



# Two Cases of KCNQ2 Encephalopathy with Unusual Findings: Clinical and Neurophysiological Follow-Up

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## Abstract

**Introduction:** KCNQ2 encephalopathy is a developmental encephalopathy characterized by neonatal-onset pharmacoresistant epilepsy with good response to sodium channel blockers, severely abnormal background EEG activity, and severe developmental delay. In spite of confirmation of this consistent and typical electro clinical syndrome, a broader spectrum of findings has been described.

**Methods:** We report our experience with two cases of genetically-confirmed KCNQ2 encephalopathy.

**Results:** Our two patients, followed-up for 2 and 9 years respectively, show typical clinical and neuroimaging findings, although some peculiarities can be recognized: The first cases developed a Rett-like neurodevelopmental phenotype, while the second patient (already described) had a neonatal ictal EEG reminiscent of epilepsy of infancy with migrating focal seizures and molecular analysis showed a pathogenic de novo deletion, which is an extremely rare finding in KCNQ2 encephalopathy.

**Conclusions:** Our cases further delineate the electroclinical and genetic heterogeneity in patients with KCNQ2 encephalopathy. Additional insights can be expected from the widespread availability of genetic testing in clinical practice.

## Introduction

KCNQ2 encephalopathy is a developmental encephalopathy characterized by neonatal-onset epilepsy (typically tonic versive seizures with autonomic signs), severely abnormal background EEG activity (suppression-burst or random focal attenuation pattern), severe developmental delay [1] and good response to sodium channel blockers in spite of severe pharmacoresistance to other antiepileptic drugs [2]. It is caused by mutations in the potassium voltage-gated channel subfamily Q member 2 (KCNQ2) [1]. Opposed to cases of benign familial neonatal-onset epilepsy, KCNQ2 encephalopathy is typically associated with missense mutations [3].

In this paper we describe two cases of KCNQ2 encephalopathy diagnosed at our centre and highlight their novel features in comparison to the available literature.

## Methods

We report on the clinical, EEG, brain Magnetic Resonance Imaging (MRI) and molecular genetics data of two unrelated patients consecutively diagnosed and regularly followed-up at the Child Neuropsychiatry Unit, Santa Maria Nuova Hospital, Reggio Emilia (Italy).

Genetic testing was undertaken by means of a targeted NGS panel for genes related to pediatric epilepsies and epileptic encephalopathies. NGS findings were validated by Sanger sequencing.

Neonatal seizures were confirmed by conventional EEG using the 10-20 system. Neonatal status epilepticus was defined as continuous seizure activity for at least 30 minutes or recurrent seizures lasting a total of 30 minutes without definite return to the baseline neurologic condition between seizures [4].

## Case Studies

### Patient 1

This is a female patient born small for gestational age (birth weight 2675 g) at 41 W.G.A. by Urgent Caesarian Section (UCS) due to stained amniotic fluid and abnormal cardiotocographic trace. Her Apgar scores were 7 at 1 minute and 8 at 5 minutes. Neonatal seizures started at 48 hours of life. Episodes were characterized by opisthotonos, tonic eye deviation to one side, clonic

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jerks of the eyelids and chewing automatisms. Her neurological examination showed severe axial hypotonia and diffuse hyporeflexia. Background activity in the neonatal period was discontinuous or semi-discontinuous with multifocal sharp waves, while ictal EEG showed focal onset of alpha-beta rhythms over the fronto-temporal areas, followed by theta sharp waves and sharp-and-wave complexes spreading to the central area and to the contralateral hemisphere. She was started on carbamazepine with good response.

During follow-up, severe developmental delay became obvious: she acquired independent walking at 4 years of age and her productive speech is still limited to bi or tri-syllabic sounds with no semantic aim. Her neurodevelopmental phenotype has since been dominated by disruption of social interaction and frequent motor stereotypies. At 9 years of age, she has severe intellectual disability, her neurological examination shows inconsistent eye contact, diffuse muscular hypotonia and hypotrophy, brisk reflexes with no pyramidal signs and severe dyspraxia. She walks with a broad-based gait and an inverted pattern. She shows multiple minor dysmorphisms (downslanting palpebral fissures, broad concha, long and thin toes and fingers) and failure to thrive. She also has limbs and truncal hypertrichosis.

From 3 to 7 years of age she was completely seizure-free. She had two seizures at 7 and 8 years of age, described as bilateral tonic-clonic. Follow-up awake EEG at 9 years of age shows independent focal epileptiform discharges in the fronto-centro-temporal regions on an unremarkable background.

Neurometabolic (plasma amino acids, urinary organic acids, very long chain fatty acids and asialotransferrin) and neurogenetic investigations (CGH-array, Angelman / Prader-Willi, FOXP1, CDKL5, UBE3A, SLC2A1, SHANK3, SCN1A) were negative. Her brain MRI, electroneurography and auditory brainstem evoked potentials are normal.

Direct sequencing of the MECP2 gene demonstrated the heterozygous missense variant c.1192G > T (p.Asp398Tyr), with discordant in silico prediction, inherited from the asymptomatic mother.

The targeted NGS panel for pediatric epilepsies detected the heterozygous missense variant NM\_172107.3 (KCNQ2): c.997C > T (p.Arg333Trp), classified as likely pathogenic, predicted to be deleterious by in silico tools and occurring de novo.

## Patient 2

Our second patient was reported previously [5]. He was born at term (birth weight 3680 g) by UCS due to maternal pre-eclampsia and abnormal cardio-tocographic trace. He was cyanotic and hypertonic at birth (Apgar scores: 3 at 1 minute, 10 at 5 minutes), but Sarnat score and umbilical cord gases were normal.

At 10 hours of age, he had his first neonatal seizure (short-lived versive tonic associated with desaturation). In the following hours, he had repeated episodes with similar semiology, sometimes with focal clonic jerking, and was transferred to our neonatal intensive care unit.

He was hypotonic, had normal head circumference and no dysmorphic features. His EEG showed a burst-suppression pattern, with synchronous and asynchronous bursts, at times associated with tonic spasms. His brain MRI showed a thin corpus callosum in its anterior third, but was otherwise normal. Lactate was raised both in plasma (31.6 mg/dl) and liquor (25 mg/dl). Inflammatory markers, blood and CSF cultures, superficial swabs were negative.

Neurometabolic screening (organic acids, acyl-carnitines, plasma amino acids) was unremarkable, as well as abdomen and heart ultrasound scans.

He was given intravenous phenobarbital with no effect. He was then unsuccessfully trialed with pyridoxine, pyridoxal-phosphate and folic acid. In the meantime, phenytoin was started, with minor effect on seizure reduction. At the time our patient was having tens of seizures per day. They arose from the temporal regions with alternating hemisphere of origin, beginning with low voltage alpha-beta rhythms, spreading to the contralateral homologous area and later to the homologous central region, and evolving into sharp theta waves and high amplitude sharps with slow waves, maximal over the left central region. In some instances, they were followed by homolateral voltage depression. Levetiracetam trial starting with i.e. boluses followed by oral maintenance resulted in an increase of seizure frequency to status epilepticus, prompting midazolam continuous infusion, followed by a second course of phenytoin and maintenance with oral topiramate, later associated with nitrazepam (with negligible results). We decided to start him on carbamazepine. Seizures ceased within three weeks. EEG still documented multifocal discharges on an abnormal background. The results of a targeted NGS panel for pediatric epilepsy confirmed a de novo heterozygous mutation in the NM\_172107.3 (KCNQ2) c.913\_915del [p.Phe305del], classified as likely pathogenic.

The infantile period was characterized by severe dysphagia (significantly improving over time). At two years of age, our patient is neurodevelopmentally delayed, has central visual impairment with convergent squint and nystagmus, axial hypotonia and a spastic-dystonic tetraplegia. He is seizure-free on carbamazepine monotherapy.

## Discussion

We described two cases of KCNQ2 developmental encephalopathy. The first patient has a previously unreported Rett-like neurodevelopmental phenotype, while the second one has several peculiarities: the ictal EEG pattern is reminiscent of Epilepsy of Infancy with Migrating Focal Seizures (EIMFS) and molecular diagnosis demonstrates a KCNQ2 gene deletion.

After first identifying KCNQ2 as the main gene involved in benign familial neonatal epilepsy, the clinical spectrum expanded to include severe, usually de novo cases of neonatal-onset refractory epilepsy associated with severely abnormal EEG and developmental delay [1], with later delineation of a specific electro clinical syndrome [2], which can be considered as an example of developmental encephalopathy [6]. Our follow-up of these two patients demonstrates a good long-term control of epilepsy (in spite of a high seizure burden in the neonatal period), associated with neurodevelopmental delay, in line with previous reports [1-3,7].

In spite of consistent literature confirmation of these core features, KCNQ2 pathogenic variants can cause varying degrees of encephalopathy severity [7], and a broader phenotype, even including nonepileptic myoclonus without neonatal seizures [8] and myokymia [9].

The clinical finding of a Rett-like phenotype has not been previously reported. Based on segregation and in silico prediction, the genetic variant on MECP2 is unlikely to play a major role in the clinical characteristics of our patient, although the potential for a modifying effect cannot be completely ruled out. Among previously

described KCNQ2 encephalopathy cases with the same genetic variant [10-12], one previously reported patient had very limited communication skills, marked bradypsychia and hand stereotypies, but no further details were provided [11].

The ictal neonatal EEG pattern of patient 2 is peculiar in that consecutive seizures alternatively involved one hemisphere, a pattern fairly reminiscent of EIMFS, an epileptic encephalopathy characterized by highly resistant focal seizures with autonomic features, onset in the first 6 months of life, post-natal microcephaly, developmental stagnation/delay, and migrating onset foci in the ictal EEG [13].

Genetic findings in patient 2 are also interesting, as missense mutations [7], with dominant-negative effect [3] initially represented the only finding associated with severe phenotypes. On the contrary, our patient and two previously reported identical twins with KCNQ2 encephalopathy share a deletion on the same amino acid residue, involving part of the pore domain, which is considered one of the KCNQ2 encephalopathy hot spots [7]. To the best of our knowledge, no other examples of single amino acids or larger deletions in KCNQ2 encephalopathy have been subsequently reported.

In conclusion, our cases further delineate the electro clinical and genetic heterogeneity in patients with KCNQ2 encephalopathy. Additional insights can be expected from the widespread availability of genetic testing in clinical practice.

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