experimental models, for example induced pluripotent stem cells derived systems, represents the first essential step towards this target (Bavassano et al. 2017).

Future advancements in clinical and basic research will bridge the gaps in our scattered knowledge on *CACNA1A* disorders and ameliorate the management and outcome of these still underdiagnosed clinical entities.

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