CLINICAL PRACTICE ARTICLE

REVISED Sodium channel myotonia may be associated with high-risk brief resolved unexplained events [version 2; peer review: 2 approved]

Gabriel Cea [1,2], Daniel Andreu[1], Elaine Fletcher[3], Sithara Ramdas[4], Richa Sud[5], Michael G. Hanna[6], Emma Matthews [6]

[1]Departamento de Ciencias Neurológicas, Universidad de Chile, Santiago, Chile
[2]Servicio de Neurología, Hospital Salvador, Santiago, Chile
[3]Department of Clinical Genetics, Centre for Genomic and Experimental Medicine, Western General Hospital, Edinburgh, EH5 2GL, UK
[4]Department of Paediatric Neurology, John Radcliffe Hospital NHS Foundation Trust, Oxford, UK
[5]Neurogenetics Unit, UCL Queen Square Institute of Neurology, London, UK
[6]Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, UK

v2 **First published:** 31 Mar 2020, **5**:57
https://doi.org/10.12688/wellcomeopenres.15798.1
Latest published: 12 May 2020, **5**:57
https://doi.org/10.12688/wellcomeopenres.15798.2

Abstract

Brief resolved unexplained events (BRUEs) have numerous and varied causes posing a challenge to investigation and management. A subset of infants with the neuromuscular disorder sodium channel myotonia, due to mutations in the *SCN4A* gene, experience apnoeic events due to laryngospasm (myotonia) of the upper airway muscles that may present as a BRUE. We sought to ascertain the frequency, severity and outcome of infants carrying the G1306E *SCN4A* mutation commonly associated with this presentation. We report 14 new cases of individuals with the G1306E mutation from three unrelated families and perform a literature review of all published cases. Infants with the G1306E mutation almost universally experience laryngospasm and apnoeic events. The severity varies significantly, spans both low and high-risk BRUE categories or can be more severe than criteria for a BRUE would allow. At least a third of cases require intensive care unit (ICU) care. Seizure disorder is a common erroneous diagnosis. Apnoeas are effectively reduced or abolished by appropriate treatment with anti-myotonic agents. Probands with the G1306E mutation who are family planning need to be counselled for the likelihood of post-natal complications. There is readily available and extremely effective treatment for the episodic laryngospasm and apnoea caused by this mutation. Proactively seeking clinical evidence of myotonia or muscle hypertrophy with consideration of CK,EMG and genetic testing in high risk BRUEs or more complex apnoeic events may reduce avoidable and prolonged ICU admissions, patient morbidity and potentially mortality.

Keywords

Sodium channel, Muscle Disease, Myotonia, Laryngospasm, Stridor, Apnoea, Channelopathy, Paediatric

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 12 May 2020	✓ report	✓ report
version 1 31 Mar 2020	? report	✓ report

1 **Sophie Nicole**, Institut génomique fonctionnelle, UM, Inserm, CNRS, Paris, France

2 **Maria Elena Farrugia**, Queen Elizabeth University Hospital, Glasgow, UK

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Emma Matthews (emma.matthews@ucl.ac.uk)

Author roles: Cea G: Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Andreu D**: Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Fletcher E**: Resources, Writing – Review & Editing; **Ramdas S**: Resources, Writing – Review & Editing; **Sud R**: Formal Analysis, Writing – Review & Editing; **Hanna MG**: Funding Acquisition, Writing – Review & Editing; **Matthews E**: Conceptualization, Funding Acquisition, Investigation, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: 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 Centre's funding scheme. Dr Matthews is supported by a Wellcome Trust Clinical Research Career Development Fellowship (209583). University College London's National Muscle Channelopathy Service is supported by National Health Service England specialist commissioning (http://www.cnmd.ac.uk). Prof Hanna is supported by the UCLH Biomedical Research Centre, and the National Highly Specialised Service (HSS) Department of Health, UK.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Cea G, Andreu D, Fletcher E *et al.* **Sodium channel myotonia may be associated with high-risk brief resolved unexplained events [version 2; peer review: 2 approved]** Wellcome Open Research 2020, **5**:57
https://doi.org/10.12688/wellcomeopenres.15798.2

First published: 31 Mar 2020, **5**:57 https://doi.org/10.12688/wellcomeopenres.15798.1

REVISED **Amendments from Version 1**

This version takes account of both reviewer's comments. We have referred to the term SNEL earlier in the manuscript to define the severe respiratory complications with laryngospasm of SCN4A myotonia, added extra clinical detail in light of points raised and included genetic analysis in the recommended investigations. We have amended Figure 3 as there was a mistake between numbers of individuals between Table 1 and the text. We have also amended the Table 2 legend and detailed the acronyms.

Any further responses from the reviewers can be found at the end of the article

Introduction

Brief resolved unexplained events BRUEs (formerly apparent life threatening events, ALTEs) are defined by the American Academy of Pediatrics (AAP) as a sudden, brief (<1 min) resolved episode of one or more of: cyanosis or pallor, absent, decreased or irregular breathing, marked change in tone (hyper or hypotonia) and altered level of responsiveness occurring before the age of one year[1]. The AAP have issued clinical guidelines on factors that allow a BRUE to be further classified as low risk or high risk[1]. Low risk events are not thought to be associated with any increased risk of death or significant detrimental outcome and recommendations are provided to minimise unnecessary investigations or hospital admissions. High-risk events are more likely to be associated with an underlying disorder. Longer events or those with an abnormal history or examination at presentation are excluded from the definition of a BRUE and should prompt further investigation.

Mutations in the *SCN4A* gene cause a form of non-dystrophic myotonia known as paramyotonia congenita or sodium channel myotonia[2]. The typical clinical presentation is of episodic myotonia (delayed muscle relaxation after contraction) affecting the limb and face muscles, exacerbated by exercise, cold temperature, potassium rich food, and associated with variable episodes of muscle weakness. Symptoms and morbidity can be significantly improved by the use of sodium channel blocking drugs e.g. mexiletine[3,4].

A subset of infants, however, present with respiratory symptoms and/or laryngospasm due to myotonia of the respiratory and upper airway muscles[5,6]. The severity of these episodes varies from self-resolving in seconds to prolonged or recurrent events known as SNEL: severe neonatal episodic laryngospasm associated with hypertonia, apnoea, loss of consciousness and bradycardia[7]. In between episodes, infants are usually well. Of the myotonic infants who present in this way the majority of them have carried the same *SCN4A* gene mutation, G1306E, p. (Gly1306Glu), usually in *De novo* form. Even in adults this mutation is regarded as somewhat of an outlier causing myotonia at the severe end of the spectrum, the description of symptoms caused by the mutation being termed "myotonia permanens"[8].

A clear understanding of the spectrum of severity and outcome is important to guide the specific monitoring and management of infants born with the G1306E mutation but there is a wider need to inform investigations for any infant presenting with recurrent apnoea or BRUE. We report 14 new cases from three unrelated families with the G1306E mutation and review the literature of all described cases to determine the extent, severity and treatment of myotonic symptoms and in particular respiratory complications.

Methods

All procedures were conducted as part of routine clinical care.

Standard protocol approval, registration and patient consent

The study was performed under the ethics guidelines issued by our institutions, with informed consent obtained from all participants for genetic studies and publication. We confirm that we have obtained permission to use images from the individuals included in this presentation, including explicit written permission from the mother to publish Figure 2.

Genetic analysis of the *SCN4A* gene was performed at the Neurogenetics Unit, National Hospital for Neurology and Neurosurgery as provided by the Channelopathy Highly Specialized National Service for rare disease. Samples underwent next-generation sequencing on an Illumina HiSeq after enrichment with an Illumina custom Nextera Rapid Capture panel (Illumina, Inc, San Diego, CA).

Case reports

Family A

This large family from Chile includes 16 affected members of five generations who carry the *SCN4A* G1306E mutation (Figure 1A). Detailed clinical history and examination were available for 12 individuals (Table 1). All 12 had myotonia evident from birth, including laryngospasm and stridor that occurred universally in affected infants. During these episodes, the mothers reported that their babies stopped breathing for a few seconds, never more than a minute; they looked startled but did not become cyanosed. The episodes were more common in winter when they occurred one to two times a day on an almost daily basis, whereas in summer they occurred two to three times per week. They occurred mainly during the day but sometimes while the infants were sleeping. Cold environment, crying and breast or bottle-feeding were common provoking factors. These episodes were present until they were approximately 18 months old and the parents ultimately learnt to deal with them without seeking medical help. There was no history of prolonged respiratory complications requiring hospitalisation. In a few cases, salbutamol was given, as either an inhaler or syrup by their paediatricians, but this worsened the episodes to the point of cyanosis.

All children had normal psychomotor development and no impairment in their activities of daily living. With increasing age, the myotonia was more generally distributed, particularly affecting the limbs and face (as is typical in older children and adults) and exacerbated by characteristic triggers of cold, physical activity, crying, emotional distress or potassium-rich food. Myotonia described as painful cramps was common in

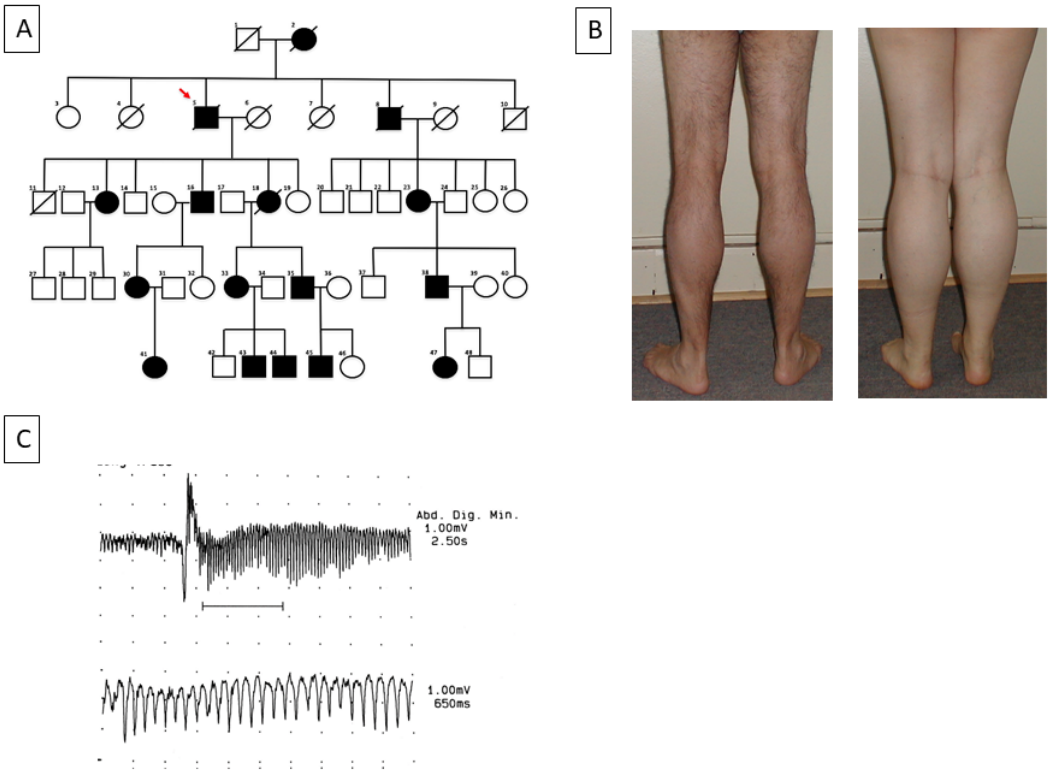

Figure 1. (**A**) Genogram of Family. Red arrow indicates index case. (**B**) Calf hypertrophy in a male (case A:16) and female (case A:30). (**C**) EMG showing myotonic activity exacerbated by needle movement from case A:30.

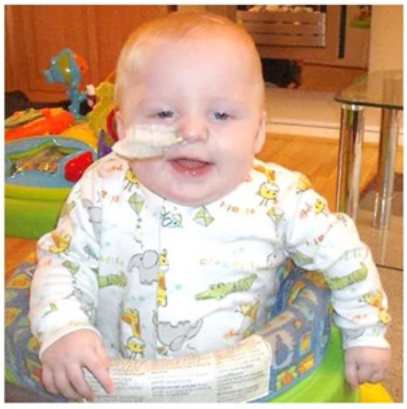

Figure 2. Case C as an infant demonstrating nasogastric tube required for feeding.

all cases and although these tended to be more frequent and incapacitating in females, they diminished in all affected family members, as they got older.

Examination demonstrated a robust physical build, more marked in the females than in the males (Figure 1B). In all patients where creatine kinase (CK) level was assessed it was normal or elevated between two- to three-fold of normal values (24–170 U/L) in all cases but one (see Table 1). The exception was a patient whose CK level rose to 3300 U/L in the context of a severe respiratory insufficiency due to influenza infection, for which she was admitted to hospital. She was admitted to the intensive care unit (ICU) for 2 months on mechanical ventilation, due to a respiratory distress syndrome, secondary systemic infections and developed a critical illness neuropathy. She did not receive any specific treatment for her myotonia. Electromyography showed permanent myotonic discharges (Figure 1C) in all cases.

In terms of treatment, most of the affected individuals chose not to take any medication as they felt symptoms were tolerable without. Eight had some benefit from using phenytoin or carbamazepine but took the medication sporadically due to side effects of feeling "floppy" and somnolent. Two were prescribed mexiletine but did not tolerate it due to a feeling of general malaise.

Other notable history was of adverse anaesthetic events in four family members (Table 1) when erroneously given volatile induction anaesthetic and depolarizing agents (suxamethonium), consisting of moderate generalized myotonia including bulbar and jaw muscles that made intubation and ventilation difficult but not impossible. The episodes lasted for approximately 10 to 15 minutes and were not associated with any increase in body temperature, but in the three cases where CK level was

Table 1. Clinical features of new cases of G1306E.

Cases	A:5	A:16	A:30	A:41	A:18	A:33	A:43	A:44	A:35	A:45	A:13	A:23	B	C
Current Age (years)	Died at 86	60	37	9	Died at 69	42	11	10	34	7	61	79	36	9
Age of onset of myotonia	Birth	Birth	Birth	Birth	Birth	Birth	Birth	Birth	Birth	Birth	Birth	Birth	Infancy	5 days
Neonatal Hypotonia	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Inspiratory stridor/ Laryngospasm	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Myotonia distribution	Generalized	Arms and legs	Generalized	Eyes, legs	Face, ocular, abdominal, arms, legs	Ocular, hands, legs	Ocular, hands, legs	Ocular, hands, legs	Ocular, hands, legs	Generalized	Generalized	Generalized	Hands, arms, legs, ocular	Generalised
Site of severe myotonia	Hands, legs	Hands	Hands, legs	Ocular, legs	Ocular, hands, legs	Hands	Legs	Arms	Hands	Ocular	Ocular, legs and hands	Ocular, legs, arms	Hands, arms and legs	Ocular, Hands, Legs
Exacerbation with cold	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Exacerbation with exercise	(+)	(+)	(+)	(+)	(+)	(+)	(-)	(-)	(+)	(+)	(+)	(+)	(+)	(-)
Anaesthetic problems	Yes	No	No	No	Yes	No	No	No	No	No	Yes	Yes	No	No
Painful cramps	Variable	Severe	Moderate	Moderate	Severe	Mild	Mild	Mild	Moderate	Mild	Moderate	Moderate	Moderate	Moderate
Food Triggers	Fish, Watermelon	Wine, watermelon cherry, banana, peach, fish, Tabaco	Wine, watermelon cherry, meat	Cherry, peach, watermelon, orange, fish	Fish, pork, meat, watermelon spinach	Fish, pork, meat, peach, cherry, banana, kiwi	Fish, pork, meat, cherry and peach	Fish, pork, meat, cherry and peach	Peach, cherry and banana	Fish, watermelon, pork, meat, cherry, peach	Watermelon, melon, banana,	melon, peach, grapes, apple, banana, tomato, fish, cucumber	None noted	None noted
Muscle hypertrophy	Calf	Calf	Calf	No	No	No	No	No	Calf	No	No	Calf	Calf, biceps, triceps	Trapezius, calf, biceps
Creatine kinase IU/L	568*/429* 166	240	445/173	NA	552* 290	260	NA	NA	240	NA	3300** 552* 250	N/A* 330	N/A	

*Following adverse anaesthetic reaction. **Associated with influenza infection and respiratory failure. NA, not available.

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available a moderate elevation was demonstrated (see Table 1). All deaths in family members were for causes unrelated to their myotonia.

Proband B

A 36-year-old Caucasian woman was born by planned caesarean section at term in the U.K. with no concerns at birth. She was combination fed by breast and bottle without choking or swallowing difficulties.

During the first year of life, she was described as having "stiffening episodes" that lasted for seconds only and self-resolved; the main trigger was crying. On one occasion she was noted to be crying, became stiff, pale and appeared to lose consciousness, but recovered quickly. No other episodes were as dramatic as this and there were no admissions to hospital.

At around 18 months of age her mother first noted her defined leg and arm muscles whilst bathing her and parents observed her calves becoming "stiff" when she climbed stairs. A clinical diagnosis of myotonia congenita was made when the patient was approximately seven years old. Subsequent genetic investigations at age 30 years demonstrated the heterozygous pathogenic variant c.3917G>A, p. (Gly1306Glu), i.e. G1306E in the *SCN4A* gene confirming a diagnosis of sodium channel myotonia. Parents both tested negative for this variant and *De novo* inheritance was confirmed.

The main effects of her myotonia in adulthood are typical of sodium channel myotonia, e.g. myotonia of the arm and leg muscles causing difficulty closing/opening hands and impaired walking speed. These symptoms last for a few seconds, or minutes at most. Cold wind and exercise are exacerbating factors and symptoms are generally better in warm climates. Examination is notable for hypertrophy of calves, biceps, and triceps muscles. Acetazolamide (250 mg) twice daily gives good symptomatic control. Two previous uneventful anaesthetics have been given, one before her myotonic disorder was diagnosed, although we do not have details of the agents administered.

Proband C

A nine-year-old non-identical male twin was born by emergency caesarean section in the U.K. for cord prolapse at 36+6 weeks gestation. He was healthy at birth with good APGAR scores. At 5 days old, he was admitted to his local hospital with recurrent episodes of apnoea, cyanosis and whole body "stiffening" that could occur up to 20 times a day. A seizure disorder was considered but EEG during these episodes was normal. His parents noted he had always had difficulty opening his eyes and choking on feeds with an unsafe swallow that required NG tube insertion (Figure 2) and subsequently PEG tube insertion. At age 8 months examination demonstrated a Herculean appearance and eyelid myotonia. There was global developmental delay. There was no family history of note. EMG demonstrated myotonic discharges and genetic investigations confirmed a *De novo SCN4A* mutation c.3917G>A; p.G1306E. He was treated with phenytoin, carbamazepine and mexiletine prior to genetic diagnosis but without benefit. Episodes of laryngospasm significantly reduced with acetazolamide and he remains on this. He continues to have daily episodes of limb muscle myotonia which impair his motor abilities. He is now taking a normal oral diet and PEG tube was removed at 6 years of age. Episodes of laryngospasm resolved by the age of 7 years.

Review of the literature

Literature review was conducted by searches of PubMed using a combination of the terms SCN4A, sodium channel myotonia, laryngospasm, stridor, and G1306E. Articles were also identified through searches of the authors own files. Only papers published in English were considered.

A review of the literature for the *SCN4A* G1306E mutation identified 30 affected individuals from 24 families. A summary of pertinent findings is summarised in Table 2 with a focus on laryngospasm, severity of respiratory complications, anaesthetic events and treatment.

The literature review mirrored the frequency of stridor/laryngospasm and respiratory events seen in our newly described patients (100%) with 25/30 (83%) reported G1306E cases experiencing these symptoms (Figure 3). Similar to our cases, this also began at birth or in the neonatal period in the majority although onset could be delayed by up to nine months of age (Table 2). A total of 11/25 (46%) of those experiencing stridor/laryngospasm who were reported in the literature had data available to demonstrate they required recurrent hospitalisation or ICU care for respiratory compromise which could be up to 6 months in duration before an accurate diagnosis was made. In every case requiring hospitalisation, the G1306E mutation had arisen *De novo* in the child. This may reflect more severe myotonia associated with de novo mutation or that in cases where parents were themselves affected they were more aware of the risk of myotonia including respiratory presentations and better prepared to manage these symptoms.

Nearly all reported cases received pharmacological treatment. The effect of treatment on laryngospasm was often dramatic and rapid with complete resolution or significant improvement of apnoeas enabling discharge from hospital within days. Adverse anaesthetic events were rare (2 cases), but fatal in one case. In both, suxamethonium had been administered[9].

Discussion and conclusions

Myotonia caused by mutations in the *SCN4A* gene was generally considered debilitating but not a life-threatening condition. More recently, the severe laryngeal and respiratory muscle presentations seen in infancy have coined the phenotype SNEL (severe neonatal episodic laryngospasm)[6,10]. In between episodes, infants usually appear well and many have been misdiagnosed with reflux, laryngomalacia or epilepsy (despite a normal EEG)[9]. Substantial delay in diagnosis is common with the more severe cases spending on average 6 months in ICU[5,6,9]. The condition is, however, very sensitive to treatment with anti-myotonic agents, usually sodium channel blockers, which have a dramatic effect on apnoeic symptoms (Table 2).

Table 2. Summary of G1306E cases reported in the literature.

Case	Sex	Age at onset of myotonia	Inheritance	Inspiratory stridor/ Laryngospasm	ICU care required	Anaesthetic reaction	Treatment	Ref
1	M	Birth	*De novo*	Yes	Yes –mask ventilation and oxygen therapy		NS	9
2	F	Birth	*De novo*	Yes			Mexiletine	9
3	F	Neonate	*De novo*	Yes			Carbamazepine and mexiletine effective	9
4	F	Birth	*De novo.* Mother of 4:1	Yes	NS but LOC reported and recurrent hospitalisation		Flecainide more effective than carbamazepine or mexiletine	9,11
4:1	M	Birth	AD Son of 4	Yes			Mexiletine – limited benefit Flecainide much more effective	9,11
5	M	Birth	*De novo*	Yes	NS but LOC reported and recurrent hospitalisation		Mexiletine better than carbamazepine	9
6	F	Infant	*De novo*	Yes			Flecainide effective Mexiletine + lamotrigine –not effective	9
7	M	Neonate	*De novo*	Yes	NS but LOC reported and recurrent hospitalisation		Mexiletine	9
8	M	Neonate	*De novo*	No			Mexiletine	9
9*	M	Neonate	Reported *De novo*	Yes	NS but LOC reported and recurrent hospitalisation	Yes – fatal MH like event	Dilantin, desipramine	9
9:1	M	Birth		Onset at 4 months			Dilantin, desipramine	9
9:2	F	Neonate		Yes		Yes succinylcholine induced event	Dilantin, despramine	9
10**	M	Birth	*De novo*	Onset at 9 months			Mexiletine	9
11	M	Early childhood	AD	No (some bulbar and respiratory symptoms reported but not severe)	No		Mexiletine, Oxcarbazepine, thiazide diuretics – no benefit	
Acetazolamide – some improvement	15							
11:1	M	Birth	AD Son of 11	No	No		None	12
12	M	Birth	*De novo*	No	No		None reported	13
13	M	Childhood	Presumed *De novo*	No	No		None reported	13

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Case	Sex	Age at onset of myotonia	Inheritance	Inspiratory stridor/ Laryngospasm	ICU care required	Anaesthetic reaction	Treatment	Ref
14	F	Birth	*De novo*	Yes	NS but recurrent hospitalisation		Carbamazepine – minimal benefit Mexiletine + Acetazolamide –minimal benefit Flecainide – good response	7
15	M	Neonate	*De novo* (+CLCN1 M485V)	Yes	No		Mexiletine – good response	14
15:1+ 15:2	M	Neonate	AD (G1306E +M485V) Monozygotic twin sons of 15	Yes	no		No treatment	14
16	M	Neonate	*De novo*	Yes	Yes – tracheostomy 3months		Carbamazepine – good response, tracheostomy removed	6
17	M	Neonate	*De novo*	yes	Yes		Mexiletine – good response	6
18	F	Birth	NS	Yes	NS		NS	15
19	M	Birth	*De novo*	Yes	Yes		Mexiletine – some benefit Further benefit from addition of acetazolamide	10
20	M	Birth	*De novo*	Yes	Yes		Carbamazepine – good response	10
21	F	8 weeks	*De novo*	Yes	Yes		Carbamazepine – good response	16
16	F	Neonate	NS – father possibly affected	Yes	No		Carbamazepine – good response	16
23	F	Neonate	AD – father affected	Yes	No		Carbamazepine – good response	16
24	M	Neonate	*De novo*	Yes	NS		Mexiletine - good response, abolished respiratory episodes	17

* Died of cardiorespiratory failure age 11 following General anaesthetic with Malignant Hyperthermia (MH) like event (severe myotonia) and hyperkalaemia.

** Died age 22 – cause unclear. NS, not specified. AD: autosomal dominant, LOC: loss of consciousness.

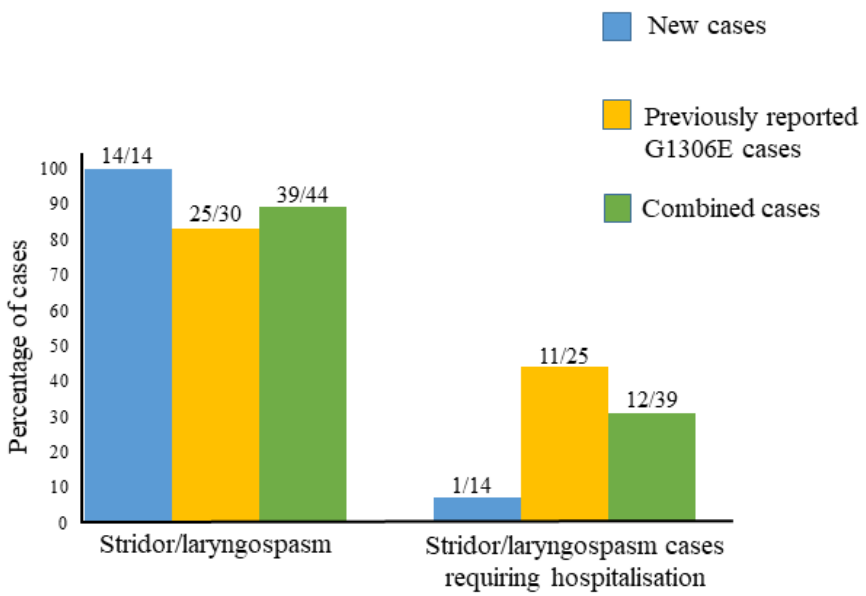

Figure 3. Frequency of G1306E cases experiencing stridor/laryngospasm and the requirement for hospitalisation.

Although several mutations have been reported to cause this phenotype, the G1306E mutation occurs in the majority of affected individuals, frequently in *De novo* form.

We report the largest single family described with the G1306E mutation and two unrelated *De novo* cases. Our cases and literature review highlight several key variables. Stridor and laryngospasm from birth are almost universal but the severity of these episodes varies considerably from a single self-resolving event to the typical SNEL phenotype with more than 20 episodes a day, prompting hospitalisation and ICU admission. If our families are combined with current literature, 31% of infants with stridor/laryngospasm require hospital intervention compared to 44% based on the literature search alone (Figure 3). Bias towards under-representing the frequency of these events may be introduced by our single large family A who were relatively mildly affected but conversely bias towards over-representing them may come from a tendency for more severe cases to be reported in the literature.

Infants with the G1306E mutation are likely to present initially to general physicians and departments with the shorter, self-resolving events potentially falling within the definition of a BRUE. In the majority these would be classified as a high-risk BRUE due to the recurrent nature of events[1]. Some of the children (those fitting the SNEL phenotype), had episodes longer than one minute and/or more complicated histories, which would exclude them from the BRUE classification. Abnormal examination is also not consistent with a BRUE e.g. Proband C who demonstrated global developmental delay, but the typical signs of a myotonic disorder can be delayed e.g. muscle hypertrophy may not be present before age 6 months or difficult to detect in a general setting. High-risk BRUEs and longer episodes with abnormal history or examination (i.e. not a BRUE) should prompt further investigations but it is notable that no recommendations exist as to what investigations should be performed or standardised[1,18].

Sodium channel myotonia is a skeletal muscle exclusive presentation. It is not feasible or suggested that CK and/or EMG be performed in every infant presenting with a possible BRUE. However, they can be helpful in the more severe cases of SNEL where delayed diagnosis is common, resulting in unnecessary and prolonged ICU stays and preventable death[10]. CK is a non-specific test which can be raised in non-neuromuscular disease e.g. post seizure and seizure disorder is a common differential diagnosis postulated in SNEL cases[19]. A normal EEG, however, should prompt consideration of a peripheral rather than central disorder. EMG demonstrating myotonia is much more indicative of the diagnosis but can be difficult to perform and interpret in young infants or may not be available outside of specialist centres. Positive results can be useful for indicating genetic analysis of the *SCN4A* gene and guiding the interpretation of any gene variants. Despite the potential limitations of investigations, there is readily available and extremely effective treatment for the laryngospasm associated with sodium channel myotonia, making it essential that this differential diagnosis and genetic testing where available, is considered in all infants presenting with a high-risk BRUE or more complex apnoeic episodes.

The mainstay of treatment for sodium channel myotonia is sodium channel blocking drugs and our literature review demonstrates efficacy from mexiletine, carbamazepine and flecainide. There is in vitro evidence that flecainide may be the the most potent treatment for the G1306E mutation[11] but there are too few clinical cases and no clinical trial to draw firm conclusions over superiority.

We recently reported *SCN4A* mutations with qualitatively similar effects on channel function in a cohort of infants who had died from sudden infant death[20]. It is generally considered that infants who present with low-risk BRUEs are not at any greater risk of sudden infant death but data are unclear for high-risk BRUEs[14]. No cases of sudden or any infantile deaths were reported in our large autosomal dominant family although their clinical severity was much less than many of the *De novo* cases. Two infants who presented with laryngospasm due to other *SCN4A* mutations have died from respiratory complications[5,10]. The association of *SCN4A* variants and sudden infant death warrants further evaluation.

Other notable differences between our family A and the majority of cases in the literature were the lack of requirement for medication and less incapacitating limb myotonia experienced in adulthood. One other autosomal dominant family previously reported to highlight a milder phenotype is also of Chilean origin[12]. To our family's knowledge, these individuals are not directly related to them but whether other genetic variants common to their ethnicity could influence the severity of clinical symptoms is unclear.

Anaesthetic agents especially suxamethonium are known to exacerbate myotonia, potentially making intubation impossible as well as causing hyperkalaemia[22,23]. Hyperkalaemia itself is cardiotoxic but in the case of *SCN4A* related myotonia is also known to exacerbate myotonic symptoms. Our case series and literature review have highlighted the gravitas of an erroneous administration of suxamethonium including fatal outcome[9]. We would emphasise that suxamethonium use be considered contraindicated in *SCN4A* related myotonia and periodic paralysis.

In summary, episodic laryngospasm and stridor typically from birth are almost universal symptoms in those with the S*CN4A* G1306E mutation and affected parents should be counselled for this when family planning. We would recommend labour take place in a hospital with senior paediatric staff and ICU facilities available. Subsequent respiratory complications during infancy are common but vary significantly in severity. An enhanced awareness of the possibility of sodium channel myotonia, with consideration of CK plus/minus EMG and genetic analysis in appropriate cases of high-risk BRUEs and more complex recurrent apnoeas could enhance diagnostic rates, reducing morbidity and potentially mortality.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of the participants' details and their images was obtained from the participants or parents/guardians of the participants.

Author contributions

All authors contributed to the revising and editing of the manuscript. GC, DA, EF and SR contributed to original draft preparation, provision of patients and data collection. RS contributed to investigation and formal analysis. MGH contributed to the acquisition of financial support. EM contributed to conceptualisation of the project, original draft preparation, data collection and literature review, and acquisition of financial support.

References

1. Tieder JS, Bonkowsky JL, Etzel RA, *et al.*: **Brief Resolved Unexplained Events (Formerly Apparent Life-Threatening Events) and Evaluation of Lower-Risk Infants.** *Pediatrics.* 2016; **137**(5): pii: e20160590.
PubMed Abstract | Publisher Full Text

2. Cannon SC: **Sodium Channelopathies of Skeletal Muscle.** *Handb Exp Pharmacol.* 2018; **246**: 309–330.
PubMed Abstract | Publisher Full Text | Free Full Text

3. 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.
PubMed Abstract | Publisher Full Text | Free Full Text

4. Suetterlin KJ, Bugiardini E, Kaski JP, *et al.*: **Long-term Safety and Efficacy of Mexiletine for Patients With Skeletal Muscle Channelopathies.** *JAMA Neurol.* 2015; **72**(12): 1531–3.
PubMed Abstract | Publisher Full Text

5. 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.
PubMed Abstract | Publisher Full Text

6. 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.
PubMed Abstract | Publisher Full Text

7. Portaro S, Rodolico C, Sinicropi S, *et al.*: **Flecainide-Responsive Myotonia Permanens With SNEL Onset: A New Case and Literature Review.** *Pediatrics.* 2016; **137**(4): pii: e20153289.
PubMed Abstract | Publisher Full Text

8. 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.
PubMed Abstract | Publisher Full Text | Free Full Text

9. 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.
PubMed Abstract | Free Full Text

10. 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.
PubMed Abstract | Publisher Full Text

11. Desaphy JF, Modoni A, Lomonaco M, *et al.*: **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.
PubMed Abstract | Publisher Full Text | Free Full Text

12. Colding-Jørgensen E, Duno M, Vissing J: **Autosomal dominant monosymptomatic myotonia permanens.** *Neurology.* 2006; **67**(1): 153–5.
PubMed Abstract | Publisher Full Text

13. Lee SC, Kim HS, Park YE, *et al.*: **Clinical Diversity of SCN4A-Mutation-Associated Skeletal Muscle Sodium Channelopathy.** *J Clin Neurol.* 2009; **5**(4): 186–91.
PubMed Abstract | Publisher Full Text | Free Full Text

14. Furby A, Vicart S, Camdessanché JP, *et al.*: **Heterozygous *CLCN1* mutations can**

modulate phenotype in sodium channel myotonia. *Neuromuscul Disord.* 2014; **24**(11): 953–9.
PubMed Abstract | Publisher Full Text

15. Brandt-Wouters E, Klinkenberg S, Roelfsema V, *et al.*: **Teaching Video NeuroImages: sodium channel myotonia can present with stridor.** *Neurology.* 2013; **80**(10): e108.
PubMed Abstract | Publisher Full Text

16. Singh RR, Tan SV, Hanna MG, *et al.*: **Mutations in *SCN4A*: a rare but treatable cause of recurrent life-threatening laryngospasm.** *Pediatrics.* 2014; **134**(5): e1447–50.
PubMed Abstract | Publisher Full Text

17. Cavalli M, Fossati B, Vitale R, *et al.*: **Flecainide-Induced Brugada Syndrome in a Patient With Skeletal Muscle Sodium Channelopathy: A Case Report With Critical Therapeutical Implications and Review of the Literature.** *Front Neurol.* 2018; **9**: 385.
PubMed Abstract | Publisher Full Text | Free Full Text

18. Piumelli R, Davanzo R, Nassi N, *et al.*: **Apparent Life-Threatening Events (ALTE): Italian guidelines.** *Ital J Pediatr.* 2017; **43**(1): 111.
PubMed Abstract | Publisher Full Text | Free Full Text

19. Horga A, Raja Rayan DL, Matthews E, *et al.*: **Prevalence study of genetically defined skeletal muscle channelopathies in England.** *Neurology.* 2013; **80**(16): 1472–5.
PubMed Abstract | Publisher Full Text | Free Full Text

20. Männikkö 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.
PubMed Abstract | Publisher Full Text | Free Full Text

21. Brand DA, Fazzari MJ: **Risk of Death in Infants Who Have Experienced a Brief Resolved Unexplained Event: A Meta-Analysis.** *J Pediatr.* 2018; **197**: 63–67.
PubMed Abstract | Publisher Full Text

22. 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.
PubMed Abstract | Publisher Full Text

23. Farbu E, Søfteland 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.
PubMed Abstract | Publisher Full Text

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Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 20 May 2020

https://doi.org/10.21956/wellcomeopenres.17445.r38700

✔ **Sophie Nicole**
Institut génomique fonctionnelle, UM, Inserm, CNRS, Paris, France

I have no further comments, the answers and manuscript changes made by the authors being convincing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neurogenetics, physiology of muscle sodium channel disorders but not medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 13 May 2020

https://doi.org/10.21956/wellcomeopenres.17445.r38701

✔ **Maria Elena Farrugia**
Department of Neurology, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Glasgow, UK

I am happy that all points were addressed effectively.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 27 April 2020

https://doi.org/10.21956/wellcomeopenres.17324.r38298

Maria Elena Farrugia
Department of Neurology, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Glasgow, UK

This is a very well written manuscript describing the phenotype of 12 new cases of individuals with sodium channel myotonia with the G1306E variant and with comparison with published cases in the literature. I have the following, relatively minor, points:

1. In my opinion the authors should mention SNEL in the introduction and this should flow from BRUE, highlighting the differences between the 2. There is the danger of the 2 terms being used interchangeably so differences in the duration of events in the 2 entities, prognostic differences and what determines how a physician classifies an event as SNEL versus BRUE would be helpful in the introduction of the manuscript. The mention on SNEL in the first paragraph of the discussion seems a bit misplaced.

2. Do we know from in vitro studies what determines an individual's response to a specific sodium channel blocker? It would be worth including this in discussion if known. I was interested that Lamotrigine was not tried in any of the cases. Is this simply coincidence?

3. Do we know why the episodes of laryngospasm tend to resolve after childhood? Are there factors in the embryology, development, maturation of laryngeal muscles that make them more susceptible in infancy? It would be interesting to hypothesise in the discussion.

4. In table 1 the plus sign under C for "exacerbation with cold" has no bracket. Does this denote something different to the rest (with brackets)? I suspect not but specify if it is.

5. The title of Table 2 is clearly erroneous. Please amend. I would also suggest denoting the abbreviations used in table 2 even though they are obvious to most.

Is the background of the cases' history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the conclusion balanced and justified on the basis of the findings?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I do very little research since nonacademic but mostly in areas of myasthenia gravis, myotonic dystrophy, fatigue in neuromuscular disorders. However, I review many manuscripts, grant and book proposals.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 01 May 2020

Emma Matthews, University College London, UK

This is a very well written manuscript describing the phenotype of 12 new cases of individuals with sodium channel myotonia with the G1306E variant and with comparison with published cases in the literature. I have the following, relatively minor, points:

1. In my opinion the authors should mention SNEL in the introduction and this should flow from BRUE, highlighting the differences between the 2. There is the danger of the 2 terms being used interchangeably so differences in the duration of events in the 2 entities, prognostic differences and what determines how a physician classifies an event as SNEL versus BRUE would be helpful in the introduction of the manuscript. The mention on SNEL in the first paragraph of the discussion seems a bit misplaced.

The reviewer makes a good point and the introduction and explanation of the term SNEL earlier in the manuscript was also suggested by another reviewer. We have done this now in the abstract and introduction.

2. Do we know from in vitro studies what determines an individual's response to a specific sodium channel blocker? It would be worth including this in discussion if known. I was interested that Lamotrigine was not tried in any of the cases. Is this simply coincidence?

We think lamotrigine may not have been tried as it has only relatively recently been identified as an effective anti-myotonic and many of the G1306E cases in the literature predate this. There is some in vitro evidence that of different sodium channel blockers flecainide may be the most efficacious for the G1306E mutation but there are no clinical trials comparing different agents yet to establish this. We have added this point to the discussion.

3. Do we know why the episodes of laryngospasm tend to resolve after childhood? Are there factors in the embryology, development, maturation of laryngeal muscles that make them more susceptible in infancy? It would be interesting to hypothesise in the discussion.

We don’t know why but we agree with the reviewer that the resolution with age implies a developmental factor(s). We hypothesise that the relative proportion of fast and slow twitch muscle fibres in different muscles and the change in these proportions with age may be one of these

developmental factors but at present this is our hypothesis only. As it is a speculative notion, requiring further research, we prefer not to include this to avoid any confusion.

4. In table 1 the plus sign under C for "exacerbation with cold" has no bracket. Does this denote something different to the rest (with brackets)? I suspect not but specify if it is.

No there was no reason for this and we have added brackets for consistency.

5. The title of Table 2 is clearly erroneous. Please amend. I would also suggest denoting the abbreviations used in table 2 even though they are obvious to most.

We have amended this and detailed the abbreviations.

Competing Interests: No competing interests were disclosed.

Reviewer Report 07 April 2020

https://doi.org/10.21956/wellcomeopenres.17324.r38296

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Sophie Nicole
Institut génomique fonctionnelle, UM, Inserm, CNRS, Paris, France

This manuscript reports the clinics of 12 patients (3 unrelated families) with brief resolved unexplained events in their neonatal period related to sodium channel myotonia and one missense mutation (G1306E) in the *SCN4A* gene. A review of the literature is done to compare the clinics with 30 patients (24 families) with this phenotype and *SCN4A* mutation already described in the literature. This disease is ultra-rare and deserves to be well described in the literature as it may be confounded with seizure disorder in neonates. However, it is a treatable disease with sodium channel blockers, has a good prognosis and may benefit from genetic counseling so well communicating on it is important.

The manuscript is well written and greatly increase the total number of patients description. To my opinion, referring to Severe Neonatal Episodic Laryngospasm (SNEL) earlier in the manuscript would help the readers not familiar with sodium channel myotonia (SCM) to get the point. The authors never use this term of “Severe Neonatal Episodic Laryngospasm (SNEL)” in the title, the abstract, the introduction or the keywords although the SNEL term is used by distinct authors in the literature and is known to be associated with (*de novo*) G1306E mutation of *SCN4A* (as indicated by the authors in the discussion). Could these episodes be really classified as “unexplained” as they are the clinical signs of neonatal SCM caused by one *SCN4A* missense mutation? I recommend the authors to best underline (title, abstract, introduction, discussion) the fact that some BRUE may be indeed “SNEL” related to SCM with efficient treatment and good prognosis. They may also more clearly discuss on the fact that any *de novo* SNEL form may become inherited (as well illustrated by family A), and so may benefit from genetic counselling.

The authors recommend to search for clinical evidence of myotonia/muscle hypertrophy with consideration of CK and EMG in case of BRUE. Why do they not recommend to search for *SCN4A* mutations, at least the few ones (including G1306E) known to cause SNEL?

Regarding Family A, 10 individuals are indicated as having available clinical elements in the text but 12 are described in table 1. How was the SCM diagnosis establish for individual A2 (*SCN4A* sequencing? Clinical report?)? Regarding the critical point which is the treatment, could the authors be more precise: how many exactly benefited from using phenytoin or carbamazepine? What were the adverse events with mexiletine? In table 1, myotonia distribution in eyes: did it mean ocular, orbital, palpebral? What is the difference between mild and moderate painful cramps? At which age was noticed muscle hypertrophy (birth? childhood? adulthood?)? What was the frequency of laryngospasm episodes?

Regarding the review of the literature, the authors indicated that all hospitalization cases were associated with *de novo* mutation. Could they further discuss about the, at least, two distinct possibilities to explain this observation, which are: 1) that may be due to the more severe SCM related to G1306E or 2) that may be due to the fact that, as one of the parents was affected by SCM, they were aware of the SNEL risk and so known how to prevent / best manage it?
The title of Table 2 is strange (and probably wrong). What do AD, LOC, GA, MH mean? How was estimated the treatment efficiency (EVA? PRO? EMG?).

Is the background of the cases' history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the conclusion balanced and justified on the basis of the findings?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neurogenetics, physiology of muscle sodium channel disorders but not medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 24 Apr 2020

Emma Matthews, University College London, UK

This manuscript reports the clinics of 12 patients (3 unrelated families) with brief resolved unexplained events in their neonatal period related to sodium channel myotonia and one missense mutation (G1306E) in the SCN4A gene. A review of the literature is done to compare the clinics

with 30 patients (24 families) with this phenotype and SCN4A mutation already described in the literature. This disease is ultra-rare and deserves to be well described in the literature as it may be confounded with seizure disorder in neonates. However, it is a treatable disease with sodium channel blockers, has a good prognosis and may benefit from genetic counseling so well communicating on it is important.

The manuscript is well written and greatly increase the total number of patients description. To my opinion, referring to Severe Neonatal Episodic Laryngospasm (SNEL) earlier in the manuscript would help the readers not familiar with sodium channel myotonia (SCM) to get the point. The authors never use this term of “Severe Neonatal Episodic Laryngospasm (SNEL)” in the title, the abstract, the introduction or the keywords although the SNEL term is used by distinct authors in the literature and is known to be associated with (de novo) G1306E mutation of SCN4A (as indicated by the authors in the discussion). Could these episodes be really classified as “unexplained” as they are the clinical signs of neonatal SCM caused by one SCN4A missense mutation? I recommend the authors to best underline (title, abstract, introduction, discussion) the fact that some BRUE may be indeed “SNEL” related to SCM with efficient treatment and good prognosis.

The authors agree with the reviewer that the term SNEL does refer specifically to the severe episodes of laryngospasm, stridor and respiratory complications associated with sodium channel myotonia. In this manuscript we have sought to illustrate that infants with the G1306E mutation (along with those with other SCN4A mutations) experience myotonia of the laryngeal and respiratory muscles that cause episodic events of variable severity. This ranges from a single relatively mild self-resolving episode lasting less than a minute through to the much more severe typical SNEL episodes. We use the term BRUE as this is more likely to be the initial category used (before diagnosis) to describe many of these cases, especially the milder ones when they first present to paediatricians who are not neuromuscular specialists. To address the reviewer’s point we have edited the introduction to include the term SNEL earlier with reference to the severe SCN4A cases and specified it again in the first paragraph of discussion.

They may also more clearly discuss on the fact that any de novo SNEL form may become inherited (as well illustrated by family A), and so may benefit from genetic counselling.

The reviewer is correct that de novo cases may then have affected children of their own as illustrated in Family A and Table 2. We agree this is important to highlight and our summary includes the recommendation that any affected individual who is family planning be counselled for the risks of having an affected child.

The authors recommend to search for clinical evidence of myotonia/muscle hypertrophy with consideration of CK and EMG in case of BRUE. Why do they not recommend to search for SCN4A mutations, at least the few ones (including G1306E) known to cause SNEL?

We agree this is important and will ultimately give a definitive diagnosis although genetic testing can still be relatively time consuming (in comparison to EMG and CK), costly and not readily available in all countries. Results should ideally be interpreted alongside clinical, EMG and CK data as without this variants of uncertain significance may cause uncertainty and diagnostic confusion. We have revised the text in the abstract, discussion and summary to include consideration of genetic analysis guided by clinical presentation and results of these other investigations.

Regarding Family A, 10 individuals are indicated as having available clinical elements in the text

but 12 are described in table 1.

This was an error and we are very grateful to the reviewer for pointing this out. We have amended the text throughout and values in figure 1 accordingly.

How was the SCM diagnosis establish for individual A2 (SCN4A sequencing? Clinical report?)?

Diagnosis was based on clinical report of several family members.

Regarding the critical point which is the treatment, could the authors be more precise: how many exactly benefited from using phenytoin or carbamazepine?

Seven patients used carbamazepine: A 13, A 16, A 35, A 43, A 44, A 45). They feel that myotonia and cramps improved but their use is sporadic because they feel floppy and somnolent when taking carbamazepine and they do not like that state. One patient used phenytoin: patient (A 23).

What were the adverse events with mexiletine?

It was taken by only two family members (patients A23, A47) as it was not available for a long time in Chile. A23 stated that she felt shaky and generally unwell while taking mexiletine.

We have added additional detail to the text regarding the use and outcome of these medications.

In table 1, myotonia distribution in eyes: did it mean ocular, orbital, palpebral?

Ocular involvement included orbicularis oculi (tonic eyelid closing) and extrinsic ocular muscle spasm (tonic gaze). The latter occurs with quick changes of gaze or when they yawn, the eye gets fixed in one position and may take a few seconds before the patient can move their eye normally. Sometimes they have diplopia during the episode. These were described by patients: A 18, A 23, A 30, A 33, A 35, A 41, A 43, A 45, A 44.
Only one patient experienced tonic eyes opening A33 (eyelid levator muscle).

What is the difference between mild and moderate painful cramps?

It is a clinical assessment. Mild cramps do not stop daily living activities; with moderate cramps, the patient experiences some pain and some interference with activities of daily living, sometimes having to stop what they are doing for a few seconds; Severe cramps lasts for some minutes or hours: “I become a robot” as they describe it. Severe cramps prevent some activities of daily living and the patient experiences more intense pain, especially when using manoeuvers like stretching or moving to try to stop the myotonia.

At which age was noticed muscle hypertrophy (birth? childhood? adulthood?)?

It is very difficult to establish a starting point with any certainty. Parents say that all their children have important muscular bulk from birth but, if they have to mention a time when it became really evident, most say after 2 years of age.

What was the frequency of laryngospasm episodes?

Please see the text describing this family in the first paragraph of Family A, line 9: “the episodes were more common in winter when they occurred one to two times a day on an almost daily basis, whereas in summer they occurred two to three times per week”.

Regarding the review of the literature, the authors indicated that all hospitalization cases were associated with de novo mutation. Could they further discuss about the, at least, two distinct possibilities to explain this observation, which are: 1) that may be due to the more severe SCM related to G1306E or 2) that may be due to the fact that, as one of the parents was affected by SCM, they were aware of the SNEL risk and so known how to prevent / best manage it?

We agree and have included discussion in the text.

The title of Table 2 is strange (and probably wrong). What do AD, LOC, GA, MH mean? How was estimated the treatment efficiency (EVA? PRO? EMG?).

The title is wrong, and we think is from a different publication substituted in the publishing process, but we have amended this to the correct title for Table 2. We have detailed the meaning of the acronyms.
Treatment efficacy had to be surmised from the detail provided in the reported publications and was described in different ways.

Competing Interests: No competing interests were disclosed.