



Impressive efficacy of the ketogenic diet in a KCNQ2 encephalopathy infant: a case report and exhaustive literature review

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Background: KCNQ2 encephalopathy is characterized by neonatal-onset epilepsy and developmental impairment, due to “de novo” KCNQ2 pathogenic variants. According to literature data, sodium channel blocking agents appear to be the best treatment options for the disease. Reports describing the use of ketogenic diet (KD) in the KCNQ2 pediatric population are limited. The non-conservative amino acid substitution p.Ser122Leu in KCNQ2 is associated with a broad spectrum of inheritance modalities, clinical phenotypes and outcomes; no previous reports of the same variant treated with KD are available in literature.

Case Description: We described a 22-month-old female with seizure onset on day 2 of life. At three months of age, she presented refractory status epilepticus (SE) that did not respond to midazolam and carbamazepine, which was added once a “de novo” p.Ser122Leu KCNQ2 variant was demonstrated. KD was the only treatment that led to cessation of seizures. The baby maintained seizures remission and achieved neurodevelopmental milestones.

Conclusions: To define an overt genotype-phenotype correlation for KCNQ2 pathogenic variants is a challenge; we propose the KD as a valuable treatment for refractory seizures and impaired neurodevelopment in infants harboring “de novo” mutations in the KCNQ2 gene.

Keywords: Developmental and epileptic encephalopathy; infant; KCNQ2 gene; ketogenic diet (KD); case report

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Introduction

KCNQ2 (Potassium Voltage-Gated Channel Subfamily Q Member 2) gene is located on chromosome 20q13.33 and encodes the Kv7.2 subunit of the voltage-gated potassium channels and expressed in the central and peripheral

nervous system from the 22nd week of gestational age. The Kv7.2 subunits are involved in the neuronal muscarine M-current, a K⁺-selective, non-inactivating, slowly activating/deactivating current, which regulates negatively neuronal excitability. Thus, KCNQ2 mutations lead to a

wide spectrum of neonatal-onset epilepsies, ranging from the benign familial neonatal epilepsy (BFNE) to the more severe phenotype known as KCNQ2 developmental and epileptic encephalopathy (KCNQ2-DEE) (1,2).

We describe an infant with KCNQ2 encephalopathy due to a “de novo” mutation in the S2 segment of the Kv7.2 subunit, whose seizures dramatically responded to the ketogenic diet (KD), whose administration led to both epilepsy control and neurodevelopmental milestone achievement. Furthermore, we conducted an exhaustive and systematic review of the available literature on several medical electronic databases (including Cochrane Library, Medline, PubMed Central, Scopus and Web of Science) in accordance with the “preferred reporting items for systematic review and meta-analysis” (PRISMA) (Figure 1).

We used the following search terms: “ketogenic diet” and “KCNQ2” or “ketogenic diet” and “KCNQ2 encephalopathy” or “ketogenic diet” and “KCNQ2” and “epilepsy”. Ten articles were found from 2016 to date; 2 studies from the reference list were added from other sources. Among them, 1 was related to the KCNQ3 gene and 5 were irrelevant and were, thus, excluded. We included 6 articles (3 retrospective cohort studies, 2 case series and 1 case report) (Table 1); all the selected studies were conducted in pediatric patients. The only filters applied were English language and human studies. In literature, reports describing the KCNQ2 variant detected in our patient are limited. None of the reported subjects was treated with a

KD. To date, the benefits of the KD in KCNQ2-related epilepsy have been demonstrated by some case reports and series. We present the following article in accordance with the CARE reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-258/rc>).

Case presentation

A female third-child of healthy unrelated parents was admitted to our department for neonatal seizures. Her familial history was negative. At the time of gestation, her father was 38, and her mother was 35 years old. Her mother denied complications during gestation, but referred reduced fetal movements. Prenatal ultrasounds did not show fetal anomalies. The child was born at 39 weeks of gestational age by spontaneous delivery. Her birth weight was 3,600 gr, length 51 cm and head circumference 35 cm (all within normal limits). The APGAR (9) score was 8 at one and 10 at five minutes, respectively. Neither dysmorphisms nor organ involvement were noted; neurological examination revealed only mild axial hypotonia. On day two of life, she presented with seizures consisting of asymmetric tonic posturing, according to the ILAE Classification of Seizures and the Epilepsies in the Neonate: her head moving to the right side and extension of her arms to the left side or vice versa (10). Motor manifestations were associated with apnea and cyanosis and followed by crying and asynchronous clonic movements of the arms. Laboratory investigations ruled out infections and inborn error of metabolism. The brain magnetic resonance imaging (MRI) revealed only a thin corpus callosum. An early-onset epileptic encephalopathies next-generation sequencing (NGS) panel was performed. The amplitude-integrated electroencephalography (aEEG) showed a sudden rise of both lower and upper margin, followed by a marked depression of the trace. Seizures were unresponsive to levetiracetam, but remitted with phenobarbital, thus the baby was discharged home. A follow-up electroencephalogram (EEG) recorded a polymorphic rhythmic background activity in the theta-delta range with a slight interhemispheric asymmetry (amplitude of 40 μ V over the right hemisphere, 20 μ V over the left). Interictal multifocal spikes, predominantly in the posterior regions of her right hemisphere, were also detected during both wakefulness and sleep (Figure 2). At three months of life, she presented with seizures with a same semiology that occurred in clusters and were resistant to treatment with phenobarbital, valproate and intravenous midazolam. The physical examination showed

Highlight box

Key findings

- The introduction of the ketogenic diet in an infant harboring a “de novo” p.Ser122Leu KCNQ2 variant resulted in both seizure control and developmental milestones achievement.

What is known and what is new?

- Response to ketogenic diet in KCNQ2 mutations in general is, so far, unpredictable and variable among cases reported in literature and summarized in the text.
- To our knowledge this is the eighth case of a patient with the missense variant c.365 C>T in the KCNQ2 gene and the first case reported to be treated, successfully, with ketogenic diet.

What is the implication, and what should change now?

- Our case enlightens the need to further assess ketogenic diet's contribution in both controlling KCNQ2-associated epilepsy and preventing KCNQ2-DEE and to further assess molecular mechanisms beyond genotype-phenotype correlation even in terms of response to treatment.

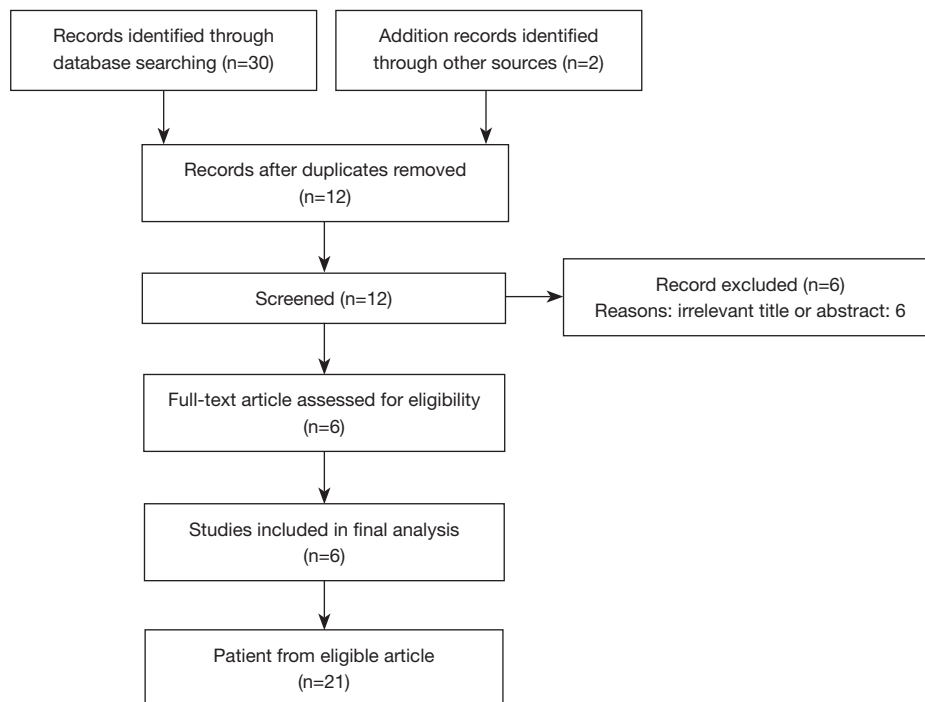


Figure 1 The PRISMA diagram: selection process of the studies included. PRISMA, preferred reporting items for systematic review and meta-analysis.

plagiocephaly, hypotonia and poor eye contact. The ictal polygraphic-video-EEG recording revealed discharges of rhythmic theta activity in the temporal regions of the right hemisphere with a tendency to spread to the left temporal ones and, subsequently, to generalize (*Figure 3*). The epilepsy NGS performed in the neonatal period revealed a p.Ser122Leu (c.365 C>T) variant in the KCNQ2 gene. Her parents tested negative, suggesting that the variant was a “de novo” mutation, assumed to be pathogenetic. After diagnosis, carbamazepine was added, without consistent benefits. Therefore, we started a KD with a 4:1 ratio between the amount of lipids and carbohydrates plus protein through nasogastric tube. This led to immediate improving of her neurological condition.

Subsequently, she continued carbamazepine associated with a KD with a 3:1 ratio and achieved complete seizure freedom over time. Neurological assessments demonstrated progressive gaining of developmental milestones and oral feeding ability with only mild delay. Improvement of the Neurological Infant score was recorded at 6 months, after KD was started. Follow-up EEG recordings showed an unmodified background activity. Under carbamazepine treatment and KD regimen the baby maintained seizure

remission and KD was discontinued at 20 months of age. The physical examination at 22 months of age evidenced: height and weight on 25–50th percentiles, head circumference on 40th percentile, residual plagiocephaly, mild axial hypotonia, stands up and walks with assistance, visually attentive and good social skills.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration (as revised in 2013). The study was approved by the ethical committee of the Medical Faculty of the University of Catania (IRB No. 780). Written informed consent was obtained from the patient’s parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Mutations in the KCNQ2 gene are involved in more than 80% of BFNE and 10% of all early-onset epileptic encephalopathies (EOEE) (11,12). BFNE shows autosomal dominant inheritance with incomplete penetrance and a

Table 1 Reported case reports and series of KCNQ2 pediatric patients treated with KD

Reference/year	No. Cases	KCNQ2 variant	Age at KD start/sex	Seizure type at onset	Epilepsy syndrome	Drugs at time of KD	Seizure control	Neurological outcomes
Thompson <i>et al.</i> 2017 (3)	1	NA	6 weeks/NA	DS neonatal seizures	–	Phenobarbital; levetiracetam; topiramate; clobazam	Daily seizures	Severe DD
Freibauer <i>et al.</i> 2018 (4)	1	De novo p.Ser247Leu plus a maternal; p.Ser374Pro	2 weeks/male	Tonic posturing with eye deviation, apnoea, bradycardia, and oxygen desaturation.	EIMFS	Phenobarbital; phenytoin; midazolam; ketamine	No seizures	Death at 1 months and 7 days
Ko <i>et al.</i> 2018 (5)	7	NA	NA/male [4]; female [3]	Neonatal tonic seizures	OS [4]	Phenytoin; oxcarbazepine	IS [7]	Profound ID [7]
Ko <i>et al.</i> 2018 (6)	6	NA	NA/male [4]; female [2]	DS neonatal seizures	OS [6]	2 or more not mentioned AEDs	>90% seizure reduction [5]	NA
Le Pichon <i>et al.</i> 2019 (7)	1	De novo p.Arg581Gln	NA/male	DS seizures	–	1 to 3 not mentioned AEDs	No seizures	NA
Lee <i>et al.</i> 2020 (8)	5	NA	NA/male [2]; female [3]	GTS [2]; GTCS [2]; MS [1]	OS [5]	Phenytoin; oxcarbazepine; phenobarbital valproate; levetiracetam topiramate vigabatrin; steroids	IS [5]	Severe ID [5]; hypotonia [2]; spasticity [3]; microcephaly [1]; eye contact [2]
Present study 2022	1	De novo p.Ser122Leu	3 months/female	Neonatal tonic posturing asymmetric seizures with asynchronous clonic movements, apnoea and cyanosis	–	Levetiracetam; phenobarbital; valproate	No seizures	Mild DD

KD, ketogenic diet; NA, not available; EIMFS, encephalopathy of infancy with migrating focal seizures; OS, Ohtahara syndrome; IS, infantile spasm; ID, intellectual disability; AED, antiepileptic drug; DS, drug-resistant; GTS, generalized tonic seizures; GTCS, generalized tonic-clonic seizures; MS, myoclonic seizures; DD, developmental delay.



Figure 2 Interictal EEG. EEG, electroencephalogram.

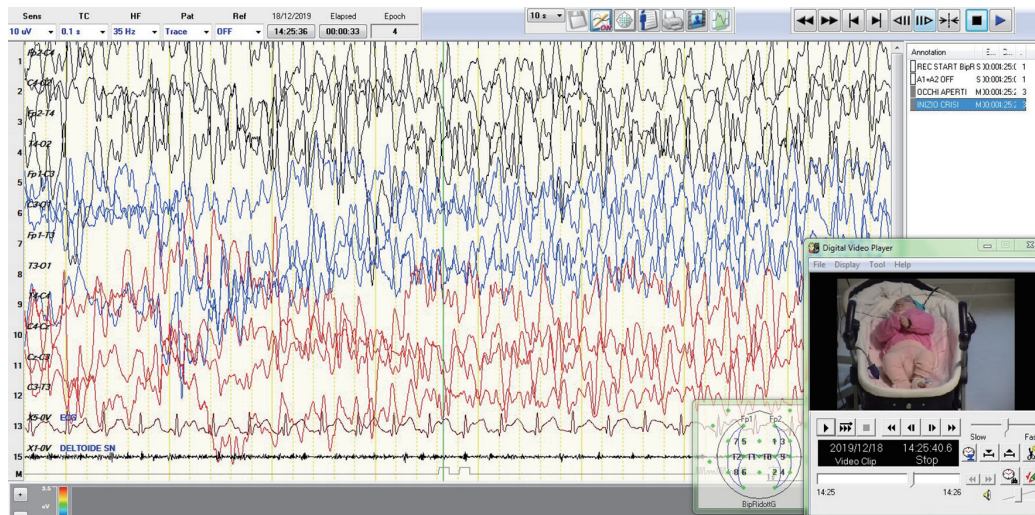


Figure 3 Ictal EEG. EEG, electroencephalogram.

high rate of inter- and intrafamilial variability and is caused by missense, splice-region, nonsense, frameshift variants and deletion pathogenic mutations in any gene region (1). Loss-of function (LoF) mutations of *KCNQ2* underlie BFNE through haploinsufficiency, resulting in a reduction of 25% of M-current activity (1). Seizures start in the first days of life and self-limit over weeks or months and are characterized by multiple episodes of asymmetric tonic posturing seizures with alternating laterality, sometimes followed by unilateral or bilateral clonic movements, associated with apnea and oxygen desaturation and rarely evolving into SE (1). Background EEG and brain MRI are unremarkable (13). Neurodevelopment is usually normal, but seizure relapse occurs in up to 25% of patients. Low dose oral carbamazepine is the first choice of treatment, leading to seizure freedom within hours from first administration (13).

KCNQ2-DEE is a much more severe neonatal-onset condition caused by “de novo” variants within critical zones of the gene. The S4 transmembrane segment, critical for channel gating, the pore domain and the A-helix and B-helix at C-terminus are the most frequently involved regions. Missense mutations cause *KCNQ2*-DEE and result in more than 25% inactivation of the voltage-gated potassium channel (13). Seizure onset and semiology is the same as in BFNE but *KCNQ2*-DEE results in progressive hypotonia, poor general movements, no visual fixation, impaired awareness, moderate to severe developmental delay and refractory epilepsy (13,14). The interictal EEG exhibits marked abnormalities, as dysmaturity, slowing, multifocal epileptiform discharges and burst suppression. The aEEG

is distinctive and consists of a sudden rise of the lower and upper margin, followed by a marked depression (14). Brain MRI can be normal or show signs of brain atrophy, hypo-myelination, thin corpus callosum or subcortical hyperintensities (14).

Sodium channel blockers (SCB) including carbamazepine, phenytoin, lidocaine and oxcarbazepine represent the best treatment option for patients with *KCNQ2* mutations according to the available literature (11,12,15). In case of refractoriness to SCB, seizure control has been reported to be achieved on other antiepileptic drugs (AEDs), including phenobarbital, levetiracetam, topiramate and valproate. Refractory patients have been reported to improve on other treatments options as well, including corticosteroids, folic acid, pyridoxine, and KD (16).

KD is a hyperlipidic, hypoglycemic, normoprotein diet regimen inducing and maintaining a chronic state of ketosis that results in neuroprotection and improvement of seizure frequency and severity by inducing an increase in cellular mitochondrial function and biogenesis, a decrease in oxidative stress, changes in potassium channels, an increase in the brain-derived neurotrophic factor (BDNF) and in the purinergic and GABAergic neurotransmission, attenuation of neuroinflammation and even changes in gut microbiota (17).

Epigenetic processes are known too to be related to changes in neuronal activity and epileptogenesis and, recently, the role of molecular mediators of epigenetic changes including non-coding RNAs, methylation of DNA and histone acetylation via de-acetylase inhibition and mitochondrial biogenesis have been hypothesized to

be involved in KD's therapeutic effects, as well (17-20); a recent transcriptional study on miRNA and mRNA's expression of eight pediatric patients affected by intractable epilepsy has demonstrated that KD induces changes at the transcriptomic level in genes encoding ion channels, neurotransmitter receptors and synapse structural proteins, resulting in down-regulation of synaptic transmission, which is the most relevant biologic pathway related to epilepsy, and subsequent decreased excitability (17). KD's use for early-onset intractable seizures has been described among pediatric patients with KCNQ2 mutations. In the case series by Thompson *et al.*, a critical neonate with KCNQ2 epileptic encephalopathy refractory to multiple AEDs (phenobarbital, levetiracetam, topiramate, clobazam), was started with KD with immediate EEG organization's improvement and seizure remission after 2 weeks (3). KD induced impressive seizure reduction, as well, in a neonate affected by encephalopathy with migrating focal seizures (EIMFS) as a consequence of a "de novo" p.Ser247Leu KCNQ2 variant plus a maternal inherited p.Ser374Pro mutation. The baby had a poor outcome regardless of the anticonvulsant poly-therapy (phenobarbital, phenytoin, midazolam and ketamine infusion, KD) (4).

Ko *et al.* reported on a cohort of seven patients harboring unspecified KCNQ2 mutations, six of which responded favorably to KD, vigabatrin and prednisolone, while only four of them improved with SCB (5). The same authors reported on a response rate of 83,3% at 3, 6 and 12 months after introducing KD in patients with KCNQ2 pathogenic variants (6).

In a more recent study, half of the patients with KCNQ-related epilepsy due to various unspecified mutations, gained seizure freedom initiating KD, in association with one or more AEDs (phenytoin, oxcarbazepine, phenobarbital, valproate, levetiracetam, topiramate or vigabatrin) or with steroid therapy (8). Le Pichon *et al.* reported an infant harboring a novel p.Arg581Gln variant in the KCNQ2 gene, who was successfully treated with KD while continuing human breast milk feeding (7).

So far, response to KD is unpredictable and variable among our case and those reported in literature; thus, it still remains unclear why some KCNQ2 mutations respond better to KD than others. Besides obvious variables, such as the adherence to KD, several plausible mechanisms have been proposed in time.

A recent preclinical study (21) demonstrated how β -hydroxybutyrate (BHB), the primary ketone body generated by ketosis, directly activates Voltage-gated

potassium channels generated by KCNQ2-5 subunits, especially KCNQ2/3 heteromers via a highly conserved S5 tryptophan on KCNQ3. It might be conceivable that mutations located in "hot zones" involving the above-mentioned interaction domains affect negatively response to KD. Furthermore, some KCNQ2 variants have been demonstrated to cause an improper channel localization in addition to causing a reduction in Kv7-associated current (4) and this has been suggested as an explanation to the variable response to specific treatments, including KD. A recent preclinical *in vitro* study described molecular mechanisms besides the response to KD in the first missense loss-of-function pathogenic variant described within the S4 segment of Kv7.3, suggesting that the type and location of mutation predicts the response to specific treatments (22). Others suggest that the unpredictable response to KD might be, instead, mutation-independent and related to changes induced by KD at the transcriptomic level (17). Unfortunately, data available to date only allow speculative hypothesis and further preclinical and clinical studies of combined analysis of gene and miRNAs' expression are needed to clearly assess this issue and to allow, in the future, to use KD as a targeted-therapy.

To our knowledge, the case presented is the eighth case reported in literature of the missense variant c.365 C>T in the KCNQ2 gene and the first case reported to be treated successfully with KD; functional damage results from the substitution of a polar serine residue with a non-polar leucine residue at codon 122 of the KCNQ2 protein in the extracellular loop between the S1 and S2 transmembrane segments of Kv7.2. A study conducted in oocytes demonstrated that the p.Ser122Leu sequence change causes a slower activation kinetics than wild-type voltage-gated potassium channel (23). Therefore, the p.Ser122Leu missense variant has been classified as pathogenic for KCNQ2-related disorders. Using the ClinVar (www.ncbi.nlm.nih.gov/clinvar) and RIKEE (rikee.org) databases we identified four studies describing seven patients harboring the same KCNQ2 variant of our subject (Table 2). Hunter *et al.* described three individuals in a pedigree, presenting with early-onset seizures and who exhibited a normal development (23).

In a proband, seizures remitted at 11 weeks after initiation of phenobarbital. In the second subject seizure control was obtained with carbamazepine at 6 weeks. In the third patient, phenobarbital and phenytoin lead to remission of seizures, but they recurred until 7 years of life (23). A study of Millichap *et al.* reported a sibling pair harboring a p.Ser122Leu KCNQ2 variant. Epilepsy was limited to the

Table 2 Reported pediatric patients with KCNQ2-associated neonatal epilepsy due to a p.Ser122Leu (c.365 C>T) variant

Reference/year	No. cases	Inheritance	Seizure control	Neurodevelopment
Hunter <i>et al.</i> 2006 (23)	3	Familial	No seizures at 11 weeks after phenobarbital [1]. No seizures at 6 weeks after carbamazepine; subsequent febrile seizures [1]. No seizures after phenobarbital and phenytoin; recurrence up to 7 years [1]	Normal
Millichap <i>et al.</i> 2016 (24)	2	Paternal	No seizures after neonatal period	Mild DD
Zhang <i>et al.</i> 2015 (25)	1	De novo	NA	Profound DD and ID
Malerba <i>et al.</i> 2020 (26)	1	De novo	Three tonic seizures relapsed until 10 years. Seizure freedom from 10 to 12 years	Normal
Present study 2022	1	De novo	No seizures at three months after KD and carbamazepine	Mild DD

DD, developmental delay; NA, not available; ID, intellectual disability.

neonatal period, whereas a mild developmental delay was noted over time. Their father suffered from neonatal seizures but he had normal intellect (24). Zhang *et al.* described a male with seizure onset on day 3 as a consequence of a “de novo” p.Ser122Leu mutation in KCNQ2. At the time of the study, he was three-year-old and had severe intellectual and developmental disabilities (25). A recent study of Malerba *et al.* reported a 12-year-old male who started with multiple tonic neonatal seizures due to a spontaneous p.Ser122Leu KCNQ2 variant. He was under oxcarbazepine and gained seizure control and normal neurodevelopment (26).

Conclusions

The present case highlights the role of the S2 transmembrane segments of the Kv7.2 subunit in the regulation of neuronal firing. We would like to propose this region of the channel as one of the KCNQ2-DEE hot zones though various phenotypes have been reported to result from the p.Ser122Leu KCNQ2 variants; our patient harboring a “de novo” KCNQ2 pathogenic variant didn’t respond to oral carbamazepine but reached complete seizure cessation and progressively achieved neurodevelopmental milestones after initiating KD. Studies describing the role of KD in pediatric KCNQ2 epilepsies are limited to small, retrospective cohorts and encourage KD’s usefulness along with one or more ongoing AEDs. None of the previously reported patients with the p.Ser122Leu variant had received KD before. Cause of genotype-phenotype variability and the subsequent possibility to predict response to specific

medications still remain unclear and need further studies with particular regard to epigenetic and transcriptomic analysis. Our experience, though based on a single case report, enlightens the strong and urgent need to perform further studies to assess KD’s potential contribution in resolving KCNQ2-associated epilepsy and to determine whether it can influence positively not only epilepsy but also neurodevelopment in infants with KCNQ2-DEE. Furthermore, larger prospective studies and randomized-controlled trials (RCTs) are needed to determine whether KD’s potential benefits on neurocognitive evolution are higher when KD is started as early as possible, as proposed for seizure control and to assess whether, in the future, KD might be considered as a potential first-line treatment in patients with KNCQ2-associated epilepsy.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-258/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration (as revised in 2013). The study was approved by the ethical committee of the Medical Faculty of the University of Catania (IRB No. 780). Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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