Muscle and brain sodium channelopathies: under-recognised, potentially fatal but treatable disorders

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Summary

Voltage gated sodium channels are essential for excitability of skeletal muscle fibres and neurones. An increasing number of disabling or fatal paediatric neurological disorders linked to mutations of voltage gated sodium channel genes are recognised. Muscle phenotypes include episodic paralysis, myotonia, neonatal hypotonia, respiratory compromise, laryngospasm/stridor, congenital myasthenia and myopathy. Recent evidence suggests a possible link between sodium channel dysfunction and sudden infant death. Increasingly recognised brain sodium channelopathy phenotypes include several epilepsy disorders and complex encephalopathies.

Together these early onset muscle and brain phenotypes have a significant morbidity and an appreciable mortality rate but there have been significant advances in understanding the pathophysiological mechanisms underlying them and these have helped to identify effective targeted therapies. The availability of effective treatments underlines the importance of increasing clinical awareness and the need to achieve a precise genetic diagnosis.

Here, we describe the expanded range of phenotypes of muscle and brain sodium channelopathies and the underlying knowledge regarding mechanisms of sodium channel dysfunction. We outline a diagnostic approach and review the available treatment options.

Introduction

Neurological sodium channelopathies are childhood onset disorders caused by mutations in genes that encode the alpha subunits of voltage gated sodium channels or their interacting beta subunits. All the voltage gated sodium channel isoforms expressed in either muscle or brain have a crucial role in tissue excitability. Their primary function is to generate and conduct action potentials. In general terms dysfunction of these channels leads to either a
reduction (loss of channel function) or increase (gain of channel function) in tissue excitability.

Sodium channelopathies are often episodic disorders. This can pose a challenge to diagnosis which relies heavily on the clinical history or may rely on examination or investigations being performed when symptoms are present. These disorders are often disabling, sometimes fatal, and crucially they are often treatable if diagnosed.

Amongst the skeletal muscle sodium channelopathies it is the recently described severe phenotypes that present in infancy and childhood which pose the biggest diagnostic challenge and consequent unmet clinical need for treatment. Amongst the brain sodium channelopathies, which are mostly severe early-onset epilepsies and epileptic encephalopathies, young children are increasingly diagnosed by generic next generation sequencing panels. However, adults and older adolescents who may have not been diagnosed in childhood and may not access the same genetic testing can remain undiagnosed without access to the correct treatment.

Muscle and brain sodium channelopathies are rare but will typically present to general physicians. Here we review how clinical presentations are linked to genetic and pathomechanistic data. We aim to raise awareness, guide diagnosis, promote effective treatment and hence potentially reduce avoidable morbidity and mortality.

**Skeletal muscle sodium channelopathies**

**Causative gene and pathophysiology**

Skeletal muscle sodium channelopathies are caused by mutations in the *SCN4A* gene which impair the ability of skeletal muscle to contract or relax\(^1\). The characteristic clinical features
of autosomal dominant muscle sodium channelopathies are disabling attacks of either muscle paralysis or myotonia.

Over the last 10 years there has been increasing recognition that infants and children have a much more diverse clinical presentation (see Table 1). We now recognise that dominant mutations in this gene can also cause neonatal hypotonia\(^2\), stridor\(^3\) and life-threatening apnoeas\(^4,5\). Recently described recessive mutations cause foetal akinesia, congenital myopathy\(^6\) and congenital myasthenia\(^7\). Furthermore, there is recent evidence that \(SCN4A\) mutations may increase the risk of sudden infant death\(^8\).

The \(SCN4A\) gene encodes the alpha sub-unit of the skeletal muscle voltage-gated sodium channel Nav1.4. It is present throughout the sarcolemma but most densely distributed at the motor end plate. A motor nerve action potential promotes acetylcholine release from the nerve terminal which activates the post-synaptic acetylcholine receptors. This in turn stimulates opening of Nav1.4 and ultimately triggers propagation of a post-synaptic action potential which results in muscle contraction (see Fig 1).

\(SCN4A\) mutations will create either a hyperexcitable membrane that results clinically in myotonia or an inexitable membrane that produces variable forms of muscle weakness including periodic paralysis, congenital myasthenia or congenital myopathy. This review focuses on the clinical presentations of \(SCN4A\) mutations and highlights under-recognised paediatric presentations. For a detailed review of the electrophysiological consequences of mutations responsible for each clinical presentation see\(^1\).

**Clinical presentations**

**Skeletal muscle sodium channelopathies: autosomal dominant disorders**
Myotonic presentations

Myotonia is delayed muscle relaxation after forceful contraction and is often experienced as muscle cramp, which can be painful, or muscle stiffness. Typically, sodium channel related myotonia affects the face and hand muscles more than the legs. Some mutations result in a pure myotonic presentation (sodium channel myotonia) and others can be associated with myotonia and episodic muscle weakness (paramyotonia congenita). Extremes of temperature, particularly cold and exertion or rest after exertion may exacerbate myotonic symptoms. Muscle hypertrophy is frequent.

Common (although only recently recognised) additional features in children include, extraocular myotonia causing strabismus or disturbed vision, contractures, toe walking, kyphosis, scoliosis, rotated glenohumeral joints and dysmorphic features (see Fig 2).

Severe neonatal episodic laryngospasm

Young children and infants with SCN4A mutations commonly experience bulbar and respiratory (including laryngeal) muscle myotonia of variable severity. The most severe presentations have been termed severe neonatal episodic laryngospasm (SNEL). Infants experience abrupt onset of upper airway muscle myotonia (frequently causing stridor although some events were silent) in combination with respiratory, and limb muscle myotonia. Variable combinations of life-threatening apnoea, hypoxia, cyanosis, bradycardia and loss of consciousness can occur. Bulbar impairment may result in failure to thrive requiring NG or PEG feeding. Symptoms are typically brief, seconds to minutes but can occur multiple times a day. This abrupt onset of recurrent, stereotyped limb stiffening with hypoxia and cyanosis is not infrequently confused with epilepsy (despite normal EEG) or hyperekplexia. Diagnostic uncertainty may result in infants spending many months in ITU with ventilatory support. Fatalities have been reported including a posthumous
diagnosis\textsuperscript{4,5}. However, in all cases described in which the diagnosis was made and treatment instigated with sodium channel antagonists there was a dramatic improvement enabling discharge from ITU\textsuperscript{18}. The respiratory and bulbar symptoms reported in children span a spectrum of severity and there are examples improving with age even when only supportive treatment has been given, suggesting a natural evolution of the phenotype\textsuperscript{3,15,17}.

**Periodic paralysis**

Mutations in \textit{SCN4A} can cause either hyperkalaemic (HyperPP) or hypokalaemic periodic paralysis (HypoPP)\textsuperscript{19-21}.

HyperPP: Age of onset is typically in the first decade\textsuperscript{22} with attacks of flaccid muscle paralysis associated with high serum potassium levels that last minutes to hours, and can occur at any time of the day. Rest after exertion often precipitates symptoms (e.g. prolonged sitting at a school desk) cold temperature or ingestion of potassium rich foods. Myotonia may also occur but paralysis is the predominant symptom.

HypoPP: Symptoms characteristically begin in the second decade. Patients experience attacks of flaccid muscle paralysis associated with low serum potassium levels typically lasting hours to days that frequently occur during the night or first thing on waking\textsuperscript{22}. This can lead to school absenteeism\textsuperscript{13} as the child will struggle to ambulate in the morning. If symptoms have resolved by the afternoon they can be misinterpreted as school avoidance. Triggers include rest after exertion and carbohydrate rich meals that stimulate insulin secretion and lower serum potassium.

The severity of muscle weakness experienced in each attack of periodic paralysis of either form is variable and may range from mild impairment to complete paralysis; e.g. a child complaining of leg weakness may still be able to stand and walk but not run or climb stairs.
which can prompt erroneous suspicion of functional neurological symptoms. Weakness may also only affect one limb e.g. the dominant hand after prolonged writing and this may be detrimental in exams. In severe attacks, quadraparesis occurs and facial and respiratory muscles, which are usually spared, may be affected especially in the very young\textsuperscript{23,24}. Potassium levels may rise or fall during an attack but not necessarily outside the normal range and therefore caution is needed in the interpretation of a normal potassium level.

**Neonatal hypotonia**

We have described transient neonatal hypotonia with bulbar and respiratory impairment in individuals with paramyotonia congenita\textsuperscript{2} and hyperPP\textsuperscript{13}. In each case symptoms self-resolved within a few days. Neonatal hypotonia is very common with a myriad of causes but the knowledge that it can be a symptom of sodium channelopathy may prevent unnecessary investigation. In addition, it allows planning for appropriate facilities and expertise during labour for affected parents.

**Skeletal muscle channelopathies: autosomal recessive disorders**

**Congenital myopathy and foetal hypokinesia**

The first series describing congenital myopathy caused by homozygous or compound heterozygous mutations in \textit{SCN4A} reported 11 individuals from six families\textsuperscript{6}. Seven of the affected cases experienced foetal hypokinesia and died in utero or within 24 hours of delivery. The surviving four demonstrated neonatal hypotonia, generalised muscle weakness including neck and facial weakness with delayed motor milestones and later spinal deformities. There were variable dysmorphic features and significant neonatal respiratory and bulbar weakness warranting ventilator support and PEG feeding. Improvement in muscle strength and function including bulbar and respiratory muscles was universal in the first
decade. Muscle biopsies were consistent with a congenital myopathy but without specific diagnostic features\textsuperscript{6}. A second report of three brothers with compound heterozygous *SCN4A* mutations confirmed a very similar phenotype\textsuperscript{25}. A much milder congenital myopathy without respiratory or bulbar compromise was subsequently reported in two brothers with compound heterozygous *SCN4A* mutations. Two sisters homozygous for one of the mutations seen in these brothers also displayed a much milder phenotype without any respiratory or persisting bulbar problems\textsuperscript{26}.

*SCN4A* mutations causing myopathy result in a loss of channel function but there is an evident spectrum of severity. In vitro studies correlate clinical severity with the degree of channel dysfunction e.g. homozygous complete loss of function is fatal\textsuperscript{6}.

**Congenital myasthenia**

*SCN4A* related congenital myasthenia was first recognised in a woman who had experienced recurrent episodes of respiratory and bulbar paralysis since birth requiring ventilator support and resulting in cerebral anoxic injury\textsuperscript{7}. She had delayed motor milestones, ptosis, ophthalmoplegia, and fatigable facial, truncal, and limb muscle weakness. Additional cases reported early onset muscle weakness with variable respiratory insufficiency, fatigability including ptosis, and ophthalmoplegia\textsuperscript{27-29}. Pyridostigmine was generally unhelpful, but acetylcholine is not diminished in this form of myasthenia. Repetitive nerve stimulation at typical diagnostic frequency of 3Hz can be normal with higher frequency stimulation required to see a decrement in CMAP. Unlike other causes of myasthenia where the motor end plate potential is inadequate to depolarise Nav1.4 channels, the end plate potential is normal but there is a use dependent reduction in Nav1.4 channel availability with failure to transmit sustained post-synaptic action potentials\textsuperscript{7}.

**Brain sodium channelopathies**
**Causative genes**

Mutations in the genes *SCN1A*, *SCN2A*, *SCN3A*, *SCN8A*, *SCN10A* and *SCN1B* have been associated with a spectrum of paroxysmal neurological disorders, primarily early-onset epileptic encephalopathies (EOEE) and other autosomal dominant epilepsy syndromes.

EOEE is the most common phenotype, but other epilepsy phenotypes include genetic (often generalised) epilepsy with febrile seizure plus (GEFS+, mainly *SCN1A/SCN1B/SCN8A/SCN9A*), benign (familial) neonatal/infantile seizures (B(F)NIS, mainly *SCN2A/SCN8A*), and a small number of cases of familial focal epilepsy with variable foci (*SCN3A*) (see Table 1).

**Clinical Presentations**

**Early-onset epileptic encephalopathies**

Mutations in sodium channel alpha subunits have been associated with severe EOEEs, including Ohtahara syndrome (OS), epilepsy of infancy with migrating focal seizures (EIMFS), early myoclonic epileptic encephalopathy (EMEE), West syndrome (WS), Lennox-Gastaut syndrome (LGS), myoclonic-astatic epilepsy (MAE) and other unclassified severe epilepsy phenotypes. OS is characterized by an early onset of spasms, mainly in the neonatal period, intractable seizures, and a suppression-burst pattern on EEG. EIMFS is characterised by intractable seizures, typically focal, beginning in the first six months of life with associated developmental plateau or regression; autonomic manifestations are common and seizures progress to become nearly continuous by age six to nine months. WS is characterized by spasms, an EEG finding termed hyspsarrhythmia, and arrest of psychomotor development. LGS is defined by a triad of multiple drug-resistant seizure types, a specific interictal EEG pattern showing bursts of slow spike-wave (SSW) complexes or generalized
paroxysmal fast activity (GPFA) and intellectual disability. MAE is characterised by a combination of myoclonic, atonic, and atypical absence seizures, with onset usually after age two years.

Dysfunction of one sodium channel can lead to multiple phenotypes and conversely the same phenotype can be due to mutations in different sodium channel genes (see Table 2).

SCN1A mutations cause a range of EOEE, including mostly Dravet Syndrome, but also OS, EIMFS, EMEE, WS, LGS and MAE. A severe phenotype with early onset developmental and epileptic encephalopathy, profound impairment, and movement disorder has also been reported mostly associated with the recurrent missense mutation p.Thr226Met.

Epileptogenic mutations generally cause loss-of-function, whereas gain-of-function is associated with mutations causing familial hemiplegic migraine.

SCN2A mutations mainly cause disease with onset in the early developmental period, but some have also been found to cause later-onset neurological diseases, or a combination of both. Mutations with a gain-of-function mechanism usually cause early onset seizures, whereas loss-of-function mutations tend to be associated with later onset seizures or neurodevelopmental phenotypes without epilepsy. SCN2A mutations account for approximately 10% of individuals with Ohtahara syndrome and are a common cause of WS with a major recurring mutation (p.Arg853Gln). The largest series of SCN2A-related epilepsy reported so far suggested two distinct phenotypic subtypes. The first group was characterised by onset before age 3 months, missense mutations with gain-of-function effects, and included OS, B(F)NIS, EIMFS and unclassified encephalopathies. In contrast, the second group with onset later than 3 months of age tended to harbour loss-of-function mutations and included WS, LGS, MAE, and focal epilepsies with EEG features of electrical status.
epileptics during sleep (ESES)\textsuperscript{43}. Epileptic encephalopathy with choreoathetoid movements has also been reported in association with SCN2A variants\textsuperscript{39}.

SCN8A-related EOEEs include OS, WS, DS and LGS. EOEE appears to result from gain-of-function mutations\textsuperscript{44}, whereas a few loss-of-function mutations have been found in those with developmental delay, intellectual disability or autism, mainly without seizures\textsuperscript{45-48}.

Clinical features of SCN8A EOEEs include developmental impairment, seizure onset in the first 18 months of life, pyramidal and extrapyramidal signs, and intractable epilepsy with multiple seizure types\textsuperscript{49}. More recently, a specific electroclinical phenotype has been described in SCN8A developmental and epileptic encephalopathies with progressive EEG background slowing and multifocal epileptiform abnormalities, prominent in the posterior quadrants\textsuperscript{50}.

SCN3A encodes the voltage-gated sodium channel Nav1.3 which is expressed at high levels during embryogenesis and early postnatal life, falling to near-undetectable levels by adulthood\textsuperscript{51,52}. Described mutant Nav1.3 channels show altered biophysical properties including prominent gain-of-function\textsuperscript{52}. SCN3A has been shown to have a prenatal role in cortical organization and neuronal migration, especially in speech and language areas, mirroring its enriched foetal expression\textsuperscript{53}. Affected individuals may present with disrupted cerebral cortical folding (polymicrogyria) of the perisylvian cortex, prominent speech and oral motor dysfunction, and EOEE\textsuperscript{52,53}.

Heterozygous de novo missense mutations in SCN3A have been shown to cause EOEEs in four patients with intractable epilepsy with onset during infancy, and severe to profound developmental delay. Two of these cases, both with the variant p.Ile875Thr, had extensive bilateral polymicrogyria\textsuperscript{52}. The security of SCN3A as an ‘epilepsy gene’, and its associated phenotypic spectrum, await reporting of further cases.
So far, biallelic mutations in \textit{SCN10A} have been reported in four patients from three families. Two of these families were consanguineous, and showed progressive neuromuscular disease with hypotonia, progressive weakness, and dysphagia. All patients had seizures with variable age of onset and semiology, and severe cognitive impairment, or developmental regression following seizure onset. Seizures responded poorly to AEDs. Subsequent search of consortia datasets identified five further cases with compound heterozygous \textit{SCN10A} mutations, two with clinical phenotypes of LGS and infantile spasms, respectively, and three with autism\textsuperscript{54}.

The \textit{SCN1B} gene encodes the sodium channel beta-1 subunit, which is linked to voltage-gated sodium channel alpha subunits and modulates a range of their functions\textsuperscript{55}. Recessive mutations in \textit{SCN1B} are reported in five children from three consanguineous families with EOEEs. Four of the five died in childhood. The seizure semiology varied but with refractory epilepsy in all cases. MRI was abnormal in four, with mostly brain atrophy. All patients had global developmental delay. Further features included spasticity and kyphoscoliosis\textsuperscript{56}.

The evolution of phenotypes in later life, including from adolescence onwards, is not fully defined for many of these conditions. The history of the early stages of the disease may help raise suspicion of an underlying sodium channelopathy, but, especially in later years, such a history may be lost, or not known to unrelated carers, which can complicate the diagnostic process.

\textbf{Dravet syndrome}

Dravet Syndrome (DS) is a severe epileptic encephalopathy with onset typically in the first year of life with prolonged, febrile and afebrile, generalized clonic or hemiconic epileptic seizures in children with no overt pre-existing developmental problems. Other seizure types, including myoclonic, focal, and atypical absence seizures, appear between the ages of 1 and 4 years. The main clinical features of DS include drug-resistant epilepsy, developmental
slowing, cognitive impairment, occurrence of status epilepticus, and an elevated risk of early mortality\textsuperscript{57}. Additional comorbidities that often develop by adulthood include dysphagia, cerebellar symptoms and gait disturbances. In at least 85\% of cases, DS is caused by \textit{de novo} \textit{SCN1A} mutations\textsuperscript{58}. The large majority of pathogenic \textit{SCN1A} variants causing DS are dominant, but there has been a report of two consanguineous families in which heterozygotes remained healthy and only homozygotes developed DS or GEFS+\textsuperscript{59}. Less frequently, DS, or a very similar phenotype, might be due to mutations in other genes: \textit{SCN2A}, \textit{SCN1B}, \textit{SCN8A}, \textit{STXBP1}, \textit{GABRA1}, \textit{GABRG2}, \textit{GABRB3}\textsuperscript{60}.

\textbf{GEFS+}

GEFS+ is a spectrum of familial autosomal dominant seizure disorders of varying severity including simple febrile seizures, which start in infancy and usually stop by the age of five years, and febrile seizures plus (FS+). FS+ involves febrile and other types of seizures, including those not related to fevers (afebrile seizures), that continue beyond childhood. Phenotypes within families affected by GEFS+ are extremely variable, including FS, FS+, epilepsies with generalised and/or focal seizures, myoclonic-astatic epilepsy (MAE), and DS. Of GEFS+ patients with known mutations, \textit{SCN1A} accounts for the largest fraction, with mutations identified in 19\% of families, followed by \textit{SCN1B} mutation in up to 8\%\textsuperscript{61}. Patients with FS/FS+ and \textit{SCN1B} mutations have later onset of FS compared to patients with mutations in \textit{SCN1A}\textsuperscript{62}.

\textbf{B(F)NIS}

B(F)NIS is an autosomal dominant self-limiting disorder in which afebrile seizures occur in clusters during the first year of life, without overt long-term neuropsychiatric sequelae. BFNIS is mostly caused by dominantly inherited \textit{SCN2A} missense mutations\textsuperscript{63}. 
A recurrent heterozygous SCN8A missense mutation has been found in association with autosomal dominant benign familial infantile seizures (BFIS) and infantile convulsions and paroxysmal choreoathetosis (ICCA)\textsuperscript{64}.

**Intellectual disability and/or autism spectrum disorder**

SCN2A mutations have also been found in patients with intellectual disability and/or autistic features without epilepsy\textsuperscript{42,65}. The autism-associated SCN2A variants showed partial or complete loss-of-function in HEK cells and more than half were predicted to introduce a premature stop codon\textsuperscript{41}.

Loss-of-function mutations in SCN8A have been associated in two children with intellectual disability and developmental delay but no seizures\textsuperscript{47}. Three individuals with autism are described with possibly/probably pathogenic compound heterozygous variants in SCN10A\textsuperscript{54}.

**Other CNS phenotypes**

At least seven mutations in the SCN1A gene have been identified in people with familial hemiplegic migraine type 3 (FHM3), a severe monogenic subtype of migraine with aura, characterized by the presence of hemiparesis as part of the aura phase\textsuperscript{66}.

Mutations in SCN2A are an established cause of neonatal epilepsy (benign infantile seizures) with late-onset episodic ataxia\textsuperscript{40}, and schizophrenia\textsuperscript{67}; although only a few cases have been reported so far.

A heterozygous truncating mutation in SCN8A has been reported in a case with cerebellar atrophy, ataxia, and mental retardation\textsuperscript{46}. A heterozygous missense SCN8A variant determining partial loss-of-function has been recently associated with autosomal dominant non-epileptic isolated upper limb myoclonus, without seizures or cognitive impairment\textsuperscript{48}.
again only one family has been reported, so these findings do not yet provide robust evidence of causation.

**Assessment and Diagnosis**

The differing physiological consequences of muscle and brain sodium channel mutations can have significant implications for appropriate therapeutic choice (see Table 2) and exemplifies the importance of obtaining a genetic diagnosis from within a generic presentation. For example, SCN4A related congenital myasthenia will not benefit from pyridostigmine and rapid genetic testing in SCN2A-related early onset epilepsy is crucial as its treatment is distinct from current guidelines for empiric neonatal seizure treatment \(^4_2\).

Muscle and brain sodium channel disorders are diverse and include presentations characterised by either episodic or fixed symptoms. For the episodic presentations including many of the epilepsies and the periodic paralyses, general examination when asymptomatic is usually normal. In the myotonic disorders, in addition to the myotonia and muscle hypertrophy, contractures, scoliosis, strabismus and dysmorphic features (see Fig 2) should all be sought in children. In Dravet Syndrome while neurodevelopmental and neurological examination are typically normal at the age of seizure onset there is often subsequent developmental delay and there may also be ataxia, pyramidal signs, crouch gait, dysphagia and movement disorders observed during the course of the disease, which may obscure the underlying diagnosis.

Even where there is permanent disability examination may not lead to a precise diagnosis e.g. fixed myopathy is a feature of SCN4A related congenital myopathy but the wider differential includes all causes of congenital myopathy. Similarly patients with SCN4A mutations may present with myasthenic symptoms but other genetic and autoimmune causes of myasthenia need to be considered. The mainstay of investigation lies in a particular focus on clinical
history combined with neurophysiologic assessment, EMG/NCS for muscle channelopathies and EEG for brain disorders. The specificity of the neurophysiology test chosen in muscle channelopathies varies with phenotype (see Table 3) and specialist tests not routinely available in every centre may be needed. CK and muscle biopsy are generally non-specific but can help to distinguish a peripheral from central disorder which for the SNEL presentations can be pivotal.

Genetic testing in both muscle and brain channelopathies is usually diagnostic. The majority of mutations that account for the sodium channel epilepsies and the severe myotonia laryngospasm cases arise de novo and lack of family history should never deter from considering a genetic diagnosis. Mutations in the CLCN-1 gene cause the closely related skeletal muscle channelopathy myotonia congenita. It should be noted that the carrier frequency of these variants is relatively high in the general population but this myotonic disorder has not been associated with laryngospasm and any variants should be interpreted with caution in infantile cases of apnoea and/or stridor. The importance of returning to the early clinical history for older adolescents and adults with epilepsy disorders cannot be overemphasised as it is the early history that is characteristically the clue to a genetic aetiology. In patients with an electroclinical phenotype of DS, SCN1A testing should be requested as the estimated likelihood of detecting a mutation in a typical DS case is 80-90%. Negative SCN1A analysis does not necessarily exclude the diagnosis, as it may be a false-negative result or clinical features may be associated with a mutation in another gene, as the DS diagnosis itself is a clinical one. SCN1A testing is also recommended for GEFS+ phenotypes.

For other EOEEs, gene panels or whole exome/genome sequencing (WES/WGS) analyses can lead to a diagnostic yield varying between 30% and 70%. A recent study in adults with treatment-resistant epilepsy and intellectual disability using the same wide sequencing
approach had a similar diagnostic rate, highlighting a significant unmet clinical need in older patients. For those with intellectual disability, autism and the other CNS phenotypes discussed, the role of sodium channel gene variants in producing the phenotype has not been fully determined and there is no current evidence of treatment implication or benefit. The clinical value in routine genetic testing of these genes for patients with these phenotypes is therefore not yet established and should be regarded with some caution.

**Treatment and prognosis**

**Skeletal muscle sodium channelopathies**

Myotonic disorders and the periodic paralyses usually benefit significantly from pharmacological therapy. Sodium channel blockers, commonly mexiletine or lamotrigine tend to be first choice for myotonic symptoms with a combination of diuretics and carbonic anhydrase inhibitors for the periodic paralyses. For the severe SNEL cases, treatment can be transformative. There is some in vitro evidence that in these cases the sodium channel blocker flecainide may be the most effective choice for the common SNEL mutation, G1306E. Even in the recessive disorders there is some evidence of efficacy from similar therapies and the possibility of treatment should always be considered, even when the examination suggests fixed weakness. A summary of pharmacological treatments is given in Table 3. All of the muscle sodium channelopathies are disabling but only SNEL and congenital myopathy have been shown to be life-limiting. In surviving infants prognosis in the episodic disorders is generally positive if treated appropriately. School absenteeism is a strong indication to treat pharmacologically as this can limit educational potential. The majority of patients remain ambulant and in full time employment but a significant minority develop a fixed proximal myopathy with requirement for walking aid and home
modifications. Cases of congenital myopathy and myasthenia are relatively few making prognosis speculative to some degree. A significant spectrum of severity has been demonstrated. Congenital myopathy has the highest mortality but the surviving cases tend to improve in the first decade and appear to be relatively stable thereafter.

Potassium and cardiac monitoring during muscle paralysis

Potassium levels can be significantly deranged in periodic paralysis, especially hypoPP and although the cardiac muscle itself is unaffected by the disease cardiac arrhythmia secondary to dyskalaemia can be significant. During acute attacks of hypoPP oral or IV potassium may be required. Caution must be taken however as potassium is held intramuscularly during an attack and will return to the plasma as the attack subsides. In combination with IV supplementation this can result in a rebound hyperkalaemia and iatrogenic mortality.

General anaesthetic considerations

Propofol and non-depolarising anaesthetic agents appear effective and safe in muscle channelopathies. A myotonic crisis can be precipitated by depolarising anaesthetics or suxamethonium, which can also provoke hyperkalaemia and fatal ventricular arrhythmia and should be avoided. Muscle rigidity including the jaw can be profound, and intubation may become impossible. Emergency treatment is with IV sodium channel blockers e.g. lidocaine and correction of hyperkalaemia.

Brain sodium channelopathies

Attempts to secure adequate seizure control are particularly important, because it can also bring about improvement in cognitive function, even in patients who have shown decline over an extended period of time, decrease the risk of injury and of sudden unexpected death in epilepsy (SUDEP).
Dravet Syndrome

First-line agents include valproate, clobazam and stiripentol\textsuperscript{82,83} with supportive data for topiramate, levetiracetam, bromides, and the ketogenic diet\textsuperscript{84}. Until recently, stiripentol was the only treatment for which a phase 3 randomized, placebo-controlled, clinical trial had been performed in patients with DS\textsuperscript{82}. More recently, a pharmaceutical-grade formulation of purified cannabidiol in oil has been shown to be more efficacious but less tolerated than placebo in controlling some types of seizures in Dravet syndrome\textsuperscript{85}. Other agents such as fenfluramine are promising therapies\textsuperscript{86}. Sodium channel-blocking antiepileptic drugs such as carbamazepine and lamotrigine are generally contraindicated but should not be entirely excluded as in certain cases they can be of benefit\textsuperscript{87}, although the reasons underlying varying treatment responses in Dravet syndrome have not been fully elucidated\textsuperscript{88}. Non-pharmacological treatment such as vagus nerve stimulation (VNS) can also be considered\textsuperscript{84}.

SCN2A-related disorders

In parallel to the observed correlation between age of onset and functional consequence of the underlying mutation, the use of non-selective sodium channel blockers, such as phenytoin and carbamazepine, can be effective in children with early infantile epilepsies (<3 months). In contrast, they are rarely effective in epilepsies with later onset (≥3 months) and can induce seizure worsening\textsuperscript{43}; therefore, non-sodium channel inhibiting AEDs should be used (e.g. levetiracetam, benzodiazepines, and valproate). There is limited evidence of efficacy of the ketogenic diet\textsuperscript{89} but no clinical trials have been performed. Prognosis associated with SCN2A disorders varies from benign outcome with often complete seizure freedom (i.e. in B(F)NIS) to refractory epilepsy with cognitive impairment and early death due to infections or status epilepticus\textsuperscript{43}.

SCN8A-related epilepsies
Most patients with SCN8A-related epilepsies have drug-resistant epilepsy. There is clinical evidence of the effectiveness of sodium channel blockers consistent with the activating effects of most SCN8A pathogenic variants, the most effective being phenytoin, carbamazepine, and oxcarbazepine, usually at supra-therapeutic doses. Ketogenic diet has been suggested to be effective in improving seizure control, but there is no robust evidence from clinical trials. Prognosis in SCN8A EOEEs is generally poor with profound impairment and increased risk of premature mortality, although a more stable course or even improvement has been reported with age.

**SCN3A, SCN10A and SCN1B related epilepsies**

In SCN3A-related EOEEs, there is preliminary evidence that phenytoin and lacosamide may offer a targeted treatment approach but more data are needed.

There are no data on potential treatments for SCN10A or SCN1B-related epilepsy, with the few EOEE patients recently described all having refractory epilepsy.

**General considerations**

Symptoms in both muscle and brain sodium channelopathies are often “triggered” by other factors which can be modified by non-pharmacological means. Examples include avoiding elevated body temperatures (warm baths, exercise on hot days, untreated fever) in Dravet Syndrome, and foods precipitating high or low potassium levels in the periodic paralyses. Where applicable all patients should have a home rescue medication e.g. involving the use of buccal midazolam for seizure disorders or potassium supplements for hypokalaemic periodic paralysis, and should have a clear protocol to guide emergency management at their local hospital in case of seizure clusters, status epilepticus or severe dyskalaemia with quadraparesis. All patients should ideally have access to a multi-disciplinary specialist
service including the support of a clinical nurse specialist and, where appropriate, school liaison.

**Recurrence risk and testing of family members**

Most of the SNEL myotonia cases and EOEEs are the result of *de novo* events\textsuperscript{91}, and thus, the risk to additional family members is thought to be low, a typical recurrence risk quoted for future pregnancies is <1%. However, a significant fraction of presumed *de novo* events is found to be gonadal or somatic mosaicism in unaffected or mildly affected parents\textsuperscript{92,93}, and has been reported to occur with *SCN1A* and *SCN2A* variants making the recurrence risk for families with a child with an apparent de novo variant higher than the general population risk.

Although the majority of EOEEs are sporadic, a WES study showed that up to 20% of genetically confirmed EOEEs are autosomal recessive with a subsequent recurrence risk for future siblings of 25%\textsuperscript{94}. More recently, parental mosaicism has also been shown to be a more common phenomenon than expected, complicating risk counselling\textsuperscript{93}.

**The risk of sudden death**

**Sudden infant death**

We recently described rare heterozygous *SCN4A* mutations in cases of sudden infant death\textsuperscript{8}. We provided evidence that the mutation may increase the risk of respiratory failure or laryngospasm when combined with other risk factors. There has been no systematic evaluation to assess if there is increased risk of death among infants born to parents affected by sodium channelopathies.

Laryngospasm has also been postulated as a contributory mechanism to SUDEP. We recently identified a child with both EEG confirmed epilepsy and a myotonic *SCN4A* mutation who experienced apnoea during seizures\textsuperscript{95}. We postulate the presence of the myotonia mutation
may increase the risk of apnoea and that laryngospasm may be a common mechanism in sudden death aetiology although this requires further research.

**Sudden unexpected death in epilepsy (SUDEP)**

Mortality in DS ranges from 3.7–17.5% with 15–61% deaths attributed to SUDEP and 25–42% to status epilepticus\(^{96,97}\). Death most commonly occurs in childhood\(^{97}\). The DS-specific SUDEP rate has been estimated at 9.32/1000-person-years (CI 4.46–19.45), including both children and adults\(^{98}\). As *SCN1A* is also expressed in the heart, a predisposition to cardiac arrhythmias has been suggested as a potential contributing factor to the elevated risk of SUDEP\(^{99}\). SUDEP has been reported in approximately 10% of published *SCN8A* cases. However, a recent study has not confirmed an increased risk of SUDEP in *SCN8A*-related epilepsies when compared to other developmental and/or epileptic encephalopathies\(^{100}\). SUDEP has also been reported in a GEFS+ family carrying a pathogenic *SCN1B* variant\(^{101}\).

More generally, a major risk factor for SUDEP is the presence and frequency of generalized tonic-clonic seizures (for example, people with three or more GTCS per year have a 15-fold increased risk of SUDEP), and seizures occurring from sleep may also increase the risk\(^{102}\). Therefore, independent of the aetiology of the epilepsy, it is important to actively manage epilepsy therapies to reduce seizure occurrences and to use nocturnal supervision, or other nocturnal precautions, to reduce SUDEP risk\(^{102}\).

**Future challenges**

Although sodium channelopathies are often very responsive to pharmacological treatment their rarity does pose a major challenge to conducting randomised controlled trials. This limits the ability to inform best practice and suggests more innovative trial design may be needed for the future\(^{103}\). In addition many of the treatments used are repurposed relatively
inexpensive drugs but if trial evidence of efficacy in a rare disease is provided this can leave them vulnerable to unintended disadvantages of orphan drug designation – namely significant price increases which in some cases has led to a lack of access for patients\textsuperscript{104}.

For the epilepsies, especially Dravet Syndrome treatment is often still a challenge. Stratifying pharmacological choice based on genetic aetiology and the removal of unhelpful drugs may often be the most effective practical step but it remains difficult to find a regime that renders DS patients completely seizure free. A major challenge lies in the development of new therapies with a current focus on gene based approaches.

It is also of concern that at present we have no treatments at all for most of the associated co-morbidities of DS e.g. intellectual disability, behavioural, sleep, feeding, or gait difficulties. Seizure control can help, but rarely does even seizure freedom (itself difficult to achieve) prevent these features, at least in adults. We are yet to see if improved seizure control from an early age does prevent all these.

**Conclusions**

Skeletal muscle and brain sodium channelopathies are rare but treatable causes of significant childhood morbidity and mortality. Pharmacological therapies are readily available and often have a dramatic benefit which correlates with targeting therapy to the underlying pathological consequence of the mutation on channel function. Identifying the genetic mutation and its functional effect is crucial, and has important implications for treatment. The biggest challenge for reducing morbidity in young onset muscle sodium channelopathies is arguably a lack of awareness of the clinical presentation in infants and young children. For brain sodium channelopathies it is essential to not overlook the importance of a detailed early life history in patients being assessed as adolescents or adults.
Author contributions

All authors wrote and provided feedback on the manuscript. EM and SB performed the literature search. EM and MGH generated tables and figures.

The authors declare no conflicts of interest.

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Search strategy and selection criteria

References for this review were identified through searches of PubMed including the search terms “sodium channels/channelopathy”, “voltage gated sodium channels”, “sodium channel epilepsy”. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.


**Figure legends**

**Fig 1:** Diagrammatic representation of neuromuscular junction transmission and excitation-contraction coupling

**Fig 2:** Clinical signs in children with sodium channel myotonia
A: Toe walking, eyelid myotonia and facial dysmorphism with short neck and hypertrophic neck and shoulder girdle muscles. B. Scoliosis, elbow and knee contractures, short neck and short stature C. Strabismus

*permissions to reproduce some previously published photographs are pending
<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Clinical Phenotype</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN4A</td>
<td>Nav1.4</td>
<td>Sodium channel myotonia and Paramyotonia congenita, Severe neonatal episodic laryngospasm (SNEL)</td>
<td>Autosomal dominant, Autosomal dominant – majority de novo</td>
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<tr>
<td></td>
<td></td>
<td><strong>Periodic paralyses</strong></td>
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<tr>
<td></td>
<td></td>
<td>Hyperkalaemic periodic paralysis, Hypokalaemic periodic paralysis</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Congenital phenotypes</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital myopathy (and/or foetal akinesia), Congenital myasthenia</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>SCN1A</td>
<td>Nav1.1</td>
<td><strong>Epileptic encephalopathies</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dravet syndrome</td>
<td>At least 85% of cases de novo dominant SCN1A, Autosomal recessive rare – two consanguineous families reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ohtahara syndrome, Epilepsy of infancy with migrating focal seizures, Early myoclonic epileptic encephalopathy, West syndrome, Lennox-Gastaut syndrome, Myoclonic-astatic epilepsy</td>
<td>Autosomal dominant/de novo</td>
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<td></td>
<td></td>
<td><strong>Epilepsy syndromes</strong></td>
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<td></td>
<td></td>
<td>GEFS+ (Up to 19% of cases due to SCN1A mutations)</td>
<td>Autosomal dominant/de novo</td>
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<td></td>
<td></td>
<td><strong>Other CNS syndromes</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Familial hemiplegic migraine</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>SCN2A</td>
<td>Nav1.2</td>
<td><strong>Epileptic encephalopathies</strong></td>
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<tr>
<td></td>
<td></td>
<td>Dravet syndrome</td>
<td>De novo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onset typically before 3 months: Ohtahara syndrome, Epilepsy of infancy with migrating focal seizures, B(F)NIS</td>
<td>Autosomal dominant/ de novo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onset typically after 3 months: West syndrome, Lennox-Gastaut syndrome, Myoclonic-astatic epilepsy, focal epilepsies with EEG features of electrical status epilepticus during sleep</td>
<td>Autosomal dominant/ de novo</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Epilepsy syndromes</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B(F)NIS</td>
<td>Autosomal dominant/de novo</td>
</tr>
<tr>
<td>SCN8A</td>
<td>Nav1.6</td>
<td><strong>Epileptic encephalopathies</strong></td>
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<td></td>
<td></td>
<td>Dravet syndrome, Ohtahara syndrome, West syndrome, Lennox-Gastaut syndrome</td>
<td>De novo</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Epilepsy syndromes</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benign familial infantile seizures, Infantile convulsions and paroxysmal choreoathetosis</td>
<td>Autosomal dominant/ de novo</td>
</tr>
<tr>
<td>SCN10A</td>
<td>Nav1.8</td>
<td><strong>Epileptic encephalopathies</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dravet syndrome</td>
<td>De novo</td>
</tr>
<tr>
<td>SCN1B</td>
<td></td>
<td><strong>Epileptic encephalopathies</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dravet syndrome</td>
<td>De novo</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Epilepsy syndromes</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GEFS+ (up to 8% of cases due to SCN1B mutations)</td>
<td>Autosomal dominant/de novo</td>
</tr>
</tbody>
</table>

Table 1: Clinical phenotypes linked to mutations in skeletal muscle and brain sodium channel genes
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Needle EMG: Myotonia</th>
<th>Motor NCS: CMAP</th>
<th>Repetitive Nerve Stimulation</th>
<th>Long Exercise Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myotonia</td>
<td>Present*</td>
<td>Normal</td>
<td>No data</td>
<td>Negative or Positive</td>
</tr>
<tr>
<td>Myotonia: SNEL</td>
<td>Present*</td>
<td>Normal</td>
<td>No data</td>
<td>Test not possible in an infant</td>
</tr>
<tr>
<td>Hyperkalemic Periodic Paralysis</td>
<td>Present</td>
<td>Normal</td>
<td>No data</td>
<td>Positive*</td>
</tr>
<tr>
<td>Hypokalaemic periodic paralysis</td>
<td>Absent</td>
<td>Normal</td>
<td>No data</td>
<td>Positive*</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Absent</td>
<td>Reduced*</td>
<td>No decrement</td>
<td>Negative</td>
</tr>
<tr>
<td>Congenital myasthenia</td>
<td>Absent</td>
<td>Normal</td>
<td>Stimulation dependent decrement in CMAP* (may require 10Hz stimulation frequency to demonstrate)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*denotes the single most useful neurophysiological test for each diagnosis  
NCS: nerve conduction studies  
CMAP: compound motor action potential

Table 2: Neurophysiological investigations most pertinent for each skeletal muscle channelopathy phenotype
<table>
<thead>
<tr>
<th><strong>Muscle sodium channelopathies</strong></th>
<th><strong>Recommended pharmacological therapies</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Myotonia</td>
<td>Sodium channel blockers: mexiletine*, lamotrigine*, flecainide, ranolazine, propafenone, carbamazepine</td>
</tr>
<tr>
<td>SNEL</td>
<td>Sodium channel blockers: Mexiletine, flecainide†, carbamazepine</td>
</tr>
<tr>
<td>Hyperkalaemic periodic paralysis</td>
<td>Potassium wasting diuretics: thiazides Carbonic anhydrase inhibitors: acetazolamide, dichlorphenamidine* Salbutamol PRN</td>
</tr>
<tr>
<td>Hypokalaemic periodic paralysis</td>
<td>Potassium sparing diuretics: aldosterone antagonists, amiloride Carbonic anhydrase inhibitors: acetazolamide, dichlorphenamidine* Oral potassium supplements PRN IV potassium if hypokalaemic induced ECG changes</td>
</tr>
<tr>
<td>Neonatal hypotonia</td>
<td>Usually none required and self-limiting but supplemental oxygen therapy and NG tube may be transiently needed</td>
</tr>
<tr>
<td>Congenital myopathy</td>
<td>Acetazolamide may benefit fluctuant symptoms in certain genotypes</td>
</tr>
<tr>
<td>Congenital myasthenia</td>
<td>Acetazolamide beneficial in one case</td>
</tr>
</tbody>
</table>

**Sodium channel epilepsies**

| Dravet Syndrome                  | First line: valproate, clobazam and stiripentol* Second line: topiramate, levetiracetam, bromides Others: Purified cannabidiol in oil*, fenfluramine **Caution:** sodium channel blocking agents frequently worsen seizures e.g. carbamazepine and lamotrigine |
| SCN2A early epilepsies (<3months) | Non-selective sodium channel blockers e.g. phenytoin and carbamazepine |
| SCN2A epilepsies (onset >3months) | Non-sodium channel inhibiting AEDs e.g., levetiracetam, benzodiazepines, and valproate **Caution:** Sodium channel blockers may worsen seizures |
| SCN8A epilepsies                  | Phenytoin, carbamazepine, and oxcarbazepine (supra-therapeutic doses may be required) |
| SCN3A epilepsies                  | Preliminary evidence for phenytoin and lacosamide |

*treatments for which there is RCT evidence available for efficacy †in vitro evidence to suggest best therapy for certain genotypes e.g. G1306E

Table 3: Recommended pharmacological therapies for muscle and brain sodium channelopathies
**Key Messages**

- There have been significant advances in understanding the mechanisms of muscle and brain diseases linked to dysfunction of voltage-gated sodium channels
- Biophysical sodium channel disruption leads to altered muscle or neuronal membrane excitability which often predicts the phenotype
- Common pathophysiological mechanisms span muscle and neuronal membranes
- The range of muscle and brain phenotypes is expanding, can be fatal, but are often treatable if diagnosed
- Diagnosis may be complex but increasing awareness is important and aided by increased availability of next generation sequencing
- Treatment with drugs that directly interact with the sodium channel or which modulate the ionic homeostatic environment are often effective in reducing morbidity and in some cases mortality