

Video/EEG findings in a KCNQ2 epileptic encephalopathy: a case report and revision of literature data

Domenico Serino¹, Nicola Specchio¹, Giuseppe Pontrelli^{1,2}, Federico Vigeveno¹, Lucia Fusco¹

¹ Neurology Division, Ospedale Pediatrico Bambino Gesù, Rome

² Amaducci Neurology Unit, Department of Neuroscience, University of Bari, Bari, Italy

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ABSTRACT – We describe the EEG findings of an infant with early-onset epileptic encephalopathy with mutation of the *KCNQ2* gene and a family history of neonatal seizures. The infant presented with multifocal drug-resistant seizures with onset during the third day of life. Family history was positive for early-onset neonatal seizures. Metabolic screening and neuroimaging were negative. Direct sequencing of *KCNQ2* from both the mother and child revealed a heterozygous cytosine-to-guanine mutation (Dedek *et al.*, 2003). Interictal EEG showed a very discontinuous pattern which evolved towards a defined burst-suppression pattern during sleep and a multifocal, random, attenuation pattern during wakefulness. Focal, tonic seizures with head deviation, sometimes followed by asynchronous and asymmetrical clonic jerks, eyelid myoclonias, and polypnoea, were recorded. Ictal EEG was characterised by focal, low-voltage, fast activity, followed by recruiting theta rhythms and bilateral, focal, spike-wave complexes, alternatively localised to one hemisphere and subsequently diffusing to the other. ACTH therapy was introduced, resulting in a significant improvement in EEG activity and gradual reduction in seizure frequency, with cessation at age 13 weeks. [*Published with video sequences*]

Key words: *KCNQ2*, epilepsy, encephalopathy, infant, burst-suppression



Correspondence:

Domenico Serino
Neurology Division,
Ospedale Pediatrico Bambino Gesù,
Piazza S Onofrio 4,
00165 Rome, Italy
<domenico.serino@opbg.net>

The *KCNQ* gene family encodes for several subunits of voltage-gated potassium channels which are expressed in the central nervous system and which are responsible for the modulation of M-current, a slowly activating, non-inactivating potassium conductance that inhibits neuronal excitability (Weckhuysen *et al.*, 2012). Mutations of the *KCNQ2* gene, which encodes for the chan-

nel Kv7.2 subunit, are closely associated with benign familial neonatal seizures (BNFS) (Biervert *et al.*, 1998; Charlier *et al.*, 1998; Singh *et al.*, 1998; Heron *et al.*, 2007). Emerging reports in the literature (Millichap and Cooper, 2012), however, demonstrate that alterations of *KCNQ2* may also be associated with an epileptic encephalopathy phenotype which differs from BNFS in both

electroclinical presentation and evolution. Early recognition of such mutations has important diagnostic, prognostic, and therapeutic implications, thus appropriate neurophysiological characterisation of such emerging phenotypes is gaining new relevance. We describe EEG findings of an infant with early-onset epileptic encephalopathy with a positive family history for adrenocorticotrophic hormone (ACTH)-responsive neonatal seizures and a missense mutation in the *KCNQ2* gene, which was also found in his mother. The genetic characteristics of the family have already been reported elsewhere (Dedek *et al.*, 2003). Our current report specifically focuses on early EEG findings.

Case study

A boy was born at term from non-consanguineous parents after an uneventful pregnancy. Due to a prolonged delivery period and poorly characterised symptoms of foetal distress, he was born by Caesarean section, with a birth weight of 4 kg and an Apgar score of 6 and 8 at 1 and 5 minutes, respectively. During his third day of life, he developed multifocal seizures, characterised by left or right head deviation and upper and lower limb involvement, and was hospitalised at another institution. At hospital, several antiepileptic drugs (AEDs) were administered (phenobarbitone, phenytoin, pyridoxine, phenobarbital, and vigabatrin) without seizure control or reduction. Computed tomography (CT) performed at days 7 and 30 and magnetic resonance imaging (MRI), performed at 18 days of life were reported as normal. At 41 days of life, the patient was first referred to our institute. Neurological examination showed diffuse hypotonus. Biochemical screening was performed (serum electrolytes, glucose level and ammonia, biotinidase screening, serum and cerebrospinal fluid (CSF) lactate and amino acids, serum ammonium, urine and CSF organic acids, urine guanidine-acetate-methyl-transferase (GAMT) and creatinine, CSF/serum glucose ratio, and sulfi-test) which yielded no significant results. MRI was normal and MR spectroscopy was within normal age parameters.

Negative results in diagnostic testing led to a more in-depth investigation of the patient's clinical history. Repeated anamnestic investigation revealed that the patient's mother had a history of cyanotic spells and convulsions during the second postnatal day. The seizures had a frequency of 2-3/day and were clinically characterised by right or left limb and facial jerks. Seizures temporarily stopped after administration of phenobarbital but reappeared after a short time. ACTH therapy was started and she became seizure-free within one month. After obtaining the above-mentioned anamnestic data, genetic testing for

mutations in the *KCNQ2* gene was undertaken. Also, ACTH therapy was introduced, resulting in a significant improvement in EEG activity and gradual reduction in seizure frequency, with cessation at age 13 weeks. PCR amplification and subsequent direct sequencing of *KCNQ2* exon 5 from both the patient's and his mother's DNA, revealed a heterozygous mutation of cytosine to guanine, leading to the substitution of serine by tryptophan at amino acid position 247 (S247W) of the predicted protein (data already published; Dedek *et al.*, 2003).

The patient underwent a follow-up period of four years, during which he was seizure-free. He presented with psychomotor delay and pyramidal paraparesis became evident by the end of the first year. Subsequent referral to his local rehabilitation unit was undertaken.

EEG and clinical findings

The patient arrived at our institution in a soporous state, alternating between apparent wakefulness and sleep and presenting with multiple daily seizures. The interictal EEG showed a very discontinuous pattern which evolved towards a defined burst-suppression pattern during sleep. Bursts showed high-voltage, delta activity associated with spikes and polyspikes, lasting for 2-3 seconds, while attenuation sequences were characterised by low-voltage activity, sometimes with recognisable, low-voltage, theta rhythms. During the waking periods, burst-suppression gave way to a multifocal, random, attenuation pattern with asynchronous, bilateral bursts and random appearance of attenuation after the paroxysms. Epileptiform activity was prevalently found over the central, temporal, and parietal regions.

Serial video-EEG monitoring showed several focal seizures which alternatively originated from both hemispheres (see *video sequences*), prevalently from the left. Seizure semiology was characterised by unilateral eye and head deviation, upper limb hypertonus sometimes followed by asynchronous and asymmetrical clonic jerks, eyelid myoclonias, and polyphnoea. Ictal EEG was characterised by focal, low-voltage, fast activity, followed by recruiting theta rhythms and bilateral, focal, spike-wave complexes, alternatively localised to one hemisphere and subsequently diffusing to the other.

One week after introduction of ACTH therapy, an improvement of the general EEG pattern and a progressive reduction of abnormalities was documented. An improved continuity of background activity with resolution of the burst-suppression pattern was also recorded.

Table 1. Reported cases of KCNQ2 encephalopathy.

Author	Age at onset	Seizure semiology	EEG	Neurological Examination	EEG evolution	Therapy	Response to AEDs	MRI	Follow-up	KCNQ2 mutation	NE at follow-up	Family history
Steinlein et al., 2007	Day 2	Neonatal Seizures	ND	Mild muscular hypotonia and joint hypomobility.	At 12 months, left frontal sharp-wave.	PB	No seizures	ND	New seizure onset at 4 years	c.939insG	At 6 years, MR, severe delay of speech and motor development.	Negative
Steinlein et al., 2007	Day 1	Neonatal Seizures	ND	ND	ND	ND	Seizures until 10 months.	ND	ND	c.939insG	At 4 years, marked retardation of speech and motor development.	Negative
Steinlein et al., 2007	Day 2	Convulsions	ND	Mild muscular hypotonia	Normal	ND	No seizures	ND	Seizure-free	c.2034delC	Speech delay, cognitive impairment.	Maternal aunt with MR.
Schmitt et al., 2005	Day 1	Tonic Seizures	Discontinuous background activity with multifocal sharp waves. (7 days)	Discontinuous ND	Ictal: at 12 months, slow delta waves over right temporal region evolving into rhythmic sharp waves.	PB, B6, PHE, VGB, VPA, CBZ, STH, LTC, TPM	Seizure-free at 15 months	Normal	Seizure-free	c1174c>T	At 4 years, severe MR	Negative
Weckhuysen et al., 2012	Day 2: Tremor noted in utero over last 2 months.	Apnoea, generalised stiffening with facial suffusion, followed by pallor and cyanosis. Duration 3 sec. Multiple seizures daily.	Continuous multifocal and bilaterally synchronous epileptiform activity. In sleep, discontinuity with marked attenuation between bursts of epileptiform discharges. (10 days).	Macrocephaly, Severe asymmetric spastic quadriplegia. Visually attentive and smiled responsively.	Significant improvement with slow background and occasional transient sharp waves over both temporal regions. (5 weeks)	PB, PHT	No response to PB; PHT started at 3 weeks and seizures eventually controlled. One hemiclonic seizure at 14 months, no further seizures.	ND	Seizure-free since age 14 months	c.638G>A	Profound MR, poor head control, smiled at 6 to 8 weeks. Unable to sit unsupported or transfer objects. Could lift head from prone but not able to support on forearms or roll over. Non-verbal.	Father with neonatal-onset epilepsy, still in therapy with CBZ.

Table 1. (Continued)

Author	Age at onset	Seizure semiology	EEG	Neurological Examination	EEG evolution	Therapy	Response to AEDs	MRI	Follow-up	KCNQ2 mutation	NE at follow-up	Family history
Weckhuysen <i>et al.</i> , 2012	Day 3	Stiffening, head and eye deviation and tonic posturing. Multiple seizures daily.	BS. 3 seizures with head and eye deviation to right, trunk to left, generalised stiffening, facial twitching. Centroparietal ictal rhythm evolving to high-voltage slowing: right sided in 2 and left sided in 1 seizure. (5 days)	Severe asymmetric spastic quadriplegia.	BS (15 days)	PB, PHT, VGB, TPM, OXC, CNZ	No response to PB, PHT, VGB, CNZ. Some improvement with TPM. OXC very effective. Run of 8 seizures at 2 years, then seizure-free until 4 years, associated with AED reduction.	ND	Seizure-free since 4 years	c.821C>T	Profound MR. Non-verbal.	Negative
Weckhuysen <i>et al.</i> , 2012	Day 2. Last 2 months of pregnancy; rhythmic jerking similar to seizures.	Generalised tonic with clonic components, lip smacking, back arching, apnoea. Multiple seizures daily.	Multifocal epileptic activity, most frequently seen in left temporal and right frontal regions. One seizure with nystagmus and intermittent bilateral clonic jerks. Ictal changes showed diffuse attenuation with multifocal spikes. (7 days)	Normal examination. Poor fine motor skills	ND	PB, midazolam infusion, folinic acid, midazolam betamethasone, VPA, pyridoxine, VGB, TPM, dexamethasone	No response to PB, temporary response to midazolam infusion. VGB initially reduced seizures and normalised EEG (7 weeks of seizure freedom). Combination of TPM, VGB and B6 controlled seizures; episodes of status epilepticus at 3 months; seizure-free from 9 months until 8 years.	ND	Seizure-free from 9 months to 8 years with 2 tonic seizures	c.613A>G	Moderate MR. Regression with status epilepticus. Unable to roll at 6 months. Walked at 16 months; 30 single words at 4 years. At 8 years, followed 2 commands and read small words. No use of toys.	Paternal aunt with seizures from day 7 to 4 years.

Table 1. (Continued)

Author	Age at onset	Seizure semiology	EEG	Neurological Examination	EEG evolution	Therapy	Response to AEDs	MRI	Follow-up	KCNQ2 mutation	NE at follow-up	Family history
Weckhuysen et al., 2012	Day 3	Tonic seizure, followed by myoclonic jerks and nystagmus. Multiple seizures daily.	BS (3 days)	Spastic quadriplegia. No visual contact.	Multifocal spikes, spike-waves and sharp waves. (2 months)	VGB, PB, VPA, TPM, PHT, CNZ, ETX, LVT, CBZ	Daily tonic seizures despite multidrug regimen.	ND	Frequent tonic seizures	c.1678C>T	Profound MR. Non-verbal.	Two uncles of father with febrile seizures.
Weckhuysen et al., 2012	Day 7	Tonic flexion spasms. Multiple seizures daily.	Multifocal epileptic activity. (2 months)	Severe spastic quadriplegia. Axial hypotonia.	Bilateral temporal sharp waves. (4 months)	VGB, VPA, TPM	Temporary response to VGB. Recurrence of extension spasms with nystagmus later in first year. Gradual decrease of seizure frequency thereafter.	ND	Seizure-free since age 2 years 6 months.	c.793G>C	Profound MR. Non-verbal.	Negative
Weckhuysen et al., 2012	Day 3	Tonic extension with clonic movements of left hemicorpus and eyelid myoclonia. Multiple seizures daily.	BS (3 days)	Widely-spaced gait, mild spasticity.	Multifocal epileptic activity. (3 weeks)	PB, CNZ, PHT, VPA, CBZ, VGB	Daily tonic seizures, often lateralised to the left. After 2 non-sporadic tonic seizures with CBZ and VGB.	ND	Seizure-free since 3 years.	c.1636A>G	Profound MR. Non-verbal.	Cousin of father with epilepsy.
Weckhuysen et al., 2012	Day 2	Tonic extension, high-pitch cry, cyanosis, and bradypnoea. Sometimes with myoclonias of arms. Multiple seizures daily.	BS (5 days)	Axial hypotonia. Walked with assistance. Widely-spaced gait.	Multifocal epileptic activity. (9 days)	PB + LVT. PB stopped at 15 months. VPA started at 3 years.	Monthly tonic or tonic-clonic seizures, often with fever. Seizure-free between 11 months and 3 years, 2 months. Tonic-clonic seizure at 3 years, 2 months.	ND	Seizure-free since 3 years, 2 months.	c.869G>A	Profound MR. Non-verbal.	Maternal grand-mother with few epileptic seizures as an older child. Sister with 1 febrile seizure.

Table 1. (Continued)

Author	Age at onset	Seizure semiology	EEG	Neurological Examination	EEG evolution	Therapy	Response to AEDs	MRI	Follow-up	KCNQ2 mutation	NE at follow-up	Family history
Weckhuysen <i>et al.</i> , 2012	Day 2	Tonic seizures with version of the head to one side, followed by cyanosis and eyelid myoclonias. Clonic movements of left more than right hemicorpus. Multiple seizures daily.	Multifocal epileptic activity most frequently seen in right frontal regions. (4 weeks)	Moderate asymmetric spastic quadripareisis.	ND	PB, VPA, CNZ	No response to PB; VPA and CNZ started at 4 weeks and seizures controlled.	ND	Seizure-free between 2 months and 2 years, 11 months. Then 1 nocturnal tonic-clonic seizure. Seizure-free since then.	c.869G>A	Profound MR. Non-verbal.	Paternal grandfather with epilepsy since age 30 years.
Borgatti <i>et al.</i> , 2004	Day 3	Brief clonic seizures. At day 5, mostly right-sided tonic-clonic seizures with oro-alimentary automatism.	Normal	Severe spastic tetraparesis.	Multifocal epileptiform abnormalities, asynchronous over both cerebral hemispheres.	PB, VGB, ACTH, PHE, VPA, CZP, B6, immunoglobulins	Control with PB until day 40. Slight improvement with ACTH. Other AEDs ineffective in reaching seizure control.	Thin corpus callosum with moderate white matter reduction and slightly enlarged lateral ventricles.	Good control until day 40, then up to 60 seizures/day. Decline in frequency between 4 and 6 years.	c.1620G>A	Severe spastic tetraparesis. Profound MR. Non-verbal.	Brother and mother with BNFS. Maternal aunt with BNFS, focal epilepsy and moderate MR.
Borgatti <i>et al.</i> , 2004	Day 3	Tonic seizures with head rotation.	Epileptiform abnormalities in the right central area.	ND	Slow temporal abnormalities over temporal right-sided regions. (31 years)	PB	Despite PB, continued seizures (<1/month) until 5 years.	Normal	Seizure-free since 5 years.	c.1620G>A	Mild dysmetria and ataxia, nystagmus, moderate MR.	Sister and niece with BNFS. Niece with BNFS, epileptic encephalopathy and profound MR.

MR: mental retardation; NE: neurological examination; BFNS: benign familial neonatal seizures; MRI: magnetic resonance imaging; VPA: valproate; CNZ: clobazam; CBZ: carbamazepine; PB: phenobarbital; VGB: vigabatrin; PHE: phenytoin; B6: pyridoxine; TPM: topiramate; OXC: oxcarbazepine.

The interictal EEG was characterised by repeated irregular spikes and polyspike-wave complexes recorded over the right frontal and temporal regions, in association with similar, yet asynchronous, abnormalities found over the left parietal and temporal regions.

During the following few weeks, seizures were still recorded, but became more and more sporadic, until finally disappearing after four weeks since the introduction of ACTH. Recorded seizures were tonic, focal seizures, characterised by upper left limb contraction, right eye and head deviation, oral automatisms, and hyperextension of the head and trunk. Ictal EEG was still characterised by focal, right central, low-voltage, fast activity, followed by a recruiting, alpha-like rhythm.

After seizure cessation, the EEG pattern showed gradual and significant improvement, with more synchronous, yet slow (3-5 c/sec), background activity. Spikes and polyspikes were still evident, especially in sleep, asynchronously over the bilateral central regions, and persisted almost unchanged in the following EEG, until the last control at the age of 3 years. Organisation of sleep activity also gradually improved.

Discussion

To date, 15 cases of *KCNQ2* mutations, underlying a very severe, early-onset epilepsy with encephalopathy, have been reported, including our own (Dedek et al., 2003; Borgatti et al., 2004; Schmitt et al., 2005; Steinlein et al., 2007; Weckhuysen et al., 2012) (table 1). The 11 case reports reported by Weckhuysen et al. (2012), Schmitt et al. (2005), and Borgatti et al. (2004) included a detailed description of both seizure semiology and EEG characteristics, while the three cases described by Steinlein et al. (2007) were generically reported to have neonatal seizures with no associated description of EEG characteristics. In accordance with our report, among the cases for which semiology was described, focal tonic seizures appear to be a constant feature. Head deviation, cyanosis, and focal clonic seizures, also described in our case, are commonly reported, while myoclonias appear not to be as frequent. In one case, as in ours, spasms were also described. Seizure frequency, when reported, is multiple daily while duration varies from seconds to several minutes. Reported EEG findings showed multifocal epileptiform abnormalities or a burst-suppression pattern. Our patient alternated between a pattern of multifocal random attenuation and burst suppression, in relation to wake/sleep cycles. In reported cases, EEG during follow-up showed either the persistence of multifocal epileptiform activity or the presence of focal, slow rhythms. In relation to therapy, an interesting finding in our case was a significant

response to ACTH therapy as opposed to the reported scarce effectiveness of other AEDs (Weckhuysen et al., 2012).

Conclusion

Our reported case highlights how cerebral activity in *KCNQ2* mutation-related epilepsy may be characterised by burst-suppression patterns with associated interictal multifocal spikes and polyspikes. Such epileptiform activity is congruous with what is clinically observed during seizures which are characterised by focal, tonic convulsions with head deviation and cyanosis, sometimes followed by focal, clonic seizures. In conclusion, we underscore the association between *KCNQ2* mutations and epileptic encephalopathy, characterised by early-onset, burst-suppression EEG patterns, and the implication that such mutations should now accordingly be taken into account in the diagnostic work-up of neonatal encephalopathies, when burst-suppression is the prevalent EEG pattern. □

Disclosures.

None of the authors of this article present potential conflicts of interests.

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Legends for video sequences

Video sequence 1

The episode is characterised by right eye and head deviation, associated with upper limb hypertonus. Twenty seconds later, the patient shifts head and gaze towards the left, while hypertonus is maintained. The EEG shows an initial train of fast, low-voltage activity originating from the left frontal regions which gives way to a high-voltage, spike-wave activity involving the left hemisphere. Together with persistent upper limb hypertonus, bilateral eyelid myoclonias also appear, in association with an increase in respiratory frequency which is maintained until the end of the seizure. Asynchronous, bilateral, clonic jerks of the upper limbs are also evident. At this point, the EEG is characterised by high-voltage, spike-wave complexes which diffuse from the left to the right hemisphere and then give way to a right-sided, alpha-like activity.

Video sequence 2

The first part of the video shows an interictal, burst-suppression pattern during apparent sleep. Bursts are characterised by high-voltage, delta waves, intermingled with spikes and polyspikes, and appear fairly synchronised and long-lasting, as do the suppression periods, characterised by low-voltage activity, sometimes with recognisable theta rhythms.

The seizure shown in the second part of the video, specular to the first reported episode, is characterised by an initial eye and head deviation to the left, followed 20 seconds later by deviation towards the right, associated with hypertonus of the upper limbs. Similar to what was recorded during the first episode, the EEG shows an initial train of fast, low-voltage activity, originating from the right frontal regions which gives way to a high-voltage, spike-wave activity involving the left hemisphere.

Key words for video research on www.epilepticdisorders.com

Syndrome: neonatal seizures

Etiology: *KCNQ2* mutation

Phenomenology: head deviation;
eye deviation;
clonic seizure;
myoclonic (eyelids)

Localization: not applicable