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

Emma Matthews[1], MRCP, Simona Balestrini[2], PhD, Prof Sanjay Sisodiya[2], FRCP, and

Prof Michael G Hanna, FRCP[1]

[1]MRC Centre for Neuromuscular Diseases, Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, and National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK

[2]Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, WC1N 3BG, and Chalfont Centre for Epilepsy, Bucks, UK

Corresponding author: Emma Matthews

emma.matthews@ucl.ac.uk Tel: 020 7679 2000 ext 84448

MRC Centre for Neuromuscular Diseases, Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, and National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK

Word counts Summary: 172 Manuscript: 5574

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 inexcitable 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)[9] and others can be associated with myotonia and episodic muscle weakness (paramyotonia congenita)[10,11]. Extremes of temperature, particularly cold and exertion or rest after exertion may exacerbate myotonic symptoms. Muscle hypertrophy is frequent[10].

Common (although only recently recognised) additional features in children include, extra-ocular myotonia causing strabismus or disturbed vision, contractures, toe walking, kyphosis, scoliosis, rotated glenohumeral joints and dysmorphic features[4,12-15] (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[13]. The most severe presentations have been termed severe neonatal episodic laryngospasm (SNEL)[5,16]. Infants experience abrupt onset of upper airway muscle myotonia (frequently causing stridor[3] although some events were silent)[4] in combination with respiratory, and limb muscle myotonia. Variable combinations of life-threatening apnoea, hypoxia, cyanosis, bradycardia and loss of consciousness can occur[16,17]. Bulbar impairment may result in failure to thrive requiring NG or PEG feeding[4]. 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[15,16]. Diagnostic uncertainty may result in infants spending many months in ITU with ventilatory support. Fatalities have been reported including a posthumous

diagnosis[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[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[3,15,17].

Periodic paralysis

Mutations in *SCN4A* can cause either hyperkalaemic (HyperPP) or hypokalaemic periodic paralysis (HypoPP)[19-21].

HyperPP: Age of onset is typically in the first decade[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[22]. This can lead to school absenteeism[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[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[2] and hyperPP[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 *SCN4A* reported 11 individuals from six families[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[6]. A second report of three brothers with compound heterozygous *SCN4A* mutations confirmed a very similar phenotype[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[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[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[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[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[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[30]. 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[31]. WS is characterized by spasms, an EEG finding termed hypsarrhythmia, and arrest of psychomotor development[32]. 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[33]. 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[34]. 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[35]. Epileptogenic mutations generally cause loss-of-function, whereas gain-of-function is associated with mutations causing familial hemiplegic migraine[36].

SCN2A mutations mainly cause disease with onset in the early developmental period[37], but some have also been found to cause later-onset neurological diseases[38,39], or a combination of both[40]. 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[41-43] *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)[43]. 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

epilepticus during sleep (ESES)[43]. Epileptic encephalopathy with choreoathetoid movements has also been reported in association with *SCN2A* variants[39].

SCN8A-related EOEEs include OS, WS, DS and LGS. EOEE appears to result from gain-of-function mutations[44], whereas a few loss-of-function mutations have been found in those with developmental delay, intellectual disability or autism, mainly without seizures[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[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[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[51,52]. Described mutant Nav1.3 channels show altered biophysical properties including prominent gain-of-function[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[53]. Affected individuals may present with disrupted cerebral cortical folding (polymicrogyria) of the perisylvian cortex, prominent speech and oral motor dysfunction, and EOEE[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[52]. The security of *SCN3A* as an ‘epilepsy gene’, and its associated phenotypic spectrum, await reporting of further cases.

So far, biallelic mutations in *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 *SCN10A* mutations, two with clinical phenotypes of LGS and infantile spasms, respectively, and three with autism[54].

The *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[55]. Recessive mutations in *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[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.

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 hemiclonic 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[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 *de novo* *SCN1A* mutations[58]. The large majority of pathogenic *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+[59]. Less frequently, DS, or a very similar phenotype, might be due to mutations in other genes: *SCN2A, SCN1B, SCN8A, STXBP1, GABRA1, GABRG2, GABRB3*[60].

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, *SCN1A* accounts for the largest fraction, with mutations identified in 19% of families, followed by *SCN1B* mutation in up to 8%[61]. Patients with FS/FS+ and *SCN1B* mutations have later onset of FS compared to patients with mutations in *SCN1A*[62].

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 *SCN2A* missense mutations[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)[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[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[41].

Loss-of-function mutations in *SCN8A* have been associated in two children with intellectual disability and developmental delay but no seizures[47]. Three individuals with autism are described with possibly/probably pathogenic compound heterozygous variants in *SCN10A*[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[66].

Mutations in *SCN2A* are an established cause of neonatal epilepsy (benign infantile seizures) with late-onset episodic ataxia[40], and schizophrenia[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[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[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[42].

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[68]. 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 [69] or clinical features may be associated with a mutation in another gene[60], 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%[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[71].

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[72-74]. 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[75,76]. 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[7,77]. 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[78].

General anaesthetic considerations

Propofol and non-depolarising anaesthetic agents appear effective and safe in muscle channelopathies[79]. A myotonic crisis can be precipitated by depolarising anaesthetics or suxamethonium, which can also provoke hyperkalaemia and fatal ventricular arrhythmia[80] and should be avoided. Muscle rigidity including the jaw can be profound, and intubation may become impossible [81]. 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[82,83] with supportive data for topiramate, levetiracetam, bromides, and the ketogenic diet[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[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[85]. Other agents such as fenfluramine are promising therapies[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[87], although the reasons underlying varying treatment responses in Dravet syndrome have not been fully elucidated[88]. Non-pharmacological treatment such as vagus nerve stimulation (VNS) can also be considered[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[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[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[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[90], the most effective being phenytoin, carbamazepine, and oxcarbazepine, usually at supra-therapeutic doses[50]. Ketogenic diet has been suggested to be effective in improving seizure control[50], 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[50].

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[52].

There are no data on potential treatments for *SCN10A or SCN1B*-related epilepsy, with the few EOEE patients recently described all having refractory epilepsy[54,56].

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[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[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%[94]. More recently, parental mosaicism has also been shown to be a more common phenomenon than expected, complicating risk counselling[93].

The risk of sudden death

Sudden infant death

We recently described rare heterozygous *SCN4A* mutations in cases of sudden infant death[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[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[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.

Acknowledgements

Part of this work was undertaken at University College London Hospitals/University College London, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. Dr Matthews is supported by a Wellcome Clinical Research Career Development Fellowship. Prof Hanna is supported by a Medical Research Council Centre grant (512225), the UCLH Biomedical Research Centre, and the National Highly Specialised Service (HSS) Department of Health UK. Dr Balestrini is supported by Muir Maxwell Trust and Drs Balestrini and Sisodiya are both supported by the Epilepsy Society.

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.

1. Cannon SC. Sodium Channelopathies of Skeletal Muscle. *Handb Exp Pharmacol* 2018; **246**: 309-30.
2. Matthews E, Guet A, Mayer M, et al. Neonatal hypotonia can be a sodium channelopathy: recognition of a new phenotype. *Neurology* 2008; **71**(21): 1740-2.
3. Matthews E, Manzur AY, Sud R, Muntoni F, Hanna MG. Stridor as a neonatal presentation of skeletal muscle sodium channelopathy. *Arch Neurol* 2011; **68**(1): 127-9.
4. Gay S, Dupuis D, Faivre L, et al. Severe neonatal non-dystrophic myotonia secondary to a novel mutation of the voltage-gated sodium channel (SCN4A) gene. *Am J Med Genet A* 2008; **146A**(3): 380-3.
5. Lion-Francois L, Mignot C, Vicart S, et al. Severe neonatal episodic laryngospasm due to de novo SCN4A mutations: a new treatable disorder. *Neurology* 2010; **75**(7): 641-5.
6. Zaharieva IT, Thor MG, Oates EC, et al. Loss-of-function mutations in SCN4A cause severe foetal hypokinesia or 'classical' congenital myopathy. *Brain* 2016; **139**(Pt 3): 674-91.
7. Tsujino A, Maertens C, Ohno K, et al. Myasthenic syndrome caused by mutation of the SCN4A sodium channel. *Proc Natl Acad Sci U S A* 2003; **100**(12): 7377-82.
8. Mannikko R, Wong L, Tester DJ, et al. Dysfunction of NaV1.4, a skeletal muscle voltage-gated sodium channel, in sudden infant death syndrome: a case-control study. *Lancet* 2018; **391**(10129): 1483-92.
9. Lerche H, Heine R, Pika U, et al. Human sodium channel myotonia: slowed channel inactivation due to substitutions for a glycine within the III-IV linker. *J Physiol* 1993; **470**: 13-22.
10. Matthews E, Fialho D, Tan SV, et al. The non-dystrophic myotonias: molecular pathogenesis, diagnosis and treatment. *Brain* 2010; **133**(Pt 1): 9-22.
11. McClatchey AI, Van den Bergh P, Pericak-Vance MA, et al. Temperature-sensitive mutations in the III-IV cytoplasmic loop region of the skeletal muscle sodium channel gene in paramyotonia congenita. *Cell* 1992; **68**(4): 769-74.
12. Desaphy JF, Carbonara R, D'Amico A, et al. Translational approach to address therapy in myotonia permanens due to a new SCN4A mutation. *Neurology* 2016; **86**(22): 2100-8.
13. Matthews E, Silwal A, Sud R, et al. Skeletal Muscle Channelopathies: Rare Disorders with Common Pediatric Symptoms. *J Pediatr* 2017; **188**: 181-5 e6.
14. Xu YQ, Liu XL, Huang XJ, Tian WT, Tang HD, Cao L. Novel Mutations in SCN4A Gene Cause Myotonia Congenita with Scoliosis. *Chin Med J (Engl)* 2018; **131**(4): 477-9.
15. Lehmann-Horn F, D'Amico A, Bertini E, et al. Myotonia permanens with Nav1.4-G1306E displays varied phenotypes during course of life. *Acta Myol* 2017; **36**(3): 125-34.
16. Caietta E, Milh M, Sternberg D, et al. Diagnosis and outcome of SCN4A-related severe neonatal episodic laryngospasm (SNEL): 2 new cases. *Pediatrics* 2013; **132**(3): e784-7.
17. Singh RR, Tan SV, Hanna MG, Robb SA, Clarke A, Jungbluth H. Mutations in SCN4A: a rare but treatable cause of recurrent life-threatening laryngospasm. *Pediatrics* 2014; **134**(5): e1447-50.
18. Portaro S, Rodolico C, Sinicropi S, Musumeci O, Valenzise M, Toscano A. Flecainide-Responsive Myotonia Permanens With SNEL Onset: A New Case and Literature Review. *Pediatrics* 2016; **137**(4).
19. Bulman DE, Scoggan KA, van Oene MD, et al. A novel sodium channel mutation in a family with hypokalemic periodic paralysis. *Neurology* 1999; **53**(9): 1932-6.
20. Fontaine B, Khurana TS, Hoffman EP, et al. Hyperkalemic periodic paralysis and the adult muscle sodium channel alpha-subunit gene. *Science* 1990; **250**(4983): 1000-2.
21. Ptacek LJ, George AL, Jr., Griggs RC, et al. Identification of a mutation in the gene causing hyperkalemic periodic paralysis. *Cell* 1991; **67**(5): 1021-7.
22. Venance SL, Cannon SC, Fialho D, et al. The primary periodic paralyses: diagnosis, pathogenesis and treatment. *Brain* 2006; **129**(Pt 1): 8-17.
23. Brancati F, Valente EM, Davies NP, et al. Severe infantile hyperkalaemic periodic paralysis and paramyotonia congenita: broadening the clinical spectrum associated with the T704M mutation in SCN4A. *J Neurol Neurosurg Psychiatry* 2003; **74**(9): 1339-41.

24. Kil TH, Kim JB. Severe respiratory phenotype caused by a de novo Arg528Gly mutation in the CACNA1S gene in a patient with hypokalemic periodic paralysis. *Eur J Paediatr Neurol* 2010; **14**(3): 278-81.
25. Mercier S, Lornage X, Malfatti E, et al. Expanding the spectrum of congenital myopathy linked to recessive mutations in SCN4A. *Neurology* 2017; **88**(4): 414-6.
26. Sloth CK, Denti F, Schmitt N, et al. Homozygosity for SCN4A Arg1142Gln causes congenital myopathy with variable disease expression. *Neurol Genet* 2018; **4**(5): e267.
27. Arnold WD, Feldman DH, Ramirez S, et al. Defective fast inactivation recovery of Nav 1.4 in congenital myasthenic syndrome. *Ann Neurol* 2015; **77**(5): 840-50.
28. Habbout K, Poulin H, Rivier F, et al. A recessive Nav1.4 mutation underlies congenital myasthenic syndrome with periodic paralysis. *Neurology* 2016; **86**(2): 161-9.
29. Elia N, Palmio J, Castaneda MS, et al. Myasthenic congenital myopathy from recessive mutations at a single residue in NaV1.4. *Neurology* 2019; **92**(13): e1405-e15.
30. Ohtahara S, Yamatogi Y. Ohtahara syndrome: with special reference to its developmental aspects for differentiating from early myoclonic encephalopathy. *Epilepsy Res* 2006; **70 Suppl 1**: S58-67.
31. McTague A, Appleton R, Avula S, et al. Migrating partial seizures of infancy: expansion of the electroclinical, radiological and pathological disease spectrum. *Brain* 2013; **136**(Pt 5): 1578-91.
32. Kato M. A new paradigm for West syndrome based on molecular and cell biology. *Epilepsy Res* 2006; **70 Suppl 1**: S87-95.
33. Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. *Epilepsia* 2011; **52 Suppl 5**: 3-9.
34. McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. *Lancet Neurol* 2016; **15**(3): 304-16.
35. Sadleir LG, Mountier EI, Gill D, et al. Not all SCN1A epileptic encephalopathies are Dravet syndrome: Early profound Thr226Met phenotype. *Neurology* 2017; **89**(10): 1035-42.
36. Bechi G, Rusconi R, Cestele S, Striano P, Franceschetti S, Mantegazza M. Rescuable folding defective NaV1.1 (SCN1A) mutants in epilepsy: properties, occurrence, and novel rescuing strategy with peptides targeted to the endoplasmic reticulum. *Neurobiol Dis* 2015; **75**: 100-14.
37. Catterall WA. Sodium channels, inherited epilepsy, and antiepileptic drugs. *Annu Rev Pharmacol Toxicol* 2014; **54**: 317-38.
38. Horvath GA, Demos M, Shyr C, et al. Secondary neurotransmitter deficiencies in epilepsy caused by voltage-gated sodium channelopathies: A potential treatment target? *Mol Genet Metab* 2016; **117**(1): 42-8.
39. Kobayashi Y, Tohyama J, Kato M, et al. High prevalence of genetic alterations in early-onset epileptic encephalopathies associated with infantile movement disorders. *Brain Dev* 2016; **38**(3): 285-92.
40. Schwarz N, Hahn A, Bast T, et al. Mutations in the sodium channel gene SCN2A cause neonatal epilepsy with late-onset episodic ataxia. *J Neurol* 2016; **263**(2): 334-43.
41. Ben-Shalom R, Keeshen CM, Berrios KN, An JY, Sanders SJ, Bender KJ. Opposing Effects on NaV1.2 Function Underlie Differences Between SCN2A Variants Observed in Individuals With Autism Spectrum Disorder or Infantile Seizures. *Biol Psychiatry* 2017; **82**(3): 224-32.
42. Sanders SJ, Campbell AJ, Cottrell JR, et al. Progress in Understanding and Treating SCN2A-Mediated Disorders. *Trends Neurosci* 2018; **41**(7): 442-56.
43. Wolff M, Johannesen KM, Hedrich UBS, et al. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. *Brain* 2017; **140**(5): 1316-36.
44. Blanchard MG, Willemsen MH, Walker JB, et al. De novo gain-of-function and loss-of-function mutations of SCN8A in patients with intellectual disabilities and epilepsy. *J Med Genet* 2015; **52**(5): 330-7.
45. Liu Y, Schubert J, Sonnenberg L, et al. Neuronal mechanisms of mutations in SCN8A causing epilepsy or intellectual disability. *Brain* 2019; **142**(2): 376-90.

46. Trudeau MM, Dalton JC, Day JW, Ranum LP, Meisler MH. Heterozygosity for a protein truncation mutation of sodium channel SCN8A in a patient with cerebellar atrophy, ataxia, and mental retardation. *J Med Genet* 2006; **43**(6): 527-30.
47. Wagnon JL, Barker BS, Ottolini M, et al. Loss-of-function variants of SCN8A in intellectual disability without seizures. *Neurol Genet* 2017; **3**(4): e170.
48. Wagnon JL, Mencacci NE, Barker BS, et al. Partial loss-of-function of sodium channel SCN8A in familial isolated myoclonus. *Hum Mutat* 2018; **39**(7): 965-9.
49. Larsen J, Carvill GL, Gardella E, et al. The phenotypic spectrum of SCN8A encephalopathy. *Neurology* 2015; **84**(5): 480-9.
50. Gardella E, Marini C, Trivisano M, et al. The phenotype of SCN8A developmental and epileptic encephalopathy. *Neurology* 2018; **91**(12): e1112-e24.
51. Li HJ, Wan RP, Tang LJ, et al. Alteration of Scn3a expression is mediated via CpG methylation and MBD2 in mouse hippocampus during postnatal development and seizure condition. *Biochim Biophys Acta* 2015; **1849**(1): 1-9.
52. Zaman T, Helbig I, Bozovic IB, et al. Mutations in SCN3A cause early infantile epileptic encephalopathy. *Ann Neurol* 2018; **83**(4): 703-17.
53. Smith RS, Kenny CJ, Ganesh V, et al. Sodium Channel SCN3A (NaV1.3) Regulation of Human Cerebral Cortical Folding and Oral Motor Development. *Neuron* 2018; **99**(5): 905-13 e7.
54. Kambouris M, Thevenon J, Soldatos A, et al. Biallelic SCN10A mutations in neuromuscular disease and epileptic encephalopathy. *Ann Clin Transl Neurol* 2017; **4**(1): 26-35.
55. Catterall WA. Voltage-gated sodium channels at 60: structure, function and pathophysiology. *J Physiol* 2012; **590**(11): 2577-89.
56. Ramadan W, Patel N, Anazi S, et al. Confirming the recessive inheritance of SCN1B mutations in developmental epileptic encephalopathy. *Clin Genet* 2017; **92**(3): 327-31.
57. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infancy: Dravet syndrome. *Adv Neurol* 2005; **95**: 71-102.
58. Zuberi SM, Brunklaus A, Birch R, Reavey E, Duncan J, Forbes GH. Genotype-phenotype associations in SCN1A-related epilepsies. *Neurology* 2011; **76**(7): 594-600.
59. Brunklaus A, Ellis R, Stewart H, et al. Homozygous mutations in the SCN1A gene associated with genetic epilepsy with febrile seizures plus and Dravet syndrome in 2 families. *Eur J Paediatr Neurol* 2015; **19**(4): 484-8.
60. Steel D, Symonds JD, Zuberi SM, Brunklaus A. Dravet syndrome and its mimics: Beyond SCN1A. *Epilepsia* 2017; **58**(11): 1807-16.
61. Zhang YH, Burgess R, Malone JP, et al. Genetic epilepsy with febrile seizures plus: Refining the spectrum. *Neurology* 2017; **89**(12): 1210-9.
62. Sijben AE, Sithinamsuwan P, Radhakrishnan A, et al. Does a SCN1A gene mutation confer earlier age of onset of febrile seizures in GEFS+? *Epilepsia* 2009; **50**(4): 953-6.
63. Misra SN, Kahlig KM, George AL, Jr. Impaired NaV1.2 function and reduced cell surface expression in benign familial neonatal-infantile seizures. *Epilepsia* 2008; **49**(9): 1535-45.
64. Gardella E, Becker F, Moller RS, et al. Benign infantile seizures and paroxysmal dyskinesia caused by an SCN8A mutation. *Ann Neurol* 2016; **79**(3): 428-36.
65. Li J, Cai T, Jiang Y, et al. Genes with de novo mutations are shared by four neuropsychiatric disorders discovered from NPdenovo database. *Mol Psychiatry* 2016; **21**(2): 290-7.
66. Dichgans M, Freilinger T, Eckstein G, et al. Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. *Lancet* 2005; **366**(9483): 371-7.
67. Carroll LS, Woolf R, Ibrahim Y, et al. Mutation screening of SCN2A in schizophrenia and identification of a novel loss-of-function mutation. *Psychiatr Genet* 2016; **26**(2): 60-5.
68. Connolly MB. Dravet Syndrome: Diagnosis and Long-Term Course. *Can J Neurol Sci* 2016; **43 Suppl 3**: S3-8.
69. Li J, Gao K, Yan H, et al. Reanalysis of whole exome sequencing data in patients with epilepsy and intellectual disability/mental retardation. *Gene* 2019; **700**: 168-75.

70. Snoeijen-Schouwenaars FM, van Ool JS, Verhoeven JS, et al. Diagnostic exome sequencing in 100 consecutive patients with both epilepsy and intellectual disability. *Epilepsia* 2019; **60**(1): 155-64.
71. Borlot F, de Almeida BI, Combe SL, Andrade DM, Filloux FM, Myers KA. Clinical utility of multigene panel testing in adults with epilepsy and intellectual disability. *Epilepsia* 2019; **60**(8): 1661-9.
72. Statland JM, Bundy BN, Wang Y, et al. Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: a randomized controlled trial. *JAMA* 2012; **308**(13): 1357-65.
73. Statland JM, Fontaine B, Hanna MG, et al. Review of the Diagnosis and Treatment of Periodic Paralysis. *Muscle Nerve* 2018; **57**(4): 522-30.
74. Andersen G, Hedermann G, Witting N, Duno M, Andersen H, Vissing J. The antimyotonic effect of lamotrigine in non-dystrophic myotonias: a double-blind randomized study. *Brain* 2017; **140**(9): 2295-305.
75. Desaphy JF, Modoni A, Lomonaco M, Camerino DC. Dramatic improvement of myotonia permanens with flecainide: a two-case report of a possible bench-to-bedside pharmacogenetics strategy. *Eur J Clin Pharmacol* 2013; **69**(4): 1037-9.
76. Farinato A, Altamura C, Imbrici P, et al. Pharmacogenetics of myotonic hNav1.4 sodium channel variants situated near the fast inactivation gate. *Pharmacol Res* 2019; **141**: 224-35.
77. Matthews E, Hartley L, Sud R, Hanna MG, Muntoni F, Munot P. Acetazolamide can improve symptoms and signs in ion channel-related congenital myopathy. *J Neurol Neurosurg Psychiatry* 2019; **90**(2): 243-5.
78. Ahmed I, Chilimuri SS. Fatal dysrhythmia following potassium replacement for hypokalemic periodic paralysis. *West J Emerg Med* 2010; **11**(1): 57-9.
79. Russell SH, Hirsch NP. Anaesthesia and myotonia. *Br J Anaesth* 1994; **72**(2): 210-6.
80. Al-Takrouri H, Martin TW, Mayhew JF. Hyperkalemic cardiac arrest following succinylcholine administration: The use of extracorporeal membrane oxygenation in an emergency situation. *J Clin Anesth* 2004; **16**(6): 449-51.
81. Farbu E, Softeland E, Bindoff LA. Anaesthetic complications associated with myotonia congenita: case study and comparison with other myotonic disorders. *Acta Anaesthesiol Scand* 2003; **47**(5): 630-4.
82. Chiron C, Marchand MC, Tran A, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. *Lancet* 2000; **356**(9242): 1638-42.
83. Kassai B, Chiron C, Augier S, et al. Severe myoclonic epilepsy in infancy: a systematic review and a meta-analysis of individual patient data. *Epilepsia* 2008; **49**(2): 343-8.
84. Wallace A, Wirrell E, Kenney-Jung DL. Pharmacotherapy for Dravet Syndrome. *Paediatr Drugs* 2016; **18**(3): 197-208.
85. Devinsky O, Cross JH, Laux L, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med* 2017; **376**(21): 2011-20.
86. Polster T. Individualized treatment approaches: Fenfluramine, a novel antiepileptic medication for the treatment of seizures in Dravet syndrome. *Epilepsy Behav* 2019; **91**: 99-102.
87. Dalic L, Mullen SA, Roulet Perez E, Scheffer I. Lamotrigine can be beneficial in patients with Dravet syndrome. *Dev Med Child Neurol* 2015; **57**(2): 200-2.
88. Andrade DM. Dravet syndrome, lamotrigine, and personalized medicine. *Dev Med Child Neurol* 2015; **57**(2): 118-9.
89. Ko A, Jung DE, Kim SH, et al. The Efficacy of Ketogenic Diet for Specific Genetic Mutation in Developmental and Epileptic Encephalopathy. *Front Neurol* 2018; **9**: 530.
90. Boerma RS, Braun KP, van den Broek MP, et al. Remarkable Phenytoin Sensitivity in 4 Children with SCN8A-related Epilepsy: A Molecular Neuropharmacological Approach. *Neurotherapeutics* 2016; **13**(1): 192-7.
91. Epi KC, Epilepsy Phenome/Genome P, Allen AS, et al. De novo mutations in epileptic encephalopathies. *Nature* 2013; **501**(7466): 217-21.

92. Halvorsen M, Petrovski S, Shellhaas R, et al. Mosaic mutations in early-onset genetic diseases. *Genet Med* 2016; **18**(7): 746-9.
93. Myers CT, Hollingsworth G, Muir AM, et al. Parental Mosaicism in "De Novo" Epileptic Encephalopathies. *N Engl J Med* 2018; **378**(17): 1646-8.
94. Helbig KL, Farwell Hagman KD, Shinde DN, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. *Genet Med* 2016; **18**(9): 898-905.
95. Turkdogan D, Matthews E, Usluer S, et al. Possible role of SCN4A skeletal muscle mutation in apnea during seizure. *Epilepsia Open* 2019; **4**(3): 498-503.
96. Skluzacek JV, Watts KP, Parsy O, Wical B, Camfield P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. *Epilepsia* 2011; **52 Suppl 2**: 95-101.
97. Dravet C BM, Oguni H, et al. Dravet Syndrome (severe myoclonic epilepsy in infancy): John Libby Eurotext Ltd, UK; 2012.
98. Cooper MS, McIntosh A, Crompton DE, et al. Mortality in Dravet syndrome. *Epilepsy Res* 2016; **128**: 43-7.
99. Frasier CR, Zhang H, Offord J, et al. Channelopathy as a SUDEP Biomarker in Dravet Syndrome Patient-Derived Cardiac Myocytes. *Stem Cell Reports* 2018; **11**(3): 626-34.
100. Johannesen KM, Gardella E, Scheffer I, et al. Early mortality in SCN8A-related epilepsies. *Epilepsy Res* 2018; **143**: 79-81.
101. Myers KA, Shevell MI, Sebire G. Sudden unexpected death in GEFS+ families with sodium channel pathogenic variants. *Epilepsy Res* 2019; **150**: 66-9.
102. Harden C, Tomson T, Gloss D, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2017; **88**(17): 1674-80.
103. Stunnenberg BC, Raaphorst J, Groenewoud HM, et al. Effect of Mexiletine on Muscle Stiffness in Patients With Nondystrophic Myotonia Evaluated Using Aggregated N-of-1 Trials. *JAMA* 2018; **320**(22): 2344-53.
104. Matthews E, Hanna MG. Dichlorphenamide efficacy in the primary periodic paralyses. *Expert Opin Orphan D* 2017; **5**(3): 285-90.

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

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

Table 1: Clinical phenotypes linked to mutations in skeletal muscle and brain sodium channel genes

	Needle EMG: Myotonia	**Motor NCS: CMAP**	**Repetitive Nerve Stimulation**	**Long Exercise Test**
Myotonia	Present*	Normal	No data	Negative or Positive
Myotonia: SNEL	Present*	Normal	No data	Test not possible in an infant
Hyperkalemic Periodic Paralysis	Present	Normal	No data	Positive*
Hypokalaemic periodic paralysis	Absent	Normal	No data	Positive*
Myopathy	Absent	Reduced*	No decrement	Negative
Congenital myasthenia	Absent	Normal	Stimulation dependent decrement in CMAP* (may require 10Hz stimulation frequency to demonstrate)	Negative

*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

	Recommended pharmacological therapies
Muscle sodium channelopathies	
Myotonia	Sodium channel blockers: mexiletine*, lamotrigine*, flecainide, ranolazine, propafenone, carbamazepine
SNEL	Sodium channel blockers: Mexiletine, flecainide†, carbamazepine
Hyperkalaemic periodic paralysis	Potassium wasting diuretics: thiazides Carbonic anhydrase inhibitors: acetazolamide, dichlorphenamide* Salbutamol PRN
Hypokalaemic periodic paralysis	Potassium sparing diuretics: aldosterone antagonists, amiloride Carbonic anhydrase inhibitors: acetazolamide, dichlorphenamide* Oral potassium supplements PRN IV potassium if hypokalaemic induced ECG changes
Neonatal hypotonia	Usually none required and self-limiting but supplemental oxygen therapy and NG tube may be transiently needed
Congenital myopathy	Acetazolamide may benefit fluctuant symptoms in certain genotypes
Congenital myasthenia	Acetazolamide beneficial in one case
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 (onset <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