Review

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Channels out of Order: A Review of Central and Peripheral Nervous System Channelopathies

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A vast range of neurological conditions impacting the central and peripheral nervous system are caused by ion channel dysfunctions, which are collectively referred to as channelopathies. These disorders, which are frequently autoimmune or genetic in nature, present as a variety of clinical syndromes, such as migraine, epilepsy, ataxia, neuropathic pain, and intermittent paralysis. The pathogenic mechanisms underlying these illnesses have been uncovered by recent developments in molecular genetics and electrophysiological research, opening up new avenues for accurate diagnosis and specialized treatment approaches. With an emphasis on important genetic variations and clinical manifestations, this study offers a targeted synthesis of channelopathies of the central and peripheral nervous system. By providing the most recent information on these complex disorders, this review aims to help physicians identify and treat channelopathies.

Keywords: channelopathies; transmembrane glycoproteins; ion channels; central nervous system; peripheral nervous system

Introduction

Neurological channelopathies constitute a diverse array of illnesses affecting the Central and Peripheral Nervous System (CNS and PNS), resulting from dysfunctions of ion channels in neuronal membranes, neuromuscular junctions and muscle membranes [1]. Ion channels are a group of transmembrane glycoproteins made up of different subunits that permit the movement of ions across cell membranes. Within CNS and PNS, they are essential for synaptic transmission and neuronal excitability (Fig. 1).

Ion channels are categorized as voltage-gated or ligand-gated channels, based on their ion specificity or gating mechanism [1]. Accordingly, channelopathies can be classified according to the type of channel affected (i.e., sodium channelopathies, potassium channelopathy, etc.) or to the specific area of the nervous system involved, since mutations of the same channel may result in different clinical phenotypes [2]. Neurological channelopathies are often genetically inherited, though they may also arise from acquired causes. Inherited channelopathies generally cause paroxysmal neurological symptoms that manifest throughout childhood or adolescence. Acquired neurological channelopathies, in contrast, manifest later in life and have several etiologies, with autoimmune illnesses being the most prevalent [3]. Our knowledge of the pathophysiology of these syndromes has increased as a result of the discovery of several pathogenic variations behind them, thanks to developments in molecular genetics [4]. Notwithstanding these advancements, nervous system channelopathies are still underdiagnosed. This fact depends on different aspects: genetic heterogeneity, phenotypic variety, infrequent occurrence of the diseases, presence of difficult-to-describe symptoms, and diverse ages of onset. Furthermore, knowledge of these rare syndromes is often prerogative of highly specialized centers only, resulting in diagnostic delays and inadequate treatment.

We performed an extensive literature review utilizing PubMed, Scopus, and Web of Science to identify pertinent English-language publications regarding CNS and PNS hereditary channelopathies. Search criteria encompassed 'neurological hereditary channelopathies', 'ion

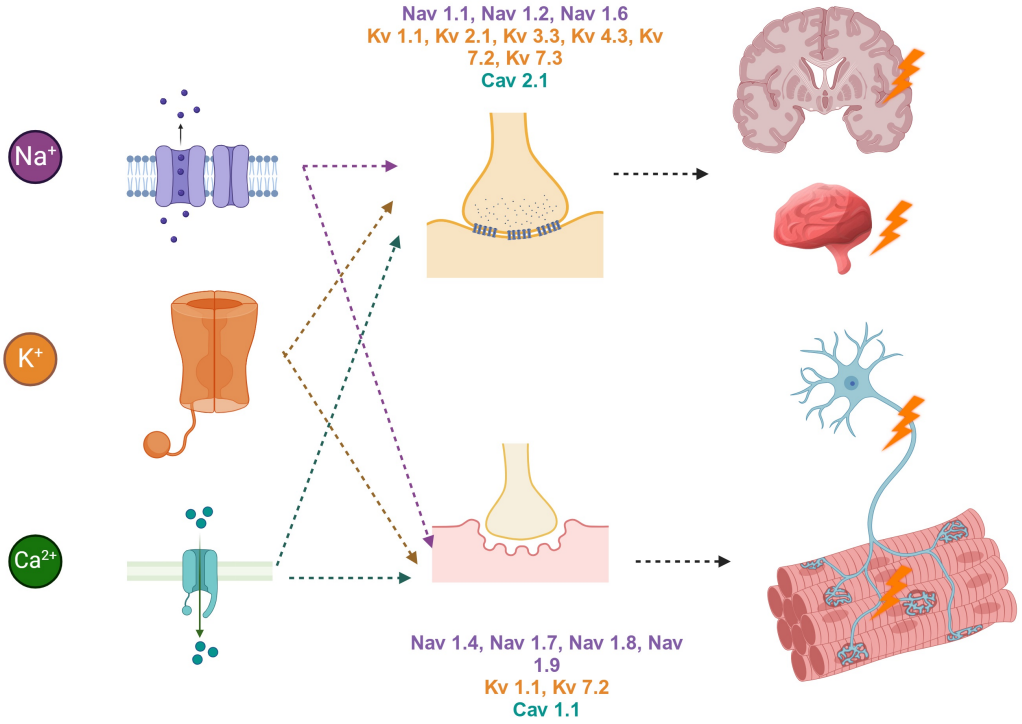

Fig. 1. Main ion channels and their distribution within central and peripheral nervous system (created in BioRender. https://www.biorender.com/).

channel mutations', 'epilepsy channelopathies', 'peripheral nerves channelopathies' and 'skeletal muscle channelopathies'. With a focus on clinical manifestations and genetic foundations, this review offers a thorough summary of hereditary channelopathies. Our goal is to provide researchers and clinicians with the knowledge they need to suspect and more accurately diagnose and treat these complex conditions.

Inherited Channelopathies of the CNS

Epileptic Syndromes

Several hereditary channel disorders of voltage-gated and ligand-gated ion channels may cause epileptic syndromes. A synthesis of principal voltage-gated ion channels and related epilepsies is reported in Table 1 (Ref. [4–18]).

Voltage-gated sodium channels (VGSCs or Nav channels), particularly involved in the pathogenesis of different types of epilepsies, are heteromeric complexes consisting of a core pore-forming alpha subunit and two smaller auxiliary beta subunits. A gene family located on chromosome 2 encodes several isoforms of the alpha subunit (Nav1.1–Nav1.9) [4,5]. Sodium voltage-gated channel alpha subunit 1 (*SCN1A*) gene encodes the alpha 1 subunit (Nav1.1) and epilepsies resulting from pathogenic variations of *SCN1A* display a distinctive feature: susceptibility to fever. Missense mutations of *SCN1A*, exhibiting both gain-of-function (GOF) and loss-of-function (LOF) effects, have been documented in generalized epilepsy with febrile seizures plus (GEFS+) [4]. On the other hand, many heterozygous *SCN1A* variants, including truncating mutations, splice-site mutations, frameshift intragenic deletions or gene duplications, and missense mutations affecting the pore-forming region of the protein, cause Dravet Syndrome (DS) [5], a developmental and epileptic encephalopathy (DEE). GEFS+ is an autosomal dominant (AD) condition characterized by febrile seizures that continue beyond the age of six, as well as focal or generalized seizures, while maintaining normal cognitive function [4]. DS, instead, is characterized by seizures and various neurological manifestations. Subjects are healthy at birth; by 5 to 8 months of age, they abruptly experience febrile seizures that are predominantly unilateral and protracted, frequently resulting in status epilepticus [6]. Following this, both febrile and afebrile seizures with diverse semiology (generalized tonic-clonic, alternating unilateral clonic, focal with reduced awareness, short myoclonic, tonic seizures, and myoclonic status epilepticus) manifest, accompanied by developmental delay [6]. Seizures are generally precipitated by elevated body temperature, resulting from fever, warm baths, physical exertion, or high ambient temperatures [19,20]. Sodium channel-blocking anti-seizure medications (ASMs) can also induce seizures, as the underlying mutations frequently lead to a LOF [19,20]. Post five years of age, epilepsy generally exhibits improvement alongside the stabilization of cognitive functioning and behavior [6].

Table 1. Voltage-gated ion channels and epilepsy.

Gene involved	Channel	Type of epilepsy
SCN1A	Nav1.1	Generalized epilepsy with febrile seizures plus [4] Dravet syndrome [5,6]
SCN2A	Nav1.2	Benign familial neonatal-infantile seizures [4] Developmental and epileptic encephalopathy [7,8]
SCN8A	Nav1.6	Familial benign infantile seizures [9] Developmental and epileptic encephalopathy [10]
KCNQ2 ***KCNQ3***	Kv7.2 Kv7.3	Familial benign neonatal seizures [4] Self-limited familial infantile epilepsy [4] Early onset encephalopathy [11,12]
KCNMA1	KCa1.1	Early onset absences [13]
KCNB1	Kv2.1	Developmental and epileptic encephalopathy [14]
KCNJ11	Kir6.2	Developmental and epileptic encephalopathy [15]
HCN1	HCN1	Febrile seizure [16] Generalized epilepsy with febrile seizures [16] Generalized epilepsy [16] Developmental and epileptic encephalopathy [16]
CACNA1A	Cav2.1	Childhood absence epilepsy [17] Other types of focal and generalized epilepsies [17,18]

CACNA1A, calcium voltage-gated channel subunit alpha1 A; *HCN1*, potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1; KCa1.1, calcium-activated potassium channel subunit alpha 1; *KCNB1*, potassium voltage-gated channel subfamily B member 1; *KCNMA1*, potassium calcium-activated channel subfamily M alpha 1; *KCNQ2*, potassium voltage-gated channel subfamily Q member 2; *KCNQ3*, potassium voltage-gated channel subfamily Q member 3; *KCNJ11*, potassium inwardly rectifying channel subfamily J member 11; Kir6.2, subunit of the ATP-sensitive potassium channel; Kv, "proper" voltage-gated potassium channels; Nav, voltage-gated sodium channel; *SCN1A*, sodium voltage-gated channel alpha subunit 1; *SCN2A*, sodium voltage-gated channel alpha subunit 2; *SCN8A*, sodium voltage-gated channel alpha subunit 8.

In adulthood, seizures evolve: they exhibit reduced temperature sensitivity and are predominantly characterized by generalized (tonic-clonic and tonic) seizures occurring during sleep. Adults with DS present cerebellar manifestations (ataxia, dysarthria, and purposeful tremor) and extrapyramidal signs [21]. More recently, GOF *SCN1A* mutations have been described in a broad range of DEE, affecting newborns and children, the former being characterized by associated movement disorders and arthrogryposis. Most of these individuals, unlike those with the "classical" DS phenotype, exhibit responsiveness to sodium channel-blocking ASMs [21]. Sodium voltage-gated channel alpha subunit 2 (*SCN2A*) gene encodes the Nav1.2 channel and its mutations with predominant GOF effects are responsible for benign familial neonatal-infantile seizures (BFNIS), a self-limiting epilepsy that commences in early infancy and is associated with a positive cognitive prognosis. Nonetheless, *de novo SCN2A* mutations have also been reported in DEE accompanied by cognitive decline and autistic characteristics. In many instances, seizures manifest later in childhood [7,8]. Finally, the sodium voltage-gated channel alpha subunit 8 (*SCN8A*) gene encodes the Nav1.6 channel and its mutations are linked to AD familial benign infantile seizures and other kinds of DEE. Familial benign infantile seizures are defined by self-limiting focal and generalized seizures, with normal neurodevelopment in nearly all instances [9]. *SCN8A*-related encephalopathy, instead, is characterized by developmental delay and drug-resistant heterogeneous seizures, including focal, tonic with autonomic symptoms, clonic, myoclonic seizures, absences, and epileptic spasms [10].

Voltage-gated potassium channels (VGKCs) are classified into four distinct types based on their structure and kinetics: "proper" voltage-gated potassium channels (Kv), calcium-activated potassium channels, potassium inwardly rectifying (Kir) channels, and tandem pore domain channels [22]. Pathogenic variants of the potassium voltage-gated channel subfamily Q member 2 (*KCNQ2*) and potassium voltage-gated channel subfamily Q member 3 (*KCNQ3*) genes, situated on chromosomes 20q13.3 and 8q24 respectively, are accountable for the bulk of potassium channelopathies. AD benign familial neonatal-infantile seizures are a benign disorder caused by diverse mutations in the *KCNQ2* and *KCNQ3* genes. Seizures commence between 2 to 8 days of life and resolve spontaneously within 12 months. Seizure types encompass tonic or apneic episodes and focal clonic seizures, with or without autonomic alterations. Motor manifestations may be local-

ized to a single body part, shift to several areas, or become generalized. Infants exhibit normalcy between seizures, and their neurodevelopment is ordinary [4]. Mutations in *KCNQ3* are related also to self-limited familial infantile epilepsy (SLFIE), characterized by seizures that commence within the first year of life and resolve by the ages of one to two years. Seizures are typically short, lasting two minutes, and manifest as daily recurring clusters. They are typically focal but may also present as widespread, resulting in diffuse hypertonia accompanied by limb jerks, head deviation, or motor cessation with unconsciousness and cyanosis. Psychomotor development is typically unremarkable. Furthermore, drug-resistant epilepsy and intellectual deficits have been reported in families with mutations in *KCNQ2* and *KCNQ3* [11,12]. Mutations in potassium calcium-activated channel subfamily M alpha 1 (*KCNMA1*) are implicated with early onset absences and paroxysmal non-kinesigenic dyskinesia [13]. Finally, pathogenic variants in the potassium voltage-gated channel subfamily B member (*KCNB1*) gene, which encodes the principal delayed rectifier and voltage-gated potassium channel of the hippocampus and cortex (Kv2.1), result in a phenotypic *spectrum* that encompasses non-syndromic intellectual disability and an encephalopathy characterized by spasms, severe developmental delay, autism *spectrum* disorder, and chronic drug-resistant epilepsy [14]. Additionally, *de novo* pathogenic mutations in potassium inwardly rectifying channel subfamily J member 11 (*KCNJ11*) of the inwardly rectifying subunit of the ATP-sensitive potassium channel (Kir6.2) channel have been linked to seizures and intellectual impairment in individuals with neonatal diabetes mellitus [15].

Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1 (HCN1), encoded by the *HCN1* gene, is permeable to potassium and, to a lesser degree, sodium, and contributes to the native pacemaker currents in the heart and neurons. Mutations in HCN1 have been described in most familial cases and over 40% of sporadic mutations result in febrile seizures, generalized epilepsy with febrile seizures, and drug-responsive idiopathic generalized epilepsies with normal or borderline cognitive abilities. Rare neonatal and infantile DEEs have also been associated with *HCN1* mutations [16].

The last family of ion voltage-gated channels causing epilepsy are **voltage-gated calcium channels**. They are classified as high voltage-activated channels (HVA) and low voltage-activated channels (LVA) [23], and regulate the influx of calcium ions, which are essential for modulating gene transcription, neurotransmitter release, enzyme function, and neurite outgrowth. The HVA calcium voltage-gated channel subunit alpha1 A (Cav2.1) channel, expressed by the calcium voltage-gated channel subunit alpha1 A (*CACNA1A*) gene, is mostly associated with neurological symptoms, including epilepsy, ataxia, and migraine. LOF mutations of *CACNA1A* have been identified in childhood absences epilepsy and episodic ataxia type 2 [17]. Severe neurological manifestations of encephalopathies have been described in cases of missense and biallelic mutations of the *CACNA1A* gene [18].

Considering ligand-gated ion channels, mutations in genes encoding for N-methyl-D-aspartate receptor (NMDAR), gamma-aminobutyric acid receptors (GABARs), nicotinic acetylcholine receptor (nAChR), and leucine-rich glioma inactivated protein 1 (LGI1) is now gaining recognition in different types of epilepsy.

Main ligand-gated ion channels and their related types of epilepsies are summarized in Table 2 (Ref. [24–28]).

NMDAR consists of two glycine-binding NR1 subunits and two glutamate-binding NR2 subunits. There are four NR2 gene products, NR2A-NR2D. NR2A subunits are encoded by the glutamate ionotropic receptor NMDA type subunit 2A (*GRIN2A*) gene, situated on chromosome 16. The phenotypic *spectrum* of *GRIN2A* mutations is diverse, resulting in isolated intellectual impairment, focal epilepsy, or epileptic encephalopathies. Language impairments are characteristic of *GRIN2A* mutations, with over 90% of people exhibiting speech difficulties, that encompass speech disorders without seizures and the epileptic aphasia *spectrum* (Landau-Kleffner syndrome and epilepsy characterized by persistent spikes and waves during slow sleep) [24]. Persistent spikes and waves during sleep enhance developmental and behavioral disturbances, thus medical intervention with benzodiazepines and corticosteroids aims at resolving this sustained epileptic activity [4]. Levetiracetam and valproic acid are among the most often utilized ASMs for patients with *GRIN2A*-related epilepsy. Also, the ketogenic diet and acetazolamide have been reported to be effective. Literature provides evidence for the utilization of memantine in seizure management. NR2B is encoded by the glutamate ionotropic receptor NMDA type subunit 2B (*GRIN2B*) gene, located on chromosome 12. Mutations in *GRIN2B* have been documented in individuals with intellectual disability and several neuropsychiatric illnesses. Epilepsy does not appear to be a prevalent characteristic of *GRIN2B* pathogenic variations; nonetheless, *GRIN2B* mutations with GOF effects have been linked to West syndrome and childhood-onset focal epilepsy, accompanied by cognitive deficits that vary according to the extent of channel malfunction [25].

Other ligand-gated ion channels causing epilepsy are **GABA-A receptors**. Mutations impacting GABA receptors, particularly those encoded by the gamma-aminobutyric acid type A receptor subunit alpha 1 (*GABRA1*) gene, are implicated in idiopathic generalized epilepsies (childhood absences epilepsy and juvenile myoclonic epilepsy) and DEEs, including Ohtahara syndrome and myoclonic-astatic epilepsy [26,29,30]. Most variations in the GABA-A receptor genes have an AD inheritance pattern.

Table 2. Ligand-gated ion channels and epilepsy.

Gene involved	Ligand-gated ion channel	Type of epilepsy
GRIN2A	NMDAR	Epileptic aphasia *spectrum* [24]
GRIN2B	NMDAR	West syndrome [25] Childhood-onset focal epilepsy with cognitive deficit [25]
GABRA1	GABAR	Genetic generalized epilepsies (childhood absence and juvenile myoclonic epilepsy) [26] Developmental and epileptic encephalopathies [26]
CHRNA2 ***CHRNA4*** ***CHRNB2***	nAChR	Sleep-related hyper motor epilepsy *spectrum* [27]
LGI1	LGI1	Epilepsy with auditory features *spectrum* [28]

CHRNA2, cholinergic receptor nicotinic alpha 2 subunit; *CHRNA4*, cholinergic receptor nicotinic alpha 4 subunit; *CHRNB2*, cholinergic receptor nicotinic beta 2 subunit; GABAR, gamma-aminobutyric acid receptor; *GABRA1*, gamma-aminobutyric acid type A receptor subunit alpha 1; *GRIN2A*, glutamate ionotropic receptor NMDA type subunit 2A; *GRIN2B*, glutamate ionotropic receptor NMDA type subunit 2B; *LGI1*, leucine-rich glioma inactivated protein 1; NMDAR, N-methyl-D-aspartate receptor; nAChR, nicotinic acetylcholine receptor.

The **nAChR** is implicated in the pathogenesis of a particular epilepsy formerly referred to as AD nocturnal frontal lobe epilepsy (ADNFLE), now included within the *spectrum* of sleep-related hyper-motor epilepsy (SHE). SHE is defined by repetitive, frequent, and short seizures that occur during non-REM sleep. Seizure semiology includes hyperkinetic or tonic seizures, paroxysmal arousals, dystonia-like episodes, and epileptic nocturnal wanderings, depending upon the localization of the epileptogenic zone [27]. SHE often commences in infancy and adolescence, although adult onset has also been documented; it profoundly impacts the quality of life, constituting a lifelong condition that is often resistant to pharmacological treatment. The underlying etiology is heterogeneous; GOF and, to a lesser extent, LOF mutations in genes that encode the alpha and beta subunits of the nAChR (cholinergic receptor nicotinic alpha 2 subunit (*CHRNA2*), cholinergic receptor nicotinic alpha 4 subunit (*CHRNA4*), cholinergic receptor nicotinic beta 2 subunit (*CHRNB2*) are responsible for hereditary types of SHE [27].

Finally, epilepsies related to mutations in **LGI1**, a component of a synaptic protein complex associated with presynaptic VGKC and postsynaptic α-Ammino-3-idrossi-5-Metil-4-isossazol-Propionic Acid (AMPA) receptors [31], are noteworthy for their specific clinical features. The *LGI1* gene, situated on chromosome 10q24, is implicated in the downregulation associated with glioblastoma oncogenesis [28,32]. Mutations in the *LGI1* gene, including truncating mutations and microdeletions leading to LOF, are implicated in epilepsy with auditory features (EAF). EAF may be familial and inherited with AD pattern or sporadic, with no notable variations in clinical presentation. Seizures originate in the lateral temporal cortex and are distinguished by simple or complex auditory hallucinations or aphasia (including both receptive and global aphasia), rapid onset of decreased awareness, and the potential progression to focal or bilateral tonic-clonic seizures [28].

Cerebellar Disorders

Channel mutations can result in two separate phenotypes of cerebellar dysfunction: a chronic, gradually progressing ataxia or a paroxysmal variant (episodic ataxia (EA)), despite potential clinical overlap (Table 3, Ref. [33–38]).

Spinocerebellar ataxias (SCA) constitute a diverse collection of AD degenerative illnesses. Among the 50 acknowledged entities, SCA6, SCA13, SCA19/22, and SCA42 are attributable to ion channel dysfunctions [39]. SCA6 is caused by 20 to 33 CAG repeat expansions in the *CACNA1A* gene [33]. It is characterized by a gradually progressing cerebellar ataxia that manifests in adulthood, occasionally as late as the seventh decade of life. It may include several additional manifestations, such as pyramidal symptoms (40–50%) or dystonia/blepharospasm (up to 25%) [39]. SCA13 results from dominant LOF or GOF mutations in the *KCN3* gene, which encodes the voltage-gated potassium channel Kv3.3 [40]. Three phenotypes exist based on the age of onset: (1) congenital cerebellar hypoplasia characterized by static trunk and limb ataxia, developmental delay with or without seizures, and behavioral disturbances; (2) slowly progressive ataxia associated with learning disabilities commencing in early childhood; (3) adult-onset ataxic-spastic syndrome [34]. SCA 19/22 are due to mutations in potassium voltage-gated channel subfamily D member 3 (*KCND3*), which encodes the voltage-gated potassium channel Kv4.3. The onset of symptoms occurs during the second and seventh decades of life. SCA19/22 often manifests as a pure slowly progressing cerebellar ataxia; however, certain instances may have pyramidal symptoms and urinary dysfunction [35]. SCA42 results from mutations in calcium voltage-gated channel subunit alpha 1 G (*CACNA1G*), which encodes the T-type voltage-gated calcium channel (Cav3.1). The characteristics resemble those of SCA19/22, along with its varied on-

Table 3. Inherited channelopathies causing cerebellar disorders.

Gene involved	Channel	Cerebellar disorders	Clinical features
CACNA1A	Cav2.1	SCA 6	Progressive cerebellar ataxia that manifests in adulthood [33]
KCNC3	Kv3.3	SCA 13	Congenital cerebellar hypoplasia [34] Slowly progressive ataxia associated with learning disabilities [34] Adult-onset ataxic-spastic syndrome [34]
KCND3	Kv4.3	SCA 19/22	Slowly progressive cerebellar ataxia [35]
CACNA1G	Cav3.1	SCA 42	Slowly progressive cerebellar ataxia [36]
KCNA1	Kv1.1	EA1	Episodic ataxia [37]
CACNA1A	Cav2.1	EA2	Episodic ataxia, interictal nystagmus [38]

CACNA1A, calcium voltage-gated channel subunit alpha1 A; *CACNA1G*, calcium voltage-gated channel subunit alpha 1 G; EA1, episodic ataxia type 1; EA2, episodic ataxia type 2; *KCNA1*, potassium voltage-gated channel subfamily A member 1; *KCNC3*, potassium voltage-gated channel subfamily C member 3; *KCND3*, potassium voltage-gated channel subfamily D member 3; SCA, spinocerebellar ataxia.

set [36]. No pharmaceutical therapies are presently available for progressive ataxias.

EA comprises AD disorders characterized by recurrent episodes of cerebellar impairment and vertigo, varying in frequency and duration. Episodic ataxia type 1 (EA1) and episodic ataxia type 2 (EA2) represent the predominant forms and the onset typically occurs prior to the age of 10. EA1 is induced by mutations in potassium voltage-gated channel subfamily A member 1 (*KCNA1*), which encodes the rapid voltage-gated potassium channel (Kv1.1) [37]. Attacks are short and typically mild, enduring from seconds to minutes [41]. They may occur spontaneously or be triggered by abrupt movements or startling stimuli. Peripheral nerve hyperexcitability coexists in over 80% of patients [42]. Mild persistent ataxia and cerebellar atrophy may progress over time [43]. EA2 is the predominant variant of EA. It is subordinate to LOF mutations of *CACNA1A*. Attacks are prolonged compared to EA1 instances. Patients may report weakness during episodes and interictal nystagmus is consistently observed [38,43]. Other exceedingly rare channelopathies causing EA exist [44,45]. Acetazolamide is efficacious in EA [43,45] and favorable outcomes in EA1 have also been shown with sodium channel antagonists, including carbamazepine, lamotrigine, and phenytoin [43]. Fampridine and 4-aminopyridine serve as alternative medications in EA2 [46].

Familial Hemiplegic Migraine (FHM)

FHM is a subtype of migraine with aura, distinguished by headache accompanied by entirely reversible visual, sensory, and verbal symptoms, as well as transitory motor weakness. Motor symptoms may exceed the length of the headache and last for beyond 72 hours. Features of FHM include confusion or reduced consciousness, which can range from drowsiness to coma, accompanied by brain edema. Head trauma may trigger attacks [47]. Hemiplegic migraine is classified as familial if at least one first- or second-degree relative experiences comparable occurrences. The inheritance pattern is AD, however, *de novo* mutations have been documented [47]. The start of FHM often occurs within the first two decades of life. The frequency exhibits significant variability and tends to diminish with advancing age. Despite the identification of numerous genes, up to 80% of cases remain etiologically unresolved. The predominant variant of FHM is secondary to *CACNA1A* mutations (FHM1), accounting for 10–15% of cases. Forty to fifty percent of *CACNA1A* cases have interictal cerebellar symptoms and may experience gradually developing ataxia during their lifetime [48]. Another ionic channel implicated in FHM is *SCN1A* (FHM3), although it constitutes less than 1% of subjects [48,49]. Patients with FHM3 may experience paroxysmal blindness, which can occur spontaneously or be triggered by eye rubbing [50]. All FHM-inducing mutations are GOF and modify the channel's kinetics. Acetazolamide is the preferred medication for FHM1 [51], while *SCN1A*-related illnesses are often managed with sodium channel blockers, such as carbamazepine or lamotrigine [49].

Paroxysmal Movement Disorders

Two variants of age-restricted paroxysmal dystonia have been identified in *CACNA1A* lineages: benign paroxysmal torticollis of infancy (BPTI) and paroxysmal tonic upward gaze (PTU). BPTI usually occurs sporadically, however some families with AD inheritance have been reported. It comprises periods of cervical dystonia lasting several days (often hours), sometimes accompanied by ataxia and emesis. BTPI commences in infancy and resolves before the age of five. Learning disabilities or migraine have been documented [51]. PTU exhibits both AD and autosomal recessive (AR) inheritance. Attacks are characterized by a tonic upward deviation of the eyes, accompanied by neck flexion and occasionally incoordination. The duration of the episodes varies from minutes to hours. The onset typically occurs within the first year of life. Ataxia, epilepsy, or developmental delay may occur

following the cessation of PTU [52,53]. At present, there is no efficacious medication accessible.

Inherited Channelopathies of the PNS

Channelopathies of Peripheral Nerves

Inherited channelopathies of peripheral nerves include: primary erythromelalgia, paroxysmal extreme pain disorder, congenital insensitivity to pain, small fiber neuropathy, familial episodic pain syndrome, neuropathies due to mutation in transient receptor potential cation channel subfamily V member 4 (TRPV4) receptor and peripheral nerve hyperexcitability syndrome. Table 4 (Ref. [54–64]) summarizes clinical and genetic features of channelopathies causing peripheral neuropathies.

Primary erythromelalgia (PE) is an uncommon AD neuropathy associated with mutations in the sodium voltage-gated channel alpha subunit 9 (*SCN9A*) gene (sodium channel Nav1.7) [54]. It is marked by recurring episodes of bilateral burning pain, erythema, warmth, and occasionally edema in the distal extremities. Symptoms are generally elicited by heat or physical exertion and tend to ameliorate with cooling. This illness typically presents in early childhood, with pain primarily affecting the lower or upper extremities, but the face and ears may be involved in rare instances. Pain frequently commences as an itching feeling and escalates to intense searing pain, enduring from a few minutes to several days. Managing PE-related pain is complex and frequently necessitates a mix of pharmacological agents, including selective serotonin reuptake inhibitors, ASMs, calcium channel blockers, and tricyclic antidepressants. Mexiletine, a non-selective sodium channel antagonist, has been documented to be useful in certain instances of PE [65].

Paroxysmal Extreme Pain Disorder (PEPD) is an uncommon AD neuropathy resulting from a mutation in the *SCN9A* gene. Clinically, it is characterized by early onset, frequently occurring in the neonatal or infant phases. It is marked by autonomic symptoms, including skin flushing, patchy color alterations, stiffening, syncope, and bradycardia. As the condition advances, bouts of severe searing pain in the rectal, ophthalmic, or submandibular regions manifest, frequently accompanied by flushing. These episodes may be induced by perineal wiping, eating, sobbing, or temperature variations, and can persist for a duration ranging from a few seconds to two hours [55]. Carbamazepine has demonstrated the highest efficacy in treatment, alleviating both the frequency and intensity of episodes.

Congenital Insensitivity to Pain (CIP) is an exceedingly rare genetic disorder with an AR inheritance pattern, resulting from mutations in the *SCN9A* gene. It is defined by a total inability to experience pain and temperature from birth, along with anosmia [56]. Another gene implicated in pain insensitivity is sodium voltage-gated channel alpha subunit 11 (*SCN11A*), which encodes the Nav1.9 channel, responsible for modulating the excitability of nociceptors to incoming stimuli. *De novo* mutations exhibiting an AD pattern have been identified in the *SCN11A* gene. Individuals with *SCN11A*-related CIP also exhibit gastrointestinal hypomotility and hypotonia [56].

Small Fiber Neuropathy (SFN) is a condition that impacts tiny nerve fibers, leading to neuropathic pain, thermal dysfunction, and autonomic abnormalities. Although some instances of SFN are attributable to immunological or metabolic disorders, the etiology remains unidentified in approximately 50% of patients [66]. Genetic factors are becoming progressively recognized, with up to 16.7% of SFN cases associated with abnormalities in sodium channel genes [67]. Genetic SFN is inherited in an AD pattern. Sodium channel-related SFN may manifest in childhood or maturity, with instances of both sporadic and familial cases documented. A prevalent manifestation is searing discomfort in the feet, although distinct mutations may result in varied symptoms [68]. Variants of *SCN9A*, associated with 5.1% of cases, generally lead to burning pain in the extremities, exacerbated by heat, accompanied by autonomic symptoms. GOF mutations in sodium voltage-gated channel alpha subunit 10 (*SCN10A*) (which encodes Nav1.8) and *SCN11A* are identified in 3.7% and 2.9% of SFN patients, respectively [57,58]. Gabapentinoids, sodium channel blockers, and antidepressants are frequently employed for neuropathic pain; nonetheless, their effectiveness is generally constrained [69]. In 2019, a clinical trial evaluated lacosamide in individuals with *SCN9A* mutations, demonstrating a notable pain reduction in patients with SFN [70].

Familial Episodic Pain Syndrome (FEPS) is a genetic condition exhibiting AD inheritance, characterized by recurring episodic pain predominantly affecting the distal lower extremities and, in certain instances, the upper extremities. Pain episodes may be induced by variables including exhaustion, cold temperatures, fasting, fluctuations in weather, and physical effort. FEPS has been categorized into three types, according to the impacted gene. FEPS1 is associated with mutations in the gene that encodes transient receptor potential cation channel subfamily A member 1 (*TRPA1*) located in small-diameter C- or Aδ-fibers of sensory, trigeminal, and dorsal root ganglia. This mutation has been identified in a Colombian family including 21 afflicted individuals [59]. Episodes commence in infancy, characterized by pain attacks induced by stimuli such as cold or effort, lasting roughly 1.5 hours. FEPS2 is linked to mutations in the *SCN10A* gene, with merely three occurrences documented across two families [60]. Symptoms comprise intermittent itching or burning pain in the lower limbs, frequently accompanied by hyperalgesia or allodynia. FEPS3 results from mutations in the *SCN11A* gene; it has been documented in more than 20 families and is linked to nine diverse mutations in *SCN11A* [61]. The syndrome often manifests in childhood with nocturnal pain episodes, following a length-dependent distribution pattern, and may occasion-

Table 4. Hereditary channelopathies of peripheral nerves.

Ion channel involved	Disease	Gene involved	Inheritance pattern	Age at onset	Main clinical features
Sodium channel	Primary erythromelalgia	*SCN9A*	AD	Early childhood	Recurrent episodes of bilateral burning pain, redness, warmth, and sometimes edema in the distal extremities [54]
	Paroxysmal extreme pain disorders	*SCN9A*	AD	Neonatal or infant	Skin flushing, patchy color changes, syncope and bradycardia. Episodes of intense burning pain in the rectal, ocular or submandibular areas associated with flushing [55]
	Congenital insensitivity to pain	*SCN9A*	AR	Neonatal	Inability to perceive pain and temperature, anosmia [56]
		SCN11A	AD		Inability to perceive pain and temperature, gastrointestinal hypomotility and hypotonia [56]
	Small fiber neuropathy	*SCN9A*	AD	No data available	Burning pain in the extremities, exacerbated by heat, and autonomic symptoms [57,58]
		SCN10A	AD		
		SCN11A	AD		
	Familial episodic pain syndrome 2	*SCN10A*	AD	Adult	Paroxysmal itching or burning pain in the lower extremities, hyperalgesia, allodynia [60]
	Familial episodic pain syndrome 3	*SCN11A*	AD	Early childhood	Night-time pain episodes in a length-dependent distribution pattern [61]
TRPA1	Familial episodic pain syndrome 1	*TRPA1*	AD	Infancy	Recurrent episodic pain in distal limbs [59]
TRPV4	Motor and sensory neuropathies	*TRPV4*	AD	Infancy to adulthood	Charcot-Marie-Tooth disease type 2C [62] Scapuloperoneal spinal muscular atrophy [62] Congenital distal spinal muscular atrophy [62]
Potassium channel	Peripheral nerve hyperexcitability	*KCNA1*	AD	Childhood, adolescence	Episodic ataxia, myokymia [63]
		KCNQ2	AD		Facial myokymia and upper limb contracture [64]

AD, autosomal dominant; AR, autosomal recessive; *KCNA1*, potassium voltage-gated channel subfamily A member 1; *SCN9A*, sodium voltage-gated channel alpha subunit 9; *SCN10A*, sodium voltage-gated channel alpha subunit 10; *SCN11A*, sodium voltage-gated channel alpha subunit 11; *TRPA1*, transient receptor potential cation channel subfamily A member 1; *TRPV4*, transient receptor potential cation channel subfamily V member 4.

ally affect proximal limbs and the neck. Autonomic symptoms have been noted in a limited number of cases. Currently, there is no definitive treatment available, except pain management.

Among the hereditary channelopathies of peripheral nerve, there are neuropathies due to mutations in *TRPV4* channels, a calcium-permeable, non-selective cation channel found in several organs and cell types. *TRPV4* expression has been observed in the skin sensory receptors, dorsal root ganglia, and, to a lesser degree, in motor neurons within PNS [71]. Mutations in the *TRPV4* gene are linked to AD skeletal dysplasias and peripheral nervous system syndromes (PNSS). PNSS encompasses Charcot-Marie-Tooth disease type 2C (CMT2C), scapuloperoneal spinal muscular atrophy (SPSMA), and congenital distal spinal muscular atrophy (CDSMA) [62]. CMT2C is a progressive peripheral motor neuronopathy marked by distal muscle atrophy, foot drop, and *pes cavus*. Laryngeal and respiratory dysfunction, sensorineural hearing loss, joint contractures, and small stature are clinical characteristics. The onset occurs from youth to maturity [72]. SPSMA is a gradually progressive lower motor neuron disorder characterized by

muscular weakness, proximal atrophy in the girdles and distal atrophy in the peroneal muscles. In extreme instances, atrophy and weakness are apparent from birth. Laryngeal dysfunction, sensory hearing loss, and kyphoscoliosis are correlated. CDSMA is a gradually increasing lower motor neuron disorder, with muscle weakness and atrophy, primarily impacting the lower extremities. Flexion contractures of the knees and hips, together with bilateral clubfoot, are frequently observed.

Peripheral nerve hyperexcitability syndromes comprise a collection of illnesses distinguished by symptoms such as myokymia, fasciculations, muscle cramps, and rigidity. These syndromes may be immune-mediated or attributable to genetic abnormalities, predominantly affecting the *KCNA1* and *KCNQ2* genes. As previously mentioned, mutations in *KCNA1* determine EA1. In 80% of cases, patients with EA1 also exhibit myokymia, characterized by persistent rippling of periorbital muscle and/or involuntary shaking of the fingers [63,73]. Recently identified new variations exhibit a broad clinical *spectrum* of EA1, including isolated neuromyotonia and muscular stiffness [74]. Pathogenic mutations of *KCNQ2* determine a wide clinical range that encompasses disorders of CNS and PNS. The R207Q variant in *KCNQ2* has been identified as a cause of pure peripheral nerve hyperexcitability, characterized by facial myokymia and upper limb contractures; this mutation exhibits a dominant LOF of the Kv7.2 channel [64]. Symptoms of peripheral nerve hyperexcitability are frequently managed with ASMs, such as carbamazepine and phenytoin.

Channelopathies of Skeletal Muscle

Skeletal muscle channelopathies (SMCs) comprise a diverse array of illnesses resulting from mutations in skeletal ion channels [75]. These mutations result in disturbances in muscle excitability, which can present in two principal forms: (1) prolonged muscular relaxation (myotonia), a characteristic feature of non-dystrophic myotonias (NDMs); (2) membrane transient inactivation leading to occasional periods of muscular weakness, typical of periodic paralyzes (PPs) [76]. SMCs and their clinical features are described in Table 5 (Ref. [77–80]).

NDMs are a category of muscle diseases predominantly defined by myotonia, a condition in which muscles struggle to relax following contraction [81]. Patients may find it challenging to describe this symptom, often employing phrases like “muscle cramping” or “feeling stiff or stuck”. Reduced temperatures exacerbate the myotonic phenomenon, but it ameliorates with repeated exercise (‘warm-up’ phenomenon). In addition to myotonia, paramyotonia (paradoxical myotonia) warrants consideration, as it is a genuine form of myotonia described as “paradoxical” due to its absence at the onset of movement and its exacerbation with exercise, rather than improvement. NDMs include: Thomsen’s congenital myotonia, Becker’s congenital myotonia, congenital paramyotonia, and sodium channel myotonia. Thomsen’s congenital myotonia and Becker’s myotonia result from mutations in the chloride voltage-gated channel 1 (*CLCN1*) gene, situated on chromosome 7q35 [77]. On the contrary, congenital paramyotonia and sodium channel myotonia are due to mutations in the *SCN4A* gene, situated on chromosome 17q24 and coding Nav1.4 in skeletal muscle [82].

Thomsen’s myotonia is an AD condition that presents at birth or early childhood. Clinically, it is distinguished solely by the myotonic phenomena, devoid of indications of muscular atrophy or weakening. One of the initial clinical manifestations in children may be the difficulty in opening the eyelids post-crying; also, some rigidity may be noted when taking the first steps. In adulthood, individuals describe rigidity and challenges in commencing movement, particularly following extended periods of inactivity. Muscle hypertrophy is infrequent during childhood but prevalent in adulthood [77]. The severity ranges from mild to moderate, and there is no progression of symptoms [77].

Becker’s myotonia is an AR condition that often manifests between the ages of 4 and 12, although onset may occur even earlier. It is marked by generalized myotonia accompanied by muscular growth, resembling a bodybuilder’s physique. Individuals with Becker’s myotonia may have a transitory weakness at the initiation of voluntary contraction, persisting from seconds to minutes, which may result in falls [77]. Approximately 60% of individuals experience enduring weakness in the girdle muscles.

Congenital paramyotonia is an uncommon genetic condition, inherited in an AD manner, characterized by myotonia that worsens with activity and/or exposure to cold [78]. Typically, clinical start manifests in early childhood with episodes of transient localized myotonia, exacerbated by muscle activity (paradoxical myotonia) [78]. A clinical examination entails the repetitive forced occlusion of the eyes. With each repetition, the challenge of relaxation escalates until the patient can no longer reopen his or her eyelids. Exposure to cold exacerbates myotonia and may induce muscle weakness in the affected areas, potentially persisting for hours and resulting in considerable functional impairments (for instance, “experiencing stiffness while swimming in the sea”, with the associated risk of drowning). Triggers of paramyotonia may encompass cold wind, ice cream, cold water, or drafts. The facial, tongue, and hand muscles are primarily impacted [78]. Congenital paramyotonia is a benign condition that may ameliorate with age; however, in certain instances, moderate weakness may endure in the later stages of the sickness. Patient management includes pharmacological treatment and the avoidance of precipitating causes. Mexiletine is efficacious for myotonia but ineffective for weakness, whilst acetazolamide may be beneficial in preventing episodes of weakness [81].

Table 5. Skeletal muscle inherited channelopathies.

Ion channel involved	Disease	Gene involved	Inheritance pattern	Age at onset	Main clinical features
Chloride channel	Thomsen's congenital myotonia	*CLCN1*	AD	2–3 yrs.	Myotonia Muscle hypertrophy in adulthood [77]
	Becker's congenital myotonia	*CLCN1*	AR	4–12 yrs.	Myotonia, muscle hypertrophy and transitory weakness [77]
Sodium channel	Hyperkalemic periodic paralysis	*SCN4A*	AD	first decade	Muscle weakness (from focal paresis to complete paralysis), lasting up to 2 hours [80]
	Congenital paramyotonia	*SCN4A*	AD	first decade	Transient localized myotonia, exacerbated by muscle activity and transitory muscle weakness in the affected area [78]
	Sodium channel myotonia	*SCN4A*	AD	first decade	Fluctuating myotonia [79] Permanent myotonia [79] Acetazolamide-responsive myotonia [79]
Calcium channel	Hypokalemic periodic paralysis	*CACNA1S*	AD	1–20 yrs.	Acute episodes of widespread weakness of varied intensity, for hours or even several days [80]

CACNA1S, calcium voltage-gated channel subunit alpha 1 S; *CLCN1*, chloride voltage-gated channel 1; *SCN4A*, sodium voltage-gated channel alpha subunit 4.

Sodium channel myotonia (SCM) is a collection of disorders characterized by muscle rigidity and stiffness, exhibiting AD inheritance and manifesting throughout the first decade of life [76,81]. SCM is clinically characterized as a myotonic illness that predominantly manifests with myotonia, but may also display supplementary traits such as fluctuating myotonia (*myotonia fluctuans*), permanent myotonia (*myotonia permanens*), or acetazolamide-responsive myotonia [81]. Traditionally, SCM has been referred to as potassium-aggravated myotonia; however, Rüdel *et al.* [79] suggested employing the term SCM in instances when potassium loading tests are not performed; also, not all patients exhibit sensitivity to potassium. Myotonia induces muscular rigidity that exacerbates following physical activity. Furthermore, periods of myotonia may be induced or exacerbated by the consumption of potassium-rich meals. In *myotonia fluctuans*, the intensity of the myotonic manifestation is inconsistent. Individuals with this illness may endure prolonged asymptomatic intervals lasting several months. In contrast, *myotonia permanens* is marked by intense, non-relenting myotonia that can occasionally impair respiratory function. Finally, acetazolamide-responsive myotonia exhibits variability in clinical severity and is frequently accompanied by pain. Treatment commences with the elimination of foods high in potassium; other interventions may include physical therapy, such as stretching or massage to alleviate muscle tension, with targeted drugs such as mexiletine, carbamazepine, or acetazolamide [81].

PPs are defined by bouts of muscular weakness or paralysis, resulting from temporary deactivation of muscle membrane excitability. These episodes may be triggered by circumstances such as post-exercise rest, fasting, or elevated carbohydrate consumption. Channelopathies manifesting with PPs comprise: hyperkalemic periodic paralysis (HyperPP) and hypokalemic periodic paralysis (HypoPP). HyperPP is an uncommon AD condition due to mutations in the sodium voltage-gated channel alpha subunit 4 (*SCN4A*) gene, marked by periods of muscular weakness or paralysis linked to increased potassium levels in the bloodstream. The estimated prevalence is approximately 1 in 200,000 [80,83]. Episodes of muscle weakness typically commence in the first decade and are marked by rapid onset of varying intensity (ranging from focal paresis to complete paralysis), lasting up to two hours. The extrinsic ocular and respiratory muscles are often not implicated. Paralytic episodes may be induced by the consumption of potassium-rich foods, fasting, post-exertional rest, mental stress, cold exposure, or pregnancy [80]. Patients can mitigate symptoms by initiating physical exercise at the onset of an incident. In contrast to hypokalemic variants, episodes transpire independently of meals, and carbohydrate consumption has a preventive function. Approximately 50% of pa-

tients have muscle stiffness or inability to relax muscles between bouts, attributable to myotonia or paramyotonia. During these episodes, elevated serum potassium levels are typical; however, some patients may exhibit normal potassium levels. The assaults, originally infrequent, escalate in strength and frequency by the fifth decade of life. Over 80% of individuals aged over 40 frequently report persistent muscle weakness, and one-third have chronic progressive myopathy [80]. Individuals lacking interictal myotonia are more prone to developing myopathy or enduring weakness than those with myotonia. The treatment strategy must include the management of acute episodes and the prevention of further occurrences. This entails behavioral measures designed to circumvent triggers and manage potassium levels via dietary modifications, diuretics, and carbonic anhydrase inhibitors. At the onset of weakness during the attack, therapy options comprise light physical exercise, ingestion of carbohydrate-rich foods, salbutamol inhalation, or intravenous administration of calcium gluconate [80]. To avert attacks, individuals may concentrate on consuming regular carbohydrate-dense meals, administering a thiazide diuretic, or employing a carbonic anhydrase inhibitor [80]. In the course of administering general anesthesia, it is crucial to refrain from using potassium, depolarizing muscle relaxants, or cholinesterase inhibitors, since these substances might intensify myotonia and potentially result in masseter spasms or rigidity in the respiratory muscles or other muscle groups [84].

HypoPP is linked to calcium channel defects, crucial for muscle activity. In fact, the electrical excitation of the plasma membrane of skeletal muscle induces the release of calcium from the intracellular reserves of the sarcoplasmic reticulum, which then activates the contractile proteins. Two essential proteins implicated in the excitation-contraction coupling mechanism are the dihydropyridine receptor (DHPR), situated in the plasma membrane, and the ryanodine receptor (RyR), located in the sarcoplasmic reticulum. These proteins engage at specialized junctions between the plasma membrane and the sarcoplasmic reticulum. The DHPR functions as a voltage-gated calcium channel, whereas the RyR serves as a calcium release channel composed of four identical subunits. Upon depolarization, the DHPR experiences a conformational shift that activates the RyR [85]. The calcium voltage-gated channel subunit alpha 1 S (*CACNA1S*) gene, which encodes the α1 subunit of the DHPR, and its mutations are responsible for HypoPP [83]. HypoPP is an uncommon condition, with an estimated prevalence of 1 in 100,000 individuals. The majority of familial instances exhibit an AD inheritance pattern, frequently demonstrating incompleteness penetrance, particularly in females [80]. Clinically, it is marked by acute episodes of widespread weakness of varied intensity, occasionally resulting in tetraplegia. Episodes of weakness generally occur in the morning upon awakening or after intense physical exertion. Typically, ocular, bulbar, and respiratory muscles remain unaffected, and the weakness endures for hours or even several days. Serum potassium levels are frequently diminished during attacks, although they may remain normal in certain instances, with no obvious relationship between potassium levels and the severity of muscle weakness [80]. The onset of the episodes typically occurs between the ages of 1 and 20 years. The incidence of assaults is greatest between the ages of 15 and 35. Multiple variables can initiate or intensify periods of weakness, such as hypokalemia, physical effort, nocturnal slumber, carbohydrate-dense diets, alcohol intake, and exposure to cold. Some individuals develop proximal myopathy, which can occur irrespective of the frequency and severity of the documented weakness episodes [86,87]. The objective of treatment is to avert bouts of weakness or to diminish their frequency and severity. Initial management entails lifestyle modifications, including the avoidance of carbohydrate-dense meals and rigorous activities [80]. In acute care, rectifying serum potassium levels may offer transient alleviation of muscular weakness [80]. Acetazolamide or dichlorphenamide are frequently recommended for long-term treatment. Dichlorphenamide has received approval for the management of HypoPP and has demonstrated a reduction in the frequency, severity, and length of attacks after prolonged treatment [88]. Anecdotal evidence indicates that acetazolamide may be beneficial as a chronic treatment for HypoPP [89]. Anesthesia must be approached with caution due to the potential dangers of pre- or post-anesthetic weakness and malignant hyperthermia [76]. The prognosis is predominantly positive, with a minimal likelihood of developing proximal myopathy, which may arise regardless of the frequency and intensity of the attacks.

Conclusions

CNS and PNS channelopathies are frequently genetically determined and heterogeneous illnesses.

Despite being classified as rare diseases individually, together they are not uncommon and encompass numerous ailments that impact quality of life either temporarily or permanently. Furthermore, the rising application of genetic technology has enhanced the global comprehension of channel architectures, kinetics, and functions, as well as the identification of novel pathogenic variations. Due to the phenotypic variability of channelopathies, their age-related progression, and the frequently subtle symptoms that patients struggle to articulate and clinicians find challenging to interpret, it is essential to recognize and suspect a channelopathy to prevent diagnostic delays and facilitate timely interventions. Preliminary management may encompass genetic counseling and tailored medication, contingent upon the implicated ion channel.

Furthermore, contacts with expert centers are of paramount importance to avert neurological decline, ensure adequate follow-up, provide prenatal counseling, and explore potential trials for forthcoming therapies.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization: LV, MB, GP, CG, and MZ. Data Curation: LV, MB, GP, CG, CB and MZ. Formal Analysis: LV, MB, GP, CB and MZ. Investigation: LV, MB, GP, CDT, FDE, CG, MM, CB and MZ. Methodology: LV, MB, GP, CB and MZ. Validation: LV, MB, GP, CDT, FDE, CG, MM, CB and MZ. Visualization: LV, MB, GP, CDT, FDE, CG, MM, CB and MZ. LV, MB, GP and CDT wrote the manuscript. All authors contributed to critical review changes in the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all works.

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Conflict of Interest

The authors declare no conflict of interest.

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