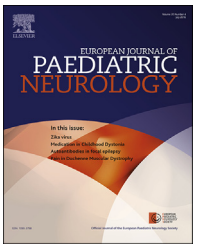
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (XXXX) XXX

ELSEVIER

Official Journal of the European Paediatric Neurology Society



Original article

Clinical and genetic spectrum of *SCN2A*-associated episodic ataxia

N. Schwarz [a], T. Bast [b,c], E. Gaily [d], G. Golla [e], K.M. Gorman [i], L.R. Griffiths [f], A. Hahn [g], J. Hukin [h], M. King [i], C. Korff [j], M.J. Miranda [k], R.S. Møller [l,m], B. Neubauer [g], R.A. Smith [f], T. Smol [n], P. Striano [o], B. Stroud [p], M. Vaccarezza [q], G. Kluger [r,s], H. Lerche [a,**], W. Fazeli [t,u,*]

[a] Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany
[b] Epilepsy Center Kork, Kehl, Germany
[c] Faculty of Medicine, University of Freiburg, Freiburg, Germany
[d] Department of Pediatric Neurology, Children's Hospital, Helsinki University Hospital, Helsinki, Finland
[e] Klinik für Kinder- und Jugendmedizin, Klinikum Lippe GmbH, Detmold, Germany
[f] Institute of Health and Biomedical Innovation, QUT, Queensland, Australia
[g] Department of Neuropediatrics, University Medical Center Giessen and Marburg, Giessen, Germany
[h] British Columbia Children's Hospital, 4480 Oak St, Vancouver, BC, Canada
[i] Children's University Hospital, Temple Street, Dublin, Ireland
[j] Pediatric Neurology, University Hospitals Geneva, Geneva, Switzerland
[k] Herlev University Hospital, Department of Pediatrics, Copenhagen, Denmark
[l] The Danish Epilepsy Centre, Dianalund, Denmark
[m] Department of Regional Health Research, University of Southern Denmark, Odense, Denmark
[n] Institut de Genetique Medicale, CHRU Lille, Université de Lille, Lille, France
[o] Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, IRCCS "G. Gaslini" Institute, Genova, Italy
[p] Golisano Children's Hospital of Southwest Florida, Fort Myers, FL, USA
[q] Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
[r] Neuropediatric Clinic and Clinic for Neurorehabilitation, Epilepsy Center for Children and Adolescents, Schoen Klinik, Vogtareuth, Germany
[s] Research Institute for Rehabilitation, Transition and Palliation, Paracelsus Medical University, Salzburg, Austria
[t] Pediatric Neurology, Department of Pediatrics, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany
[u] Institute for Molecular and Behavioral Neuroscience, Faculty of Medicine, University of Cologne, Cologne, Germany

ARTICLE INFO

Article history:
Received 8 January 2019
Received in revised form

ABSTRACT

Background: Pathogenic variants in *SCN2A* are associated with various neurological disorders including epilepsy, autism spectrum disorder and intellectual disability. Few reports

* *Corresponding author*. Pediatric Neurology, University Children's Hospital Cologne, 50937 Cologne, Germany. Fax: +49 221 478 32739.
** *Corresponding author*. Center of Neurology, University of Tuebingen, Dept. of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, Hoppe-Seyler-Str. 3, 72076 Tuebingen, Germany. Fax: +49 7071 29 4488.
E-mail address: walid.fazeli@uk-koeln.de (W. Fazeli).

https://doi.org/10.1016/j.ejpn.2019.03.001

Please cite this article as: Schwarz N et al., Clinical and genetic spectrum of *SCN2A*-associated episodic ataxia, European Journal of Paediatric Neurology, https://doi.org/10.1016/j.ejpn.2019.03.001

1 March 2019
Accepted 1 March 2019

Keywords:
Acetazolamide
Episodic ataxia
Epilepsy
SCN2A

have recently described *SCN2A*-associated episodic ataxia (EA). Our study identifies its broader clinical and genetic spectrum, and describes pharmacological approaches.

Results: We report 21 patients with *SCN2A*-associated EA, of which 9 are unpublished cases. The large majority of patients present with epileptic seizures (18/21, 86%), often starting within the first three months of life (12/18, 67%). In contrast, onset of episodic ataxia ranged from 10 months to 14 years of age. The frequency of EA episodes ranged from brief, daily events up to 1–2 episodes per year each lasting several weeks. Potential triggers include minor head traumas and sleep deprivation. Cognitive outcome is favorable in most patients with normal or mildly impaired cognitive development in 17/21 patients (81%). No clear genotype–phenotype correlations were identified in this cohort. However, two mutational hotspots were identified, i.e. 7/21 patients (33%) harbor the identical pathogenic variant p.A263V, whereas 5/21 (24%) carry pathogenic variants that affect the S4 segment and its cytoplasmic loop within the domain IV. In addition, we identified six novel pathogenic variants in *SCN2A*. While acetazolamide was previously reported as beneficial in *SCN2A*-associated EA in one case, our data show a conflicting response in 8 additional patients treated with acetazolamide: three of them profited from acetazolamide treatment, while 5/8 did not.

Conclusions: Our study describes the heterogeneous clinical spectrum of *SCN2A*-associated EA, identifies two mutational hotspots and shows positive effects of acetazolamide in about 50%.

1. Introduction

The implementation of next generation sequencing methods has led to the identification of numerous ion channel genes as cause of neurologic disorders including epilepsy, autism, intellectual disability or ataxia. The eight forms of episodic ataxia (EA) described so far belong to the group of hereditary ataxia. Type 1 episodic ataxia (EA1) presents with episodes of generalized ataxia triggered by stress or emotions. Pathogenic variants in *KCNA1*, encoding the potassium channel $K_V1.1$, are causative for the episodes, which last seconds to minutes.[1] Episodic ataxia type 2 (EA2) is characterized by acetazolamide-responsive ataxic episodes, which last hours to days and are caused by pathogenic variants in *CACNA1A*, encoding the calcium channel $Ca_V2.1$.[2] Episodic ataxia types 3–8 are very rare and are only described in individual case studies.

SCN2A encodes the alpha subunit of the voltage gated neuronal sodium channel $Na_V1.2$.[3] Pathogenic variants in *SCN2A* have been associated with a broad spectrum of epilepsy subtypes potentially accompanied by intellectual disability and/or autistic traits.[4] In addition, few cases of *SCN2A*-associated EA were reported.[5–11] These few reports do not allow the establishment of genotype–phenotype correlations, which would be a prerequisite for the implementation of targeted/precision medicine approaches.[12]

SCN2A-associated EA was first described in 2010[8] with the report of a *SCN2A* gain-of-function pathogenic variant in a patient with neonatal-onset seizures. While seizures were well controlled and only occurred sporadically from 18 months of age onwards, the boy developed episodes of ataxia. Since then, 11 additional patients were reported.[5–7,9–11]

We collected all available patients with *SCN2A*-associated EA within an international collaboration to analyze the clinical course of unpublished and previously published patients. We here describe the clinical course, genetic background and pharmacological attempts in a total of 21 patients with *SCN2A*-associated EA.

2. Methods

Patients with *SCN2A*-associated EA were collected within an International collaboration with co-authors of our previously published *SCN2A* case study[4] and other research networks including NETRE (= network therapy rare epilepsies). An according questionnaire was generated and filled out by all co-authors. The questionnaire enquired inheritance mode, details regarding episodic ataxia such as age at onset, specific symptoms and clinical course during EA episodes, duration and frequency of episodes, and treatment for ataxia. In addition, details regarding epilepsy (if existing) such as onset of epilepsy, seizure types and anti-convulsive treatments were collected. Cognitive status and assessment of psychomotor development of the patients was asked for. Written informed consent for research and publication was obtained from the families. All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Genetic testing for pathogenic variants in *SCN2A* was performed according to the evaluation by the treating physicians in either a research or a diagnostic laboratory. Inclusion criteria were the existence of pathogenic or likely pathogenic variants in *SCN2A*

Please cite this article as: Schwarz N et al., Clinical and genetic spectrum of *SCN2A*-associated episodic ataxia, European Journal of Paediatric Neurology, https://doi.org/10.1016/j.ejpn.2019.03.001

according to ACMG standards and guidelines[13] as well as a phenotype of episodic ataxia. Exclusion criteria were the existence of pathogenic or likely pathogenic variants in genes that have previously been associated with episodic ataxia. Tumors or malformations of the posterior fossa as a potential origin for the development of ataxia were excluded by cranial imaging. Our study was focused on patients with an episodic course of ataxia. Patients with persistent ataxia (e.g., developing under anticonvulsant therapy) were excluded in this study.

3. Results

A total of 21 patients with *SCN2A*-associated EA was collected. Nine patients were not previously published (Patients 1 to 9, Table 1). We collected updates regarding the clinical course of the twelve previously published patients (Patients 10 to 21, see Table 2). Subordinated clinical data are shown in Supplementary Table 1 (Suppl. Table 1). The male/female ratio was 13:8. Age at last visit reported here differed between 1.5 and 31 years.

3.1. *Episodic ataxia: phenotype*

While epileptic seizures mostly occurred during the first three months of life (12/18), the first episode of ataxia never occurred before 10 months (Patient 2) (see Fig. 1). Much later onsets up to 14 years (Patient 20) were also noticed. We excluded a few reported patients with permanent ataxia, which has been described as potential secondary effect of chronic pharmacological treatment with phenytoin and other anti-convulsive medications.[14,15]

The frequency of episodes differs between daily in two cases (Patients 1 and 18), weekly to monthly in most cases (Patients 2–4, 6–13, 19–21), and at most 1–3 episodes every year in Patients 5 and 14–17 (Tables 1 and 2).

The duration of each EA episode is heterogeneous between patients: while most patients showed episodes lasting minutes to maximum several hours (Patients 1–4, 6–13, 18,19), periods lasting days up to weeks were also reported (Patients 5, 14–16). The three familial cases previously published by us[5] obviously present a peculiar phenotype, characterized by the lack of seizures, a relatively low frequency of episodes (1–2 per year) and unusually long durations of each episode (around 3 weeks each). This will be further discussed below.

As extensively discussed in the context of (genetic) epilepsies,[16] paroxysmal events can be triggered by external factors such as minor head injuries, sleep deprivation, alcohol ingestion, photostimulation, and others. Whether immunological processes such as vaccinations might trigger the onset and occurrence of paroxysmal events including epileptic seizures is still under debate.[17]

In our cohort, several triggers of EA episodes were identified (Tables 1 and 2). These included sensory stimuli, e.g., a sudden noise and vibrations of the body. In addition, the menstruation cycle triggered EA episodes in one patient (Patient 6). Of note, two of a total of four EA episodes in Patient 14 were temporally associated with prior vaccinations.[5]

3.2. *Epilepsy in patients with SCN2A associated episodic ataxia*

Pathogenic variants in *SCN2A* can lead to a spectrum of epileptic seizures.[4] Previous reports of *SCN2A* associated EA described cases with co-occurrence of seizures,[6–11] but absence of epilepsy in three familial cases was also reported.[5] In our study, these three previously reported familial cases remained the only ones within our cohort that did not experience epileptic seizures,[5] while every other patient did (18/21, 86%). In most cases with epilepsy, seizures started within the first three months of life (12/18, 67%), with neonatal-onset seizures in 9/12 (75%) patients. Given the early onset of epileptic seizures, these cases are presumably based on pathogenic gain-of-function variants in *SCN2A*.[4,18] Therefore, sodium channel blockers and phenytoin in particular were the anti-convulsive medications of choice. Eleven out of 18 patients still required anti-convulsive treatment at the last recorded visit, all of them received a sodium channel blocker. Five patients did not receive any anti-convulsive medication at the last visit.

3.3. *Pharmacological treatment of episodic ataxia*

While early-onset *SCN2A*-associated epileptic seizures may well respond to treatment with sodium channel blockers and phenytoin in particular,[4] the best treatment of *SCN2A*-associated EA has yet to be determined. Treatment with the carbonic anhydrase inhibitor acetazolamide is well established for *CACNA1A*-associated episodic ataxia type 2[19] and has once been reported to be successful for *SCN2A*-associated EA.[7]

At last visit, 11 of the 18 patients with epileptic seizures still received anti-convulsive treatment, which included a sodium channel blocker in all cases. In almost all cases (9/11), treatment with sodium channel blockers (for dosages see Tables 1 and 2) did not have any positive effect on episodic ataxia. There were two exceptions (Patient 5 and 8). In patient 5, carbamazepine – initially given as anti-convulsive drug – led to a strong improvement of ataxic and dysarthric episodes, i.e. a reduction in the frequency from weekly episodes to sporadic events. This was a case with a very late onset of EA at 6 years of age. In patient 8, levetiracetam led to a moderate reduction of the EA frequency.

As to patient 11, about 6 months after withdrawal of valproic acid – that had been initiated for his epilepsy and was then stopped due to seizure freedom – EA episodes increased from 2 to 3 per year to 2 per month, while each episode became longer (from 1–2 min to 30–60 min each). It remains unclear whether this observation reflects a causal relationship or whether this was a temporal co-incidence. Positive effects of valproic acid treatment on EA were not reported in any other patient within our cohort.

Acetazolamide was previously reported as beneficial in a single case with *SCN2A*-associated EA,[7] this case is part of our study (Patient 17). Thus, acetazolamide was now tried as potential treatment in eight other patients within our cohort. The dosage ranged from 4.3 mg/kg body weight/day (Patient 1) to 30 mg/kg body weight/day (Patient 12). Five of these eight patients did not profit from acetazolamide treatment. Adverse events were not reported. However, one patient (Patient 19)

Please cite this article as: Schwarz N et al., Clinical and genetic spectrum of *SCN2A*-associated episodic ataxia, European Journal of Paediatric Neurology, https://doi.org/10.1016/j.ejpn.2019.03.001

Table 1 – Unpublished cases of patients with *SCN2A* associated episodic ataxia.

	Patient 1	Patient 2	Patient 3 (sister of P4)	Patient 4 (brother of P3)	Patient 5
Gender, age	F, 11y	F, 2y	F, 3y	M, 7y	M, 8y
Pathogenic variant, inheritance	c.2960G > T p.S987I *de novo*	c.4952T > G p.F1651C *de novo*	c.788C > T p.A263V inherited from father	c.788C > T p.A263V inherited from father	c.3754A > G p.I1252V *de novo*
Age at ataxia onset	4y 6m	10m	18m	3y	6y
Frequency of episodes	Daily episodes since onset of ataxia	2 per month	4 per month	2 per month	3 per year
Duration of single episode of ataxia	1–1.5 min	12–24 h	Several hours	1–12 h	24–48 h
Triggers for ataxia	Whole body movement (e.g., after a car trip)	None	None	None	None
Treatment of ataxia: specific/AED	Acetazolamide (4.3 mg/kg/d)	None/phenytoin as AED	None/phenytoin as AED	None/phenytoin as AED	None/carbamazepine as AED
Effect of treatment on ataxia: specific/AED	None	–/None	–/None	–/None	CBZ: strong improvement of ataxic/dysarthric episodes (from weekly freq. to sporadic episodes)
Epilepsy	Hemiclonic seizures + apneas	Generalized tonic–clonic seizures	Generalized tonic–clonic seizures and complex-partial seizures	Generalized tonic–clonic seizures and complex-partial seizures	Complex partial seizures
Age at seizure onset	First day of life	5th postnatal day	2m	10th postnatal day	6m
Current anti-epileptic medication and dosage	None	Phenytoin, 9.5 mg/kg/d	Phenytoin, 6 mg/kg/d	Phenytoin, 6 mg/kg/d	Carbamazepine, 20 mg/kg/d
Cognitive status/development	Normal	Mild global developmental delay; muscular hypotonia	Normal; Bayley-III: motor delay; muscular hypotonia	Bayley-III: global delay; muscular hypotonia	Mild global developmental delay with delay of speech and motor delay

	Patient 6	Patient 7	Patient 8	Patient 9
Gender, age	F, 19y	M, 16y	M, 14y	M, 5y
Pathogenic variant, Inheritance	c.3973G > A p.V1325I inheritance unknown	c.788C > T, p.A263V mother tested: negative father passed away	c.5311T > C p.Y1771H *de novo*	c.1028A > G p.D343G *de novo*
Age at ataxia onset	3y	2.5y	1y 6m	3y
Frequency of episodes	Every 6–8 weeks, clusters with up to 3/week possible	4–5 per month	4 per week	1 per month
Duration of single episode of ataxia	Initially for 1–2days, currently only minutes	Typically hours; currently until he awakens next day	5 min	Seconds – max. 1 min
Triggers for ataxia	Menstruation cycle, sleep deprivation, physical stress	Stress, excitement, poor sleep, fatigue	None	None
Treatment of ataxia: Specific/AED	Carbamazepine (1050 mg/d), Sultiam, oxcarbazepine, lamotrigine, acetazolamide, topiramate	Acetazolamide 3 × 250 mg/oxcarbazepine 2 × 1200 mg	None/levetiracetam and perampanel as AED	None/oxcarbazepine as AED
Effect of treatment on ataxia: specific/AED	Information not available	None	–/levetiracetam: moderate diminution of the frequency of episode of ataxia	–/ None

Please cite this article as: Schwarz N et al., Clinical and genetic spectrum of SCN2A-associated episodic ataxia, European Journal of Paediatric Neurology, https://doi.org/10.1016/j.ejpn.2019.03.001

Epilepsy	Generalized tonic and tonic–clonic seizures	Generalized tonic–clonic seizures and atypical absences – currently seizure free	Myoclonic seizures and absences	Generalized tonic–clonic seizures
Age at seizure onset	6w	2nd postnatal day	1y 6m	6m
Current anti-epileptic medication and dosage	None	Oxcarbazepine 2 × 1200 mg/d, Lacosamide 2 × 100 mg/d	Levetiracetam, 53 mg/kg/day Perampanel, 0.1 mg/kg/day	Oxcarbazepine, 20 mg/kg/day
Cognitive status/development	Normal	Average IQ; average verbal and working, low average visual motor fluency and very low visual reasoning	Severe intellectual disability with lack of speech and no walking abilities	Mild global developmental delay with delay of speech and motor delay

AED = anti-epileptic drug, CBZ = Carbamazepine, F = female, IQ = intelligence quotient, M = male, m = month, w = week, y = year.

showed a major improvement regarding both the quantity and quality of EA: frequency of episodes was reduced from several daily episodes to 1–2 episodes per week, and the severity of ataxia became milder during EA episodes since acetazolamide treatment has been started. The current acetazolamide dosage in this patient is 21 mg/kg body weight/day. In addition, two further patients (Patient 20 and Patient 21) showed minor improvements under acetazolamide treatment.

Taken together, acetazolamide might indeed have a beneficial effect on EA episodes, yet around half of our patients did not profit from this treatment. As no adverse events were reported, we suggest that acetazolamide should be tried under close monitoring of serum bicarbonate levels.

3.4. *Genetic findings and genotype–phenotype correlations*

As depicted in Fig. 2, the EA associated pathogenic *SCN2A* variants are widespread among the $Na_V1.2$ alpha subunit. Six pathogenic variants were hitherto not described, i.e., p.D343G (Patient 9) being located in the cytoplasmic loop between domain I and domain II, p.S987I (Patient 1) in the cytoplasmic loop between domain II and domain III, p.I1252V (Patient 5) in the second segment of domain III and p.V1325I (Patient 6) in the cytoplasmic loop between segment four and five of domain III. The two further novel pathogenic variants were p.F1651C (Patient 2), which is located in the cytoplasmic loop between segments four and five of domain IV, and p.Y1771H (Patient 8), which is located within segment six of domain IV.

There is one obvious mutational hotspot (p.A263V) that affects the S5 segment of the domain I within the $Na_V1.2$ alpha subunit – 7 out of 21 patients we describe harbored this particular pathogenic variant. In addition, 5/21 patients (24%) carry pathogenic variants that affect the S4 segment and its cytoplasmic loop within the domain IV (Patients 2, 14–17).

The pathogenic variants mostly occurred *de novo*, yet inherited variants in one family with three affected individuals (Patients 12–14), another family where the affected father (patient 20) harbored the pathogenic variant that was inherited to the daughter (patient 21) and one family with two affected children (Patients 3 and 4) are also included. In the latter cases, the father harbored the pathogenic variant that was inherited to both children. The father himself was healthy and did not show any neurologic abnormalities.

4. Discussion

Our study describes the clinical course, genetic background and pharmacological treatment approaches of *SCN2A*-associated episodic ataxia. Despite a large heterogeneity within the cohort, the majority of patients is characterized by similar features: co-occurrence of epileptic seizures with neonatal–/early infantile seizures; favorable outcome with unimpaired or only slightly impaired cognitive development at the time of last visit; currently insufficient treatment alternatives for EA with mostly lack of response to sodium channel blockers and conflicting responses to acetazolamide.

Please cite this article as: Schwarz N et al., Clinical and genetic spectrum of *SCN2A*-associated episodic ataxia, European Journal of Paediatric Neurology, https://doi.org/10.1016/j.ejpn.2019.03.001

Table 2 – Previously published cases of patients with *SCN2A* associated episodic ataxia.

	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14
Previously published	Schwarz et al., 2016 (PMID: 26645390)	Schwarz et al., 2016 (PMID: 26645390)	Liao et al., 2010 (PMID: 20956790) Schwarz et al., 2016 (PMID: 26645390)	Schwarz et al., 2016 (PMID: 26645390)	Fazeli et al., 2018 (PMID: 30165711)
Gender, age	M, 6y	F, 12y	M, 18y	M, 14y	M, 3.5y
Pathogenic variant, inheritance	c.788C > T p.A263V *de novo*	c.4565G > C/c.5644C > G p.G1522A/p.R1882G inherited/*de novo*	c.788C > T p.A263V *de novo*	c.5644C > G p.R1882G *de novo*	c.4949T > C, p.L1650P inherited from equally affected mother
Age at ataxia onset	15m	20m	1.5y	3.7y	12m
Frequency of episodes	1–2 per month	1–2 per week	3–4 per month	1 per month	4 within 2 years
Duration of single episode of ataxia	Several hours to 1 day	Rarely repeating over 2 h	Several hours	30 min	3 weeks
Triggers for ataxia	Vibrations	None	None	None	Potentially vaccinations
Treatment of ataxia: specific/AED	None	None	Lamotrigine 2 × 200 mg/day	Lamotrigine 2 × 50 mg/day	Acetazolamide (30 mg/kg/d)
Effect of treatment on ataxia: specific/AED	–	–	–/ None	–/50% reduction of episodes	None
Epilepsy	Bilateral tonic seizures evolving into secondary generalized tonic–clonic seizures – currently seizure free	Generalized tonic–clonic seizures – currently seizure free	Generalized tonic–clonic seizures at age of 6.5 and 14 years; Trigger for seizures: Fever, infection, minor head trauma	Bilateral tonic–clonic seizures with reduced oxygen saturation and unresponsiveness – currently seizure free	No
Age at seizure onset	Postnatal day 7	1m	First day of life	Postnatal day two	–
Current anti-epileptic medication and dosage	None	None	Lamotrigine (400 mg/day)	Lamotrigine (100 mg/day)	–
Cognitive status/development	Development slightly retarded	Normal	Specific (visual and visuomotor) cognitive dysfunction	Developmental delay of speech	Lower normal range

	Patient 15	Patient 16	Patient 17	Patient 18	Patient 19
Previously published	Fazeli et al., 2018 (PMID: 30165711)	Fazeli et al., 2018 (PMID: 30165711)	Leach et al., 2016 (PMID: 27328862)	Johannesen et al., 2016 (PMID: 27159988)	Gorman et al., 2017 (PMID: 28065826)
Gender, age	M, 1.5y	F, 28y	M, 8y	F, 3y	M, 5y
Pathogenic variant, inheritance	c.4949T > C, p.L1650P inherited from equally affected mother	c.4949T > C, p.L1650P unknown (parents not available for testing)	c.217G > A, p.G1634D *de novo*	c.788C > T p.A263V *de novo*	c.788C > T p.A263V *de novo*
Age at ataxia onset	13m	3y	11m	13m	20m
Frequency of episodes	1 in total	4 within 15y	Two in the first six years, no ataxia at present	Daily episodes up to a few per week	1 per 6 weeks
Duration of single episode of ataxia	5 days to 3 weeks	3 weeks	No information, since well controlled on acetazolamide	Minutes to cluster of max. 1 day	2–5 min, which recur in clusters which last from 0.5 to 4 h
Triggers for ataxia	None	None	Fever, trauma	Fright (sudden noise, a simple falling), pain	None
Treatment for ataxia	Acetazolamide (20 mg/kg/d)	None	Acetazolamide (18 mg/kg/d)	None	Acetazolamide (21 mg/kg/day)
Effect of treatment on ataxia	No effect	–	Complete regression of ataxia under Acetazolamide	–	Major improvement in balance and episodes of ataxia (from several daily to 1–2/week)
Epilepsy	No	No	Generalized tonic–clonic seizures	Generalized tonic seizures and complex-partial seizures	Generalized tonic seizures

Please cite this article as: Schwarz N et al., Clinical and genetic spectrum of SCN2A-associated episodic ataxia, European Journal of Paediatric Neurology, https://doi.org/10.1016/j.ejpn.2019.03.001

Age at seizure onset	–	–	11m	3rd postnatal day	2nd postnatal day
Current anti-epileptic medication and dosage	–	–	Carbamazepine (16 mg/kg/d)		Sodium valproate (34 mg/kg/day), Phenytoin (10 mg/kg/day)
Cognitive status/development	Developmental delay of speech	ID	ID autism spectrum disorder	Normal	Normal
			Patient 20 (father of P21)		Patient 21 (daughter of P20)
Previously published			Maksemous et al., 2018 (PMID: 30314295)		Maksemous et al., 2018 (PMID: 30314295)
Gender, age			M, 31y		F, 8y
Pathogenic variant, inheritance			c.3973G > T, p.V1325F *de novo*		c.3973G > T, p.V1325F inherited from father
Age at ataxia onset			14 years		21 months
Frequency of episodes			Intermittent, up to a few per week		Intermittent, up to a few per week
Duration of single episode of ataxia			NA		NA
Triggers for ataxia			Exertion, minor head trauma		Exertion, minor head trauma
Treatment for ataxia			Acetazolamide (dose under adjustment)		Acetazolamide (dose under adjustment)
Effect of treatment on ataxia			Limited		Marginal
Epilepsy			Atonic seizures		Atonic seizures
Age at seizure onset			14 years		21 months
Current anti-epileptic medication and dosage			None		None
Cognitive status/development			Some learning difficulties		Mild-moderate global developmental delay

AED = anti-epileptic drug, F = female, ID = intellectual disability, M = male, m = month, NA = not available, w = week, y = year.

The co-occurrence of epileptic seizures in patients with pathogenic *SCN2A* variants is not surprising.[4] Noteworthy, *SCN2A* associated EA primarily affects patients with milder cases of *SCN2A* associated epilepsy, whereas only two of our patients showed severe developmental delay. Yet, EA may be underestimated and insufficiently reported in patients with *SCN2A* epileptic and developmental encephalopathy possibly because ataxia is harder to identify in severely handicapped patients. In addition, persistent ataxia is known as secondary adverse event during medication with phenytoin,[14,15] it is therefore challenging to disentangle the causality between the pathogenic *SCN2A* variant and ataxia in encephalopathic patients under multi-drug treatment. Four of our patients showed divergent signs of intellectual impairment: while Patient 16 showed an IQ of 71 with particular impairment in her speech development,[5] Patient 17 showed traits of autism spectrum disorder. Given that this particular patient showed a seizure onset at 11 months and based on previous reports,[4,18] we assume that this particular variant (p.G1634D) may be a pathogenic loss-of-function variant.

While epileptic seizures mostly occurred within the first three months of life (12/18 patients), EA onset was earliest at 10 months of life. The most probable explanation is the divergent expression of $Na_V1.2$ within myelinated nerve fibers compared to parallel fibers forming the axons of cerebellar granule cells which project to cerebellar Purkinje cells. As shown by Liao et al., $Na_V1.2$ is expressed very early during development in the hippocampal CA1 region,[20] whereas its cerebellar expression increases during postnatal development in mice.[8] The latest time point of EA onset was at 14 years of age, the explanation for this heterogeneity regarding EA onset remains unknown. Triggers for the onset of EA in this patient were not identified. Genetic and environmental factors acting as modifiers might influence the onset of paroxysmal events such as EA and epilepsy.[9,21]

Treatment options for *SCN2A* associated EA remain insufficient. Our study shows that sodium channel blockers such as phenytoin – though beneficial for the treatment of neonatal–/early-onset *SCN2A* associated epilepsy[4] – are not as promising for EA treatment as the treatment with acetazolamide. The underlying mechanisms are not understood. Early-onset *SCN2A* associated epileptic seizures are generally thought to be caused by pathogenic gain-of-function *SCN2A* variants. Given that pathogenic gain-of-function *SCN2A* variants can lead to EA,[10] we hypothesized that EA in these patients similarly profits from treatment with sodium channel blockers as their epilepsy does, but we could not confirm this in most of the cases.

The only patient with a supposed loss-of-function variant (patient 17) responded dramaticaly to acetazolamide immediately after initiation of treatment.[7] Acetazolamide was also effective in patient 19 with a pathogenic variant that is known to cause a gain-of-function effect (p.A263V).[8] Thus, acetazolamide might represent a treatment option in *SCN2A*-associated EA irrespective of the type of pathogenic variant. While two additional individuals (Patients 20 and 21) slightly benefited from acetazolamide treatment, the majority (5/9) did not respond to acetazolamide. While the differences in acetazolamide dosages (4.3 mg–30 mg/kg body weight/day) may play an important role, there are also cases with higher

Please cite this article as: Schwarz N et al., Clinical and genetic spectrum of *SCN2A*-associated episodic ataxia, European Journal of Paediatric Neurology, https://doi.org/10.1016/j.ejpn.2019.03.001

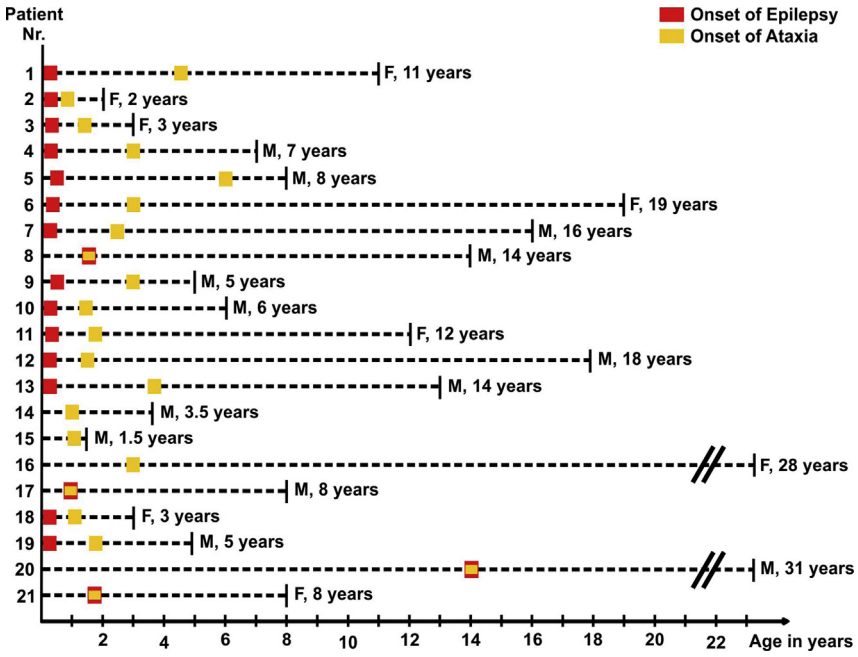


Fig. 1 – Onsets of epileptic seizures versus ataxia for all patients.

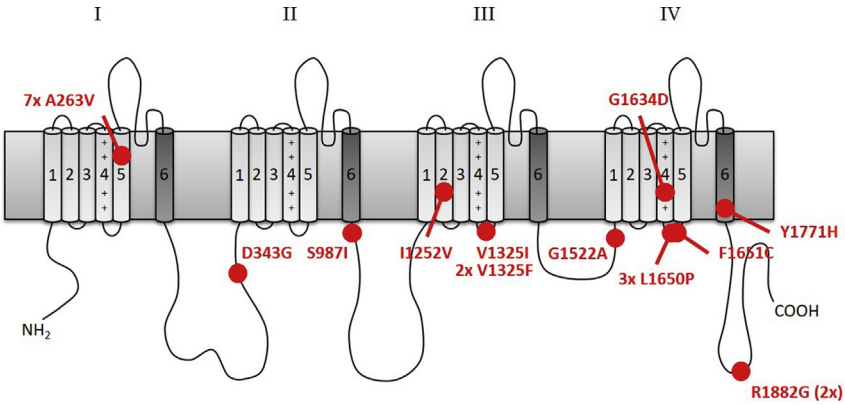


Fig. 2 – Overview of the *SCN2A* pathogenic variants found in patients with episodic ataxia.

dosages (Patients 14 and 15) that did not respond to the treatment. Of note, the latter were familial cases with a very peculiar phenotype (no seizures, low frequency and long duration of EA episodes, specific impairment of speech development),[5] for which EA treatment may be particularly challenging. We would encourage caregivers to try treatment with acetazolamide in *SCN2A* associated EA in dosages up to 30 mg/kg body weight/day (and maybe even higher). Given that carbamazepine showed major improvement in one case (Patient 5), this would be our second line treatment recommendation for these patients, knowing that further studies are needed to establish a reliable treatment regimen. Of note, despite insufficient treatment alternatives, our data are encouraging for the majority of the patients who showed an unimpaired or only slightly impaired cognitive outcome (17/21 patients, i.e. 81%). This observation should be kept in mind when treating and counseling patients with *SCN2A*-associated EA.

Finally, we identified one mutational hotspot and one region within $Na_V1.2$ encompassing several cases. 7/21 patients harbored the same pathogenic gain-of-function variant (p.A263V) that has previously been shown as mutational hotspot for *SCN2A*-associated epilepsy.[4] Though genotype–phenotype correlations have been attempted for *SCN2A*,[22] this particular pathogenic variant has been associated with a wide range of epileptic phenotypes from self-limited disease courses to epileptic encephalopathy, e.g., Ohtahara syndrome.[4] 6/7 patients in our cohort (p.A263V) showed neonatal-onset seizures, one patient showed seizure onset at 2 months of life. EA onset was comparable between patients, i.e., between 18 and 36 months. 5/7 patients showed a normal development.

The second hotspot is located within the domain IV affecting the S4 segment (p.G1634D) and the neighboring cytoplasmic loop linking S4 and S5 (p.L1650P in three familial cases, plus p.F1651C). The S4 segment represents the voltage

Please cite this article as: Schwarz N et al., Clinical and genetic spectrum of *SCN2A*-associated episodic ataxia, European Journal of Paediatric Neurology, https://doi.org/10.1016/j.ejpn.2019.03.001

sensor of each domain which plays a crucial role for the gating of $Na_V1.2$.[23] The voltage sensor and the cytoplasmic loop between S4 and S5 are involved in the inactivation of the channel.[24,25] The pathogenic variant p.L1650P found in the three familial cases of EA – lacking epileptic seizures – has been described in a patient with epileptic encephalopathy,[26] emphasizing the challenge in genotype–phenotype correlations. A patient with a pathogenic *de novo SCN2A* missense variant (p.L1660W) affecting this cytoplasmic loop was described with recurrent encephalopathic episodes of which at least one might have been an episode of ataxia.[27] Finally, a pathogenic variant in the homologous gene *SCN8A* at the exact same position as in our three familial cases was described in a patient with epileptic encephalopathy.[28] These data emphasize the pathophysiologic importance of this region for *SCN2A*-associated disorders.

In conclusion, *SCN2A*-associated EA represents a rare, though potentially underestimated disorder in which a pharmacological attempt with acetazolamide or a sodium channel blocker should be performed.

Funding

N.S. was in part supported from the intramural research funding program of the Faculty of Medicine Tübingen (Fortüne 2381-0-0). J.H. conducted her work within the GARD study (protocol H09-01228) and TIDEX Study (protocol H12-00067).

Conflict of interest

All authors declare that they have no conflict of interest.

Acknowledgments

We are grateful to the participating patients and families.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.03.001.

REFERENCES

1. Browne DL, Gancher ST, Nutt JG, Brunt ERP, Smith EA, Kramer P, et al. Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1. *Nat Genet* 1994;**8**(2):136–40.
2. Jen J, Kim GW, Baloh RW. Clinical spectrum of episodic ataxia type 2. *Neurology* 2004;**62**(1):17–22.
3. Catterall WA. From ionic currents to molecular mechanisms: the Structure and function of voltage-gated sodium channels. *Neuron* 2000;**26**:13–25.
4. Wolff M, Johannesen KM, Hedrich UBS, Masnada S, Rubboli G, Gardella E, et al. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. *Brain* 2017;**140**(5):1316–36.
5. Fazeli W, Becker K, Herkenrath P, Düchting C, Körber F, Landgraf P, et al. Dominant SCN2A mutation causes familial episodic ataxia and impairment of speech development. *Neuropediatrics* 2018;**49**(06):379–84.
6. Gorman KM, King MD. SCN2A p.Ala263Val variant a phenotype of neonatal seizures followed by paroxysmal ataxia in Toddlers. *Pediatr Neurol* 2016;**67**:111–2.
7. Leach EL, Karnebeek CDM Van, Townsend KN, Tarailo-graovac M, Hukin J, Gibson WT. Episodic ataxia associated with a de novo SCN2A mutation. *Eur J Paediatr Neurol* 2016;**20**(5):772–6.
8. Liao Y, Anttonen AK, Liukkonen E, Gaily E, Maljevic S, Schubert S, et al. SCN2A mutation associated with neonatal epilepsy, late-onset episodic ataxia, myoclonus, and pain. *Neurology* 2010;**75**(16):1454–8.
9. Maksemous N, Smith R, Sutherland H, Sampaio H, Griffiths L. Whole-exome sequencing implicates SCN2A in episodic ataxia, but multiple ion channel variants may contribute to phenotypic complexity. *Int J Mol Sci* 2018;**19**(10):3113.
10. Schwarz N, Hahn A, Bast T, Müller S, Löffler H, Maljevic S, et al. Mutations in the sodium channel gene SCN2A cause neonatal epilepsy with late-onset episodic ataxia. *J Neurol* 2016;**263**(2):334–43.
11. Johannesen KM, Miranda MJ, Lerche H, Møller RS. Letter to the editor: confirming neonatal seizure and late onset ataxia in SCN2A Ala263Val. *J Neurol* 2016;**263**(7):1459–60.
12. Reif PS, Tsai M-H, Helbig I, Rosenow F, Klein KM. Precision medicine in genetic epilepsies: break of dawn? *Expert Rev Neurother* 2017;**17**(4):381–92.
13. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;**17**(5):405–23.
14. Shanmugarajah PD, Hoggard N, Aeschlimann DP, Aeschlimann PC, Dennis GJ, Howell SJ, et al. Phenytoin-related ataxia in patients with epilepsy: clinical and radiological characteristics. *Seizure* 2018;**56**:26–30.
15. Moon H-J, Jeon B. Can therapeutic-range chronic phenytoin administration cause cerebellar ataxia? *J Epilepsy Res* 2017;**7**(1):21–4.
16. Balamurugan E, Aggarwal M, Lamba A, Dang N, Tripathi M. Perceived trigger factors of seizures in persons with epilepsy. *Seizure* 2013;**22**(9):743–7.
17. Scheffer IE. Vaccination triggers, rather than causes, seizures. *Epilepsy Curr* 2015;**15**(6):335–7.
18. 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* 2016;**82**(3):224–32.
19. Zasorin NL, Baloh RW, Myers LB. Acetazolamide-responsive episodic ataxia syndrome. *Neurology* 1983;**33**(9):1212–4.
20. Liao Y, Deprez L, Maljevic S, Pitsch J, Claes L, Hristova D, et al. Molecular correlates of age-dependent seizures in an inherited neonatal-infantile epilepsy. *Brain* 2010;**133**(Pt 5):1403–14.
21. Corey LA, Pellock JM, Kjeldsen MJ, Nakken KO. Importance of genetic factors in the occurrence of epilepsy syndrome type: a twin study. *Epilepsy Res* 2011;**97**(1–2):103–11.
22. Sanders SJ, Campbell AJ, Cottrell JR, Moller RS, Wagner FF, Auldridge AL, et al. Progress in understanding and treating SCN2A – mediated disorders. *Trends Neurosci* 2018;**41**(7):442–56.
23. Marban E, Yamagishi T, Tomaselli GF. Structure and function of voltage-gated sodium channels. *J Physiol* 1998;**508**(3):647–57.

24. Lerche H, Peter W, Fleischhauer R, Pika-Hartlaub U, Malina T, Mitrovic N, et al. Role in fast inactivation of the IV:S4-S5 loop of the human muscle Na+ channel probed by cysteine mutagenesis. *J Physiol* 1997;**505**(2):345–52.
25. Alekov AK, Peter W, Mitrovic N, Lehmann-Horn F, Lerche H. Two mutations in the IV/S4-S5 segment of the human skeletal muscle Na+ channel disrupt fast and enhance slow inactivation. *Neurosci Lett* 2001;**306**(3):173–6.
26. Trump N, McTague A, Brittain H, Papandreou A, Meyer E, Ngoh A, et al. Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis. *J Med Genet* 2016;**53**(5):310–7.
27. Fukasawa T, Kubota T, Negoro T, Saitoh M, Mizuguchi M, Ihara Y, et al. A case of recurrent encephalopathy with SCN2A missense mutation. *Brain Dev* 2015;**37**(6):631–4.
28. Ohba C, Kato M, Takahashi S, Lerman-Sagie T, Lev D, Terashima H, et al. Early onset epileptic encephalopathy caused by de novo SCN8A mutations. *Epilepsia* 2014;**55**(7):994–1000.

Please cite this article as: Schwarz N et al., Clinical and genetic spectrum of *SCN2A*-associated episodic ataxia, European Journal of Paediatric Neurology, https://doi.org/10.1016/j.ejpn.2019.03.001