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ORIGINAL ARTICLES

Myotonia permanens with Nav1.4-G1306E displays varied phenotypes during course of life

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Introduction. Myotonia permanens due to Nav1.4-G1306E is a rare sodium channelopathy with potentially life-threatening respiratory complications. Our goal was to study phenotypic variability throughout life.

Methods. Clinical neurophysiology and genetic analysis were performed. Using existing functional expression data we determined the sodium window by integration.

Results. In 10 unrelated patients who were believed to have epilepsy, respiratory disease or Schwartz-Jampel syndrome, we made the same prima facie diagnosis and detected the same heterologous Nav1.4-G1306E channel mutation as for our first myotonia permanens patient published in 1993. Eight mutations were de-novo, two were inherited from the affected parent each. Seven patients improved with age, one had a benign phenotype from birth, and two died of respiratory complications. The clinical features age-dependently varied with severe neonatal episodic laryngospasm in childhood and myotonia throughout life. Weakness of varying degrees was present. The responses to cold, exercise and warm-up were different for lower than for upper extremities. Spontaneous membrane depolarization increased frequency and decreased size of action potentials; self-generated repolarization did the opposite. The overlapping of steady-state activation and inactivation curves generated a 3.1-fold window area for G1306E vs. normal channels.

Discussion. Residue G1306 Neonatal laryngospasm and unusual distribution of myotonia, muscle hypertrophy, and weakness encourage direct search for the G1306E mutation, a hotspot for de-novo mutations. Successful therapy with the sodium channel blocker flecainide is due to stabilization of the inactivated state and special effectiveness for enlarged window currents. Our G1306E collection is the first genetically clarified case series from newborn period to adulthood and therefore helpful for counselling.

Key words: muscular and respiratory tract diseases, neonate, stridor

Introduction

Myotonia is defined as slowed muscle relaxation after voluntary contraction. It is experienced by patients as muscle stiffness. Symptoms are caused by recessive or dominant mutations in the ClC1 chloride channel or by dominant mutations in the Nav1.4 sodium channel of skeletal muscle. Typically, myotonia lessens with muscle usage, the so-called warm-up phenomenon. However, not all forms of myotonia have a warm-up phenomenon. For example, there is a rare form of myotonia whose severity never varies and is therefore termed myotonia permanens. This phenotype was originally acknowledged by (1) as new entity in a patient (Table 1, patient 4) previously published elsewhere (2). The phenotype is characterized by severe, continuous myotonia associated with a unique EMG pattern of persistent myotonic activity. Additionally, stiffness and hypertrophy of facial, bulbar, neck and shoulder muscles and episodes of respiratory distress are predominant features. The underlying SCN4A mutation encodes p.G1306E, a glycine-to-glutamate substitution. G1306 is highly conserved in all voltage-gated sodium channels and situated in the fast inactivation gate of the sodium channel Nav1.4 i.e., the intracellular loop connecting domains III and IV of the channel protein. The main pathogenetic mechanism is thought to be a slowed and incomplete channel inactivation (2).

Alongside epilepsy and respiratory diseases, the disorder has been diagnosed as myogenic type of Schwartz-

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Table 1. Life course of myotonia permanens patients with the *SCN4A*-p.G1306E mutation. Abbreviations: CMZ, carbamazepine; DPH, diphenylhydantoin. * DPH reduced apnoeic episodes but not the myotonia; SNEL, severe neonatal episodic laryngospasm; R, added to the patient number, means a relative. Symbols: + present; - absent; (+) mild; 0 mother and 5 siblings healthy and G1306E excluded, father with no history of myotonia; · parents deceased with no history of myotonia; 2 siblings, both healthy.

Patient number	Current age	Gender	Neonatal onset	De-novo G1306E	Age of examination	Inspiratory stridor	Laryngospasms	Loss of consciousness	Hypertrophy & myotonia	Painful muscle cramps	Persistent EMG activity	Weakness	Factors which provoke myotonia and respiratory distress throughout life	Medication response to	Remarks	Course during life
1	22	m	+	+	Birth 2 y 3.5 y 7 y 13 y 22 y	+ + + + - 	+ + + + 	+ + - - - -	+ + + + + +	+ + + 	 + + 	- - - - - -	Heat exercise	See text	Disease misinterpreted as laryngomalacia, epilepsy; bent posture; failure to thrive	SNEL reduction, constant myotonia
2	8	f	+	+	Birth 5 y	- -	+ -	- -	- +	 +	 +	- -	K-rich food; frequent suffocation after oral liquid intake	Mexiletine	Large tongue, failure to thrive; if falling unable to get up for 2min	SNEL reduction, constant myotonia
3	2	f	+	+	1 mo 1 y 2 y	+ + +	+ + +	- - -	+ + +	+ + +	 	- - -	Infections, K-rich food, coldness	CMZ, mexiletine effective. Not effective: acetazolamide aggravation by penicilline	Disease misinterpreted as epilepsy, tracheomalacia; bent posture, rotated arms, swallowing of liquids impaired, clenched hand	SNEL reduction, constant myotonia
4	50	f	+	+°	Birth 6 y 26 y 36 y	+ + - -	+ + (+) (+)	+ + - -	+ + + +	+ + + +	 + + 	- - - -	Cortico-steroid, stress, infection, exercise, pregnancy	Barbiturate, flecainide superior to mexiletine, CMZ, tocainide, quinidine	Disease misinterpreted as epilepsy, SJS Lerche et al. 1993 Desaphy et al. 2013	SNEL reduction, constant myotonia
4R	12	m	+	-	Birth 5 y	+ -	+ -	- -	+ +	+ +	 +	- -		Flecainide superior to mexiletine	Rotated arms, Desaphy et al. 2013; severe orbicularis, eyelid, tongue m.	SNEL reduction, constant myotonia
5	17	m	+	+	Birth 3 mo 1.5 y 10 y 17 y	+ + + - -	+ + + - -	+ - - - -	- + + - -	- + + + +	 + 	- - - - -	Sleep, coldness	Mexiletine superior to CMZ, DPH*	Disease misinterpreted as epilepsy, SJS; no painful cramps	SNEL reduction, constant myotonia
6	63	f	+	+‘	Infant 42-63 y	+ -	+ -	- -	+ +	+ +	+ +	(+)	Exercise, coldness, K-rich food	Effective are flecainide, to-cainide. not effective are: mexiletine, lamotrigine		SNEL reduction, constant myotonia
7	50	m	+	+	3 mo 6 mo 41-46 y	+ + -	+ + -	+ + -	+ + +	+ + +	 +	- - +	Exercise	Mexiletine	Disease misinterpreted as epilepsy, stomach hiatus, painful rectus cramping, bent posture	SNEL reduction, constant myotonia
8	67	m	-	+	9 mo Adult	- -	- -	- -	+ +	+ +	 ?	- -	Exercise	Mexiletine	Mild phenotype	Constant myotonia
9	-	m	+	+	1 mo 3 mo 11 y	+ + -	+ + +	+	+ + +	+ + +	+		Coldness, exercise	Heat, dilantin, desipramine	Died at age 11 y of cardiorespiratory insufficiency due to severe myotonic reaction	Lethal
9R1	22	m	-	-	Birth 4 mo 1 y 22 y	- + + -	- + + -	- - - -	- - + +	 + + +	+ 		Coldness, elevated K+	Dilantin, desipramine	Weakness neck, shoulder girdle, upper arms	SNEL reduction, constant myotonia
9R2	43	f	+	+	5 day 14 mo	+ +	+ +	- -	+ +	+ +	+ +		Pain, cold, exercise	Dilantin, desipramine	Succinylcholine-induced event	SNEL reduction, constant myotonia
10	-	m	+	+	Birth 9 mo 20 mo 4 y 21 y	- + +	- + +	- - - -	+ + + + +	+ + + +	 + 	- - - -	Excitement	Mexiletine	Bent posture, failure to thrive, died at age 22 y	Lethal

Jampel syndrome (3, 4). Next to severe cases with potentially lethal laryngospasm, a very mild case of myotonia permanens has been reported (1). The questions on severity and prognosis are still a matter of debate. Although myotonia permanens is a rare entity, it is important that a pediatrician is familiar with this sodium channelopathy because it is life- threatening but treatable and, usually, misdiagnosed. Only limited clinical information is available in pediatric handbooks. This led us to pool 10 unrelated cases to evaluate the spectrum and phenotypic changes during the course of life (Table 1).

Patients and methods

Patients

The study was approved by the Ethics Committee of Ulm University. Written informed consent was taken from patients or their parents for publishing their pictures, clinical and genetic examination, and study of their history.

Genetics

Whole EDTA blood was drawn for extraction of genomic DNA. Using primers specific for exon 22 and the corresponding exon-intron boundaries (2), DNA was amplified by PCR and products bi-directionally sequenced with Applied Biosystems BigDye terminator v3.1 as per the manufacturer's instructions. The resulting sequencing reactions were resolved on an ABI3730 genetic analyzer (Applied Biosystems, Foster City, CA).

Excised muscle experiments

Previously unpublished experiments of excised quadriceps fiber segments obtained from patient 4 in 1993 were performed using capacity-compensated microelectrodes of 3-5 MOhm. Twitch force was analyzed for 3; 5; and 7 mM potassium (2, 4). The force of the muscle bundles, which were mounted in a sylgard-bottomed chamber, superfused at 37°C and stimulated supramaximally with single pulses of 0.2 ms duration, were measured with a strain gauge. The standard solution contained (in mM): NaCl 107.7; KCl 3.48; $CaC1_2$ 1.53; $MgSO_4$ 0.69; $NaHCO_3$ 26.2; $NaH2P0_4$ 1.67; Na gluconate 9.64; glucose 5.5; sucrose 7.6 (315 mosm/l). The pH was adjusted to 7.4 by 95% 0_2 and 5% CO_2.

Re-evaluation of published results

Our previously published data on heterologously expressed G1306E and wildtype (WT) Nav1.4 channels in HEK cells from 1995 (5) were re-evaluated, particularly, to demonstrate the presence of a sodium window current in the mutant and to compare the percentage of sodium channels which can be activated at near-threshold potentials. Data points for steady-state activation (g/V) and steady-state inactivation were fitted by applying the Boltzmann function for the distribution of two-states (closed and open channels). The fits were used to determine the sodium window by integration.

Results

Genetics

All ten patients harbored a heterozygous *SCN4A* mutation c.3917G>A encoding G1306E in the major voltage-gated Nav1.4 sodium channel of skeletal muscle. In eight independent cases, the mutation recurred de-novo; in two families, affected relatives inherited the mutation in an autosomal dominant fashion (4R, 9R1, 9R2, Table 1). None of the unaffected parents or healthy siblings carried the mutation.

Clinical features over time

In the neonatal period, patients experienced episodes of severe laryngospasms, resulting in acute hypoventilation and cyanosis and, in five patients, unconsciousness (Table 1). For example, these episodes occurred up to several times per day and demanded mask ventilation or an oxygen supply in patient 1 (Fig. 1). Such cyanotic spells were life-threatening and required recurrent hospitalization of up to six months each. Several spells led to apnoea (SO2=30%), opisthotonus, and unconsciousness and responded to barbiturate. In half of the patients, cyanotic episodes associated with apnoea and falls were interpreted as epileptic seizures even though the EEG was normal. This view was supported by the beneficial response to the administration of carbamazepine and barbiturates, drugs which block sodium channels and exert antimyotonic effects. Startling and sucking elicited the laryngospasm which was initially mistaken for laryngomalacia or gastroesophageal reflux. Chewing and swallowing was also impaired, leading to a transient failure to thrive in three patients.

In infancy and early childhood, an inspiratory stridor occurred in 80% of the patients. An example for an inspiratory stridor is shown in Figure 2 (patient 3) and the video (stridor.avi). Stridor EEG readings during awake, drowsy, and asleep states were normal. These patients developed episodes of shortness of breath when startled or during mental stress later in life, i.e. in adolescence and adulthood. These symptoms responded to anti-myotonic treatment. It is important to note that respiratory difficulties

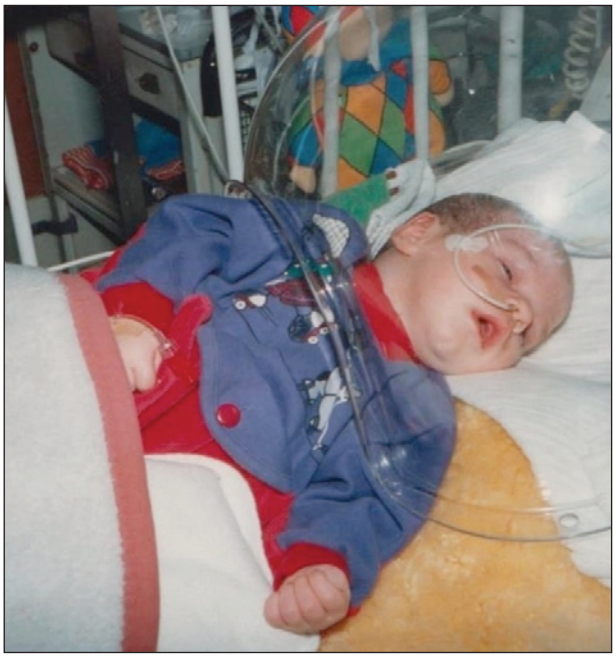

Fig. 1. Patient 1 with neonatal respiratory distress as infant. In infancy and childhood, laryngospasm and myotonic stiffness of the ventilatory muscles resulted in cyanosis and demanded oxygen supply.

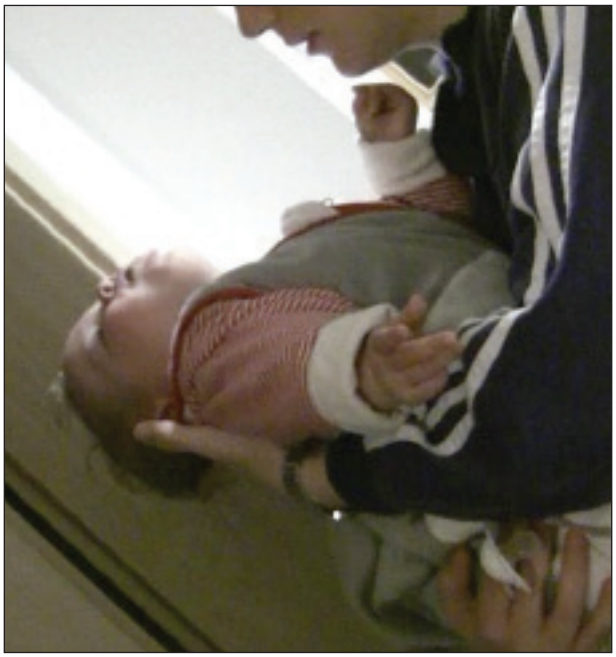

Fig. 2. Still image of the inspiratory stridor of patient 3 in the first month of life. The image is associated by a video (stridor.avi).

can worsen during anesthesia with muscle relaxants: at 11 years of age, patient 9 experienced increasing respiratory distress during general anesthesia and died of cardiorespiratory insufficiency due to a severe myotonic reaction, which was associated with initial jaw clenching and late occurrence of hyperkalemia and increased body temperature resembling a malignant-hyperthermia-like event.

In pre-school childhood, the habitus showed slow movements, excessive sweating and open mouth with drooling. In four patients, shoulder girdle and arms were typically rotated inwardly, with elevated shoulders, antero-flexion of the trunk (patient 1, Fig. 3A), and a bell-shaped thorax (patient 2, Fig. 3B). One patient, originally diagnosed with Schwartz-Jampel syndrome (SJS) (3) had laryngeal stridor, high-pitched voice, mask-like facies, myotonic and hypertrophic shoulder, neck and upper arm muscles (patient 10, Fig. 4A-C). Movements were scarce and slow. During locomotion there was toe-walking and the arms were held in semi-flexion.

Myotonia was present at all ages. Continuous muscle activity superimposed by myotonic bursts could be recorded in the EMG of the affected muscles, even during sleep. If a patient was startled, the EMG activity transiently increased further. Myotonia worsened with potassium- rich food in all three patients. Unexpectedly, the clinical responses of some muscle groups differed considerably. In facial and bulbar muscles, the myotonia worsened during repetitive exercise and cooling. Lid muscles were especially sensitive to cold and presented with paradoxical lid myotonia, even more extreme than in paramyotonia. In contrast, the myotonia disappeared in cooled forearm muscles. Trunk and upper extremities did

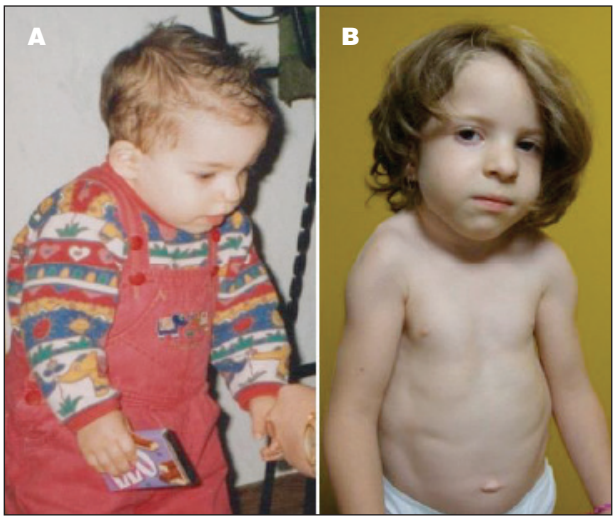

Fig. 3. A: Patient 1 with bent posture in childhood. **B**: Patient 2 with bell-shaped thorax and inwardly rotated shoulder girdle and pectoralis muscles. Note the hypertrophy of neck muscles and the mentalis.

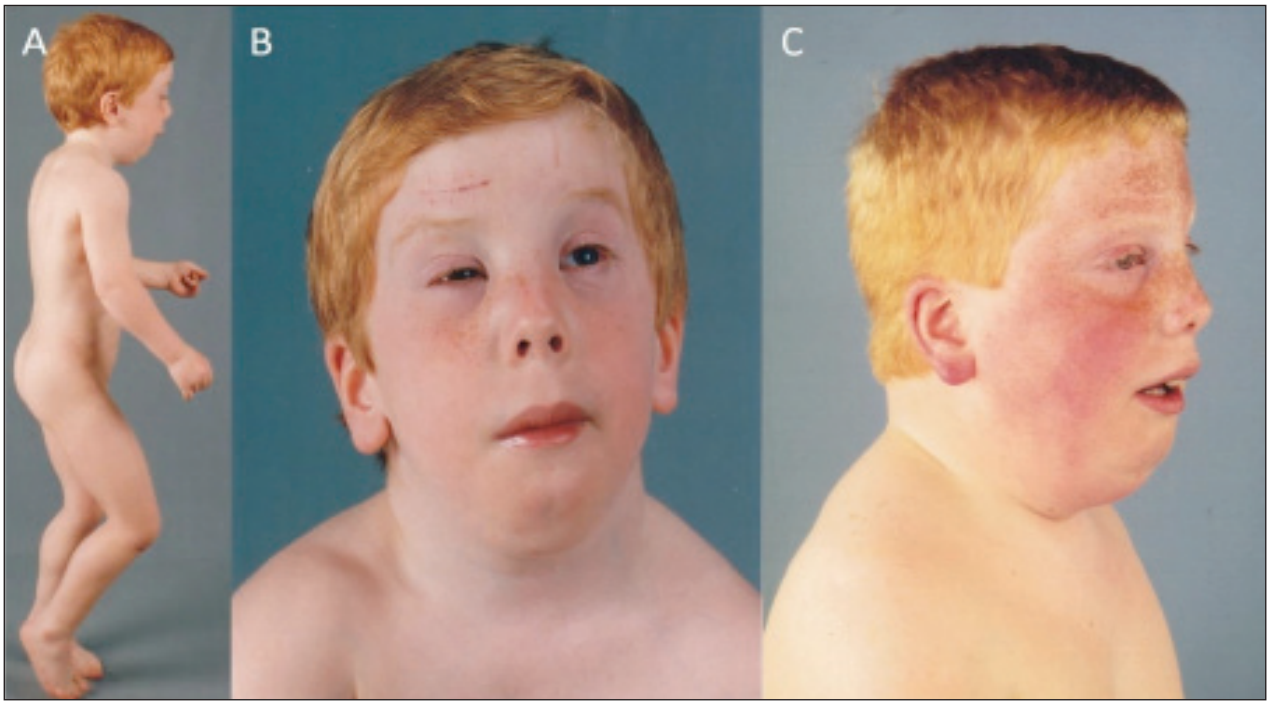

Fig. 4. Boy (patient 10) with postnatal laryngospasm and myotonia at age of 4.5 (A, B) and 11 years (C). **A**: Toe walking associated with involuntary closing the fists; **B**: The boy was asked to close his eyes whereby he also activated his mouth and other facial muscles; due to the myotonic stiffness of the hypertrophic muscles, the patient often fell following a sudden movement and injured himself. **C**: Short neck and hypertrophic neck and shoulder girdle muscles. Prior to detection of a G1306E sodium channel mutation causing myotonia permanens, the patient was thought to have a myogenic form of Schwartz-Jampel syndrome.

not show warm-up phenomenon so that patients were unable to arise from floor for minutes after falling, however, the lower extremities showed a warm-up phenomenon much like that in recessive, chloride channel myotonia. A milder phenotype with interrupted EMG activity was observed in one patient who originally had the clinical diagnosis of Becker myotonia and no respiratory episodes in childhood (patient 8).

Muscle hypertrophy was also present at all ages (Table 1). It was most pronounced in neck, face (particular the mentalis muscle), bulbar, shoulder and proximal arm muscles as shown for patient 3 (Fig. 5A), patient 4R (Fig. 5B), patient 5 (Fig. 5C), and patient 4 (Fig. 5D), the mother of the boy 4R. She enabled us to coin the term myotonia permanens as new entity. The hypertrophy corresponded well with myotonia and with painful cramps of working muscles, outlasting subsequent rest from which 90% of patients suffered. Motor development was delayed when without treatment.

Surprisingly, we found several instances of muscle weakness in the patients. One patient presented with hypotonia at birth and 40% of all patients presented with episodic or mild continuous weakness (Table). The episodes ranged from relatively sudden events of lower limbs for a few days with consequent falling (patient 7) up to mild but fixed proximal leg weakness (patient 6). Patient 10 had a weak such as an infant.

Generally, myotonic symptoms responded to antiepileptic and antiarrhythmic drugs. Since carbamazepine caused adverse effects at higher dosages, mexiletine and flecainide were most frequently used. Our patients generally preferred flecainide since, for example, flecainide was able to suppress the continuous activity completely when muscles were at rest (patient 6).

Excised muscle experiments

Muscle fiber segments obtained from patient 4 showed spontaneous membrane depolarizations similar to those previously published for patient 10 (4). The depolarizations were followed by intracellular myotonic bursts consisting of waxing action potential frequency and waning amplitude with subsequent self-generated repolarization characterized by an inverse pattern (Fig. 6). Pathological spontaneous muscle activity and twitch forces revealed an approximately 4-fold higher amplitude after elevation of potassium from 3 to 7 mM.

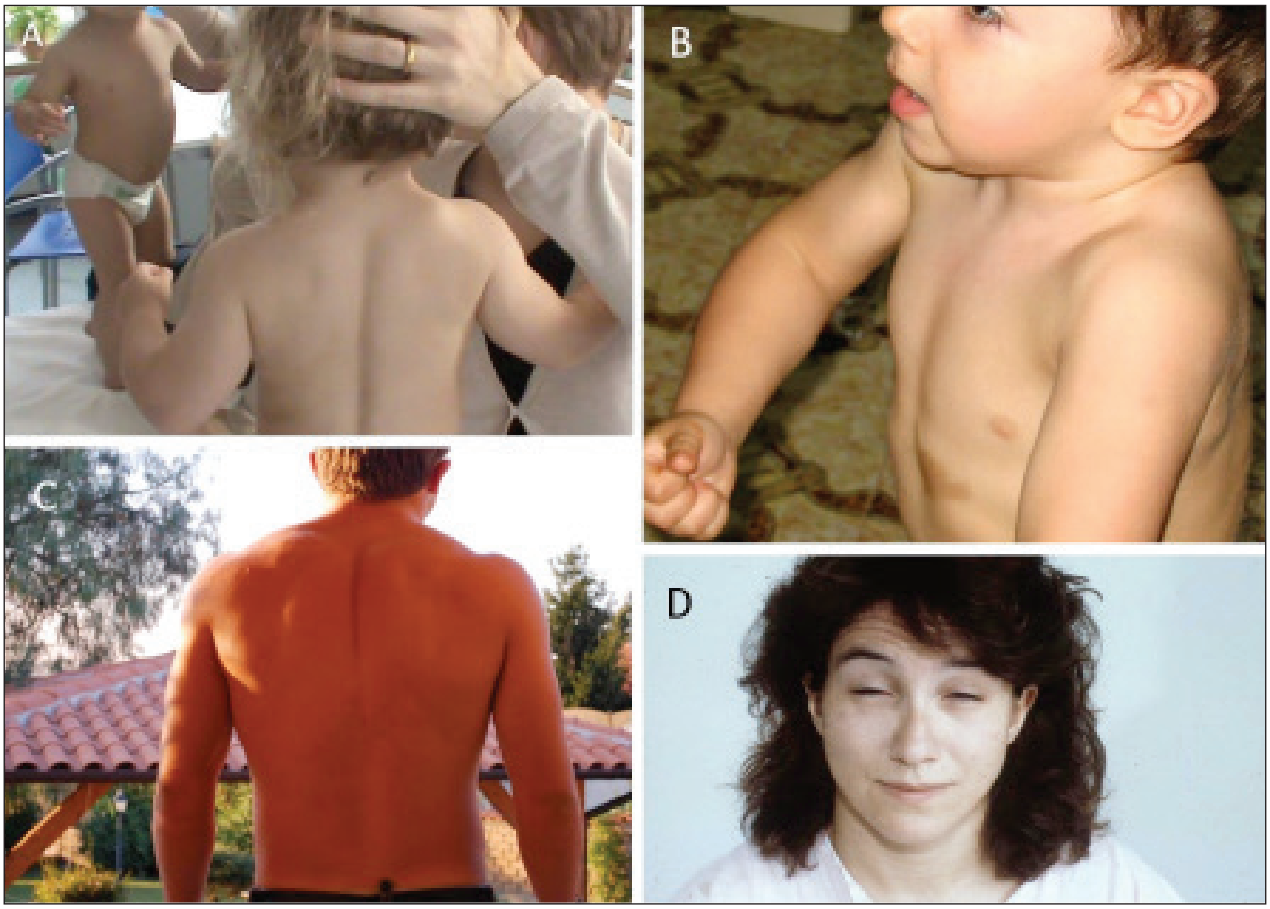

Fig. 5. Myotonic stiffness and muscle hypertrophy in 4 patients at different ages. Note the short neck and the hypertrophic shoulder, back and upper arm muscles. **A**: infancy (patient 3), **B**: childhood (patient 4R), **C**: adolescence (patient 5), **D**: Adulthood (patient 4); the picture shows the face of the first patient world-wide who was reported by Lerche et al. 1993 under the diagnosis of myotonia permanens. Note the blepharospasm.

Forearms cooled in water of 15°C for 30 min had the same effect, however, rewarming completely abolished myotonia.

Evaluation of fit parameters using the current dots published in our G1306E/V/A paper (5)

Using Boltzmann distribution I/Imax = A/(1+exp((V-V0.5)/k))+I0, the best current fits of the dots of the steady-state curves were achieved for the following parameters: for inactivation of WT channels: A = 0.98, V0.5 = -56 ± 1 mV, k = 9.1 mV; and for inactivation of G1306E channels A = 0.95, V0.5 = -41 ± 1 mV, k = 8.3 mV (N = 8-12). The amplitude factors A and the slopes k did not differ significantly between WT and G1306E, only the 15 mV right-shift of the inactivation curve was significant ($p < 5\%$) (Fig. 7 A). The fit parameters for activation of WT channels were: A = 0.95, V0.5 = -11.5 ± 1 mV, k = -7.2 mV and for activation of G1306E channels

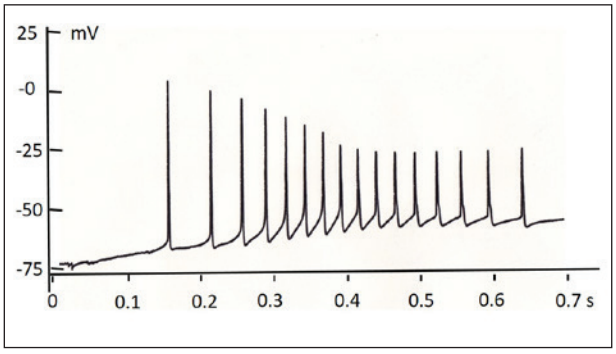

Fig. 6. Intracellular recording of a so far unpublished myotonic burst from a freshly excised muscle fiber of patient 4 when she was biopsied in 1993.

A = 0.95, V0.5 = -17±1 mV, k = -7.1 mV (N = 8-12). While A were the same, k did not substantially differ and I0 was zero, the midpoint of G1306E channel activation

was shifted significantly to the left by 5.5 mV ($p < 5\%$) (Fig. 7B). This left-shift led to a decreased electrical threshold that increases muscle excitability. Additionally, we determined the percentage of channels, which could be opened near the electrical threshold of approximately -65 mV: 89% of G1306E and 72% of WT channels (Fig. 7A).

Window currents and their integration

The superimposition of the steady-state curves for inactivation and activation showed an overlap which corresponded to the window currents for WT and G1306E (Fig. 7C). For the integration of the window currents, the above mentioned Boltzmann distribution for the two channel states (open = activated and closed = inactivated) was used. The increased window current was caused by the left-shift of activation and the right-shift of inactivation. These shifts produced an approximately 3-fold G1306E window current at -30 mV and a 3.1-fold window area for G1306E vs. normal channels. The increased computed areas i.e., the integral sodium influx may generate weakness by depolarizing the membrane close to the threshold and inactivating co-existing wildtype channels in vivo. Due to kinetic and steady- state properties that depend on each other, the right-shift of the inactivation curve increases the number of „activatable" channels at physiologically relevant test voltages. This peculiar property of the G1306E channel may further contribute to the severe and permanent myotonia.

Discussion

Clinical features

Our study is the first to examine a G1306E cohort from the neonatal period to adulthood. It expands knowledge of the phenotype presented in previous single case reports and enables early prima facie diagnosis which changes the patient´s life. The presence of postnatal respiratory symptoms such as laryngospasm and stridor has been described for several Nav1.4 mutations including G1306E, I693T, A799S, N1297K, and T1313M (2, 6-13). Also for the milder myotonia fluctuans caused by G1306A, severe postnatal cyanosis has been reported (14). A milder G1306E phenotype we found in one patient is similar to (1) who reported father and son with severe myotonia aggravated by exercise and potassium, but only moderate impairment by the condition, even without treatment. In contrast, the presence of various degrees of weakness and the different reactions to exercise (exacerbation or warm-up) and cold (exacerbation or disappearance of myotonia) have not yet been reported. This could be due to the physical examinations focusing on muscle especially affected by myotonia (eyelid and hand) for diagnosis whilst ignoring the lower extremities.

Differential diagnoses

Paroxysmal motor phenomena, obstructive sleep apnoea, opisthotonus, and unconsciousness may have led to the frequent suspicion of the diagnosis *epilepsy* in newborns. However these paroxysmal motor phenomena in euglycemic neonates are most likely brain stem release signs (15). Epileptic activity was finally excluded by several conventional and special EEGs such as video-EEG. Another differential diagnosis, the very rare Schwartz-Jampel syndrome (SJS), requires more extensive clinical, radiological, and EMG investigation. SJS is characterized by delayed onset after birth, blepharospasms and mask-liked face, reduced tendon reflexes, and short stature (16). Lack of osteochondrodysplasia in the x- ray is an exclusion criterion. The atypical myotonia in SJS can be confirmed by EMG because the discharges are neurogenic and characterized by high frequency and low voltage. Since the existence of a myogenic SJS has long been disproven, we encourage to drop this term in the future.

Pathogenesis and treatment

Until now, mainly the degree of the slowing of kinetics of inactivation with destabilization of the inactivated state was held responsible for the clinical severities of the Nav1.4 mutations G1306A, G1306V, and G1306E (5,17). Our evaluation suggests that i) lowering of the G1306E threshold, ii) increased window currents, and iii) increased mutant channel availability at near-threshold potentials may contribute decisively to the phenotype. Additionally, the window current may explain the increased effectivity of flecainide as shown for the homologous heart Nav1.5 channel (18, 19). Flecainide can be started in the neonatal period and will permit a lifelong treatment of symptoms (7, 20).

Conclusions

Myotonia permanens is a very rare disease. Our collection of 10 unrelated patients is a genetically clarified case series from newborn period to adulthood and is relevant for parent counselling and early prima facie diagnosis. Unusual distribution of myotonia, muscle hypertrophy, and weakness should not exclude a genetic test for the G1306E mutation – especially if laryngospasm or respiratory difficulties are present – because therapy is available: flecainide.

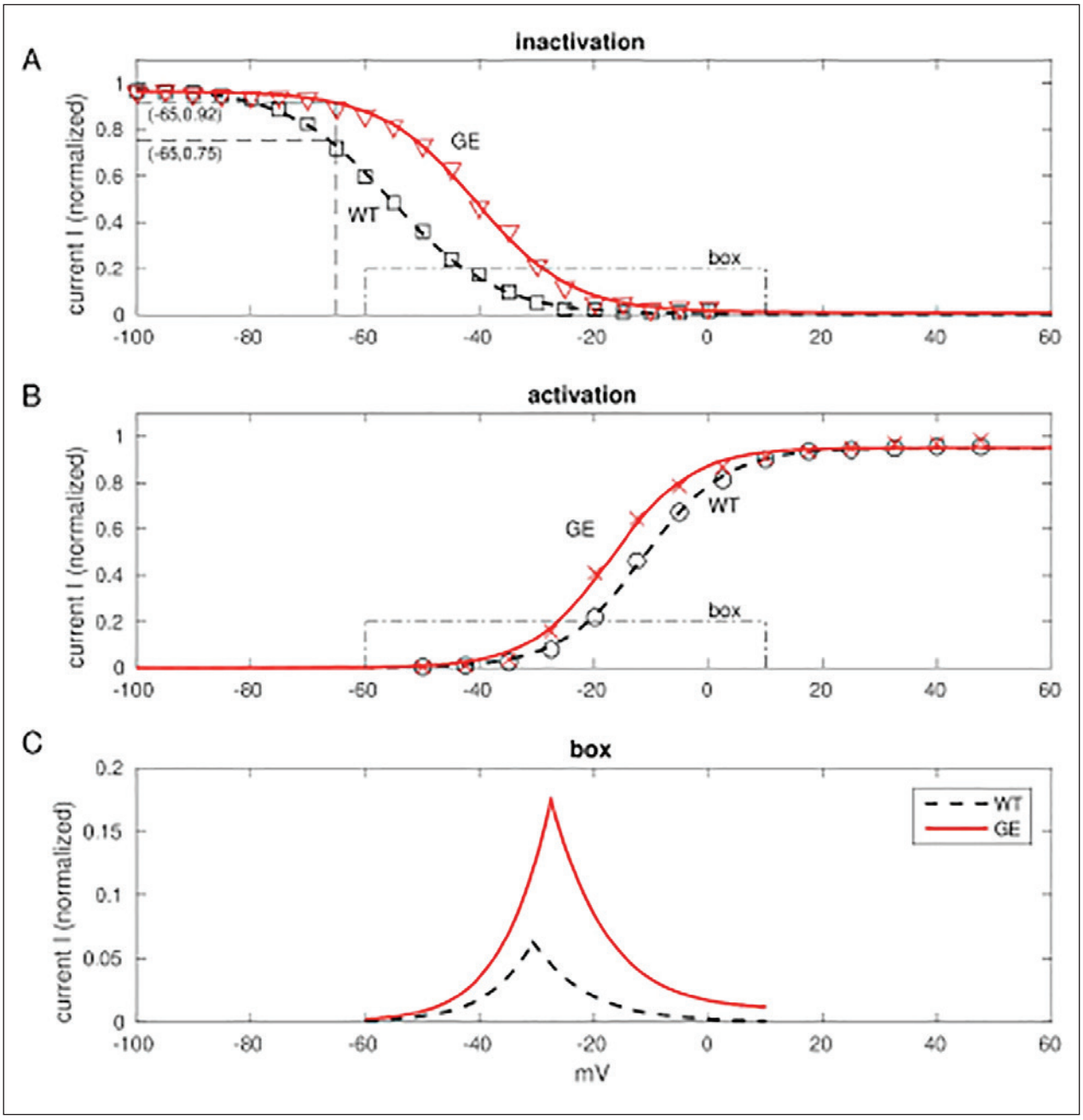

Fig. 7. A-C: Measured values (spots) and Boltzmann fits (lines) of steady-state inactivation (**A**) and steady-state activation (**B**) for normal (WT) and G1306E (GE) mutant channels. The currents were normalized to the maximum sodium current. The deviation between spots (dashedlines) and fits (continuous lines) is minimal for WT and neglectable for physiologically relevant voltages of the mutant channel. The percentage of channels which are not inactivated at an electrical threshold of -65 mV is higher for G1306E (92%) than for WT (75%). As steady-state inactivation at 0 mV was induced by a relatively short 35-ms pulse to the indicated test voltage, we also applied 500-ms prepulses and found no change in the size of the shift. C: The overlapping area (box) of the fits in A and B shows the current size and the voltage range of the window current. The two triangles were used for integration.

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