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Abstract

**Introduction.** The exact prevalence of Benign Familial Neonatal Epilepsy (BFNE) is unknown due to the likelihood of overlooking the disease and not diagnosing affected patients correctly. The rare autosomal dominant inherited disorder occurs usually within a few days after birth to an otherwise healthy newborn, and disappears after one to four months. Most patients develop no psychomotor deficiencies, nor any other forms of seizures. The disorder is most commonly linked to the KCNQ2 gene, with mutations located on chromosome 20q13.33; which cause voltage gated potassium channel changes. This clinically rare condition presents as repeated tonic-clonic episodes of focal and generalized convulsions; which is effectively treated with anti-epileptic therapy.

**Case report.** We describe a five-day old affected male infant, with genetically proven KCNQ2 gene mutation, in addition to a positive familial history of epilepsy, with verified KCNQ2 gene mutations. Seizures did not reoccur after several episodes in the fifth day of life and further psychomotor development of the child was proved normal.

**Conclusion.** Neonatal seizures have extensive differential diagnosis. However, BFNE should be suspected when the most common neonatal seizure causes have been excluded, and factors such as the hereditary factor in addition to the typical clinical course resembling BFNE, can be observed. Genetic identification of BFNE has resulted in easier and more specific diagnosis of this rare neonatal seizure disorder and is therewith the GOLD standard diagnostic measurement for this disorder.

**Keywords:** benign familial neonatal epilepsy, KCNQ2 gene, neonatal neurology, epilepsy

Apstrakt

**Uvod.** Prevalencija benigne familijarne neonatalne epilepsije (BFNE) je nepoznata zato što mnogi pacijenti ostaju nedijagnostikovani, odnosno bolest se ne prepozna. Ovo retko, autozomno dominantno, nasledno oboljenje se ispoljava u prvih nekoliko dana od porođaja, kod novorođenčeta bez drugih tegoba i povlači se posle jedan do četiri meseca. Kod većine pacijenata se kasnije ne javljaju napadi ili drugi psihomotorni poremećaji. Oboljenje je nejčešće povezano sa KCNQ2 genom i mutacijama lokalizovanim na hromozomu 20q13.33, što dovodi do naponom posredovanih promena kalijumovih kanala. Oboljenje se retko sreće u kliničkom radu i manifestuje se toničko-kloničkim epizodama fokalnih i generalizovanih napada koje se efikasno leće antiepileptičnom terapijom.
**Introduction**

Benign Familial Neonatal Epilepsy (BFNE) is a rare autosomal dominant inherited disorder, manifested as sudden and generalized seizures occurring for the first time during the first days of life, in an otherwise healthy fetus. Usually no specific antenatal history is present in BFNE patients, with equal gender distribution. Generally, an Apgar score of minimum 7 is within the first minutes of life achieved. The neonatal seizures are characterized by afebrile, repeated tonic-clonic episodes of focal and generalized seizures, accompanied by hypertonia. The seizures are usually disappearing within one to four months after the first onset, and most patients live thereafter a seizure-free life. Due to the spontaneous resolution of BFNE, it is rather controversial if it should be treated. However, to prevent damage due to seizure attacks, anti-epileptic therapies are advised to be administered for no longer than six months.

Most cases have shown no psychomotor development impairment after the seizures, however some studies may suggest otherwise. In one hand, the risk for subsequent occurrence of febrile seizures is stated to be 5%, which corresponds to the average frequency in the general population; on the other hand, a significantly higher risk with 11% of subsequent epilepsy could be observed, which differs to the general population. The published article “Benign familial neonatal convulsions: A family with a rare disorder”, describes based on molecular analysis cases; reoccurring seizure disorders and developmental delay in BFNE affected individuals. The familial analysis of multiple generations was showing as expected, clinical heterogeneity in phenotypes expressing KCNQ2 mutations. Thus, it is in our opinion inconclusive whether this condition causes late effects of neurological development. This autosomal dominant inherited disorder, is caused by mutations which are most often inherited from affected parents. For instance, this type
of mutations in the KCNQ2 gene, located on chromosome 20q13.33, have shown to be significantly homogenous with a voltage dependent delayed reaction of the rectifying potassium channel gene, KCNQ1. Another relevant gene which was found in BFNE affected patients, KCNQ3, which is mapped on chromosome 8q24. Both mutations are part of the KQT-like family and may cause voltage gated potassium channel changes, which are not only the cause of BFNE, but also several other epileptic disorders.

Studies have shown that recorded Electroencephalograph (EEG) changes alone, are not specific diagnostic measurements to the condition. Interictal EEG waves may be unchanged or only show mild changes with focal or multifocal abnormalities, whereas ictal EEG may begin with a brief flattening of EEG waves, followed by asymmetric spike and wave complexes. Most individuals affected by BFNE present with normal EEG readings, and only a small percentage of may show theta pointu alternant pattern.

Hence the well-established connection of potassium gated channel dysfunctionality, the neurological hyperexcitability is likely to be due impaired repolarization of action potentials. Besides potassium, calcium channel and nicotinic acetylcholine receptor subunit defects, some biochemical markers are known as specific diagnostic measurements of neonatal epilepsy conditions. Besides routine testing for sepsis, serum electrolyte markers; such as hyponatremia, hypocalcemia and hypoglycemia, have been found to be another possible metabolic cause of these conditions. However in BFNE it is important to note that neither infectious, nor metabolic disturbances are the cause of disease but rather the M-type potassium channel protein disinhibition due to genetic mutation.

In this report we present the first recorded patient in Serbia with suspicious clinical and genetically proven diagnosis of Benign Familial Neonatal Epilepsy.

Case Report

A five-day old male infant was referred to our Neonatal Unit in Belgrade, Serbia; due to recurrent episodes of afebrile seizures.

The patient was born to a 32-year-old mother by caesarian section due to placenta previa at 37, 2 gestational weeks. At birth, his Apgar scores were 9 and 9, at 1 and 5 min, respectively. After the delivery, the fetus received Vitamin K and Hepatitis B vaccine. He was the second child of healthy parents without any complications during pregnancy up to the delivery. Historically, the 32-year-old healthy father, confirmed a positive history of neonatal seizures for himself. He reported to have
taken Phenobarbital therapy up to 3 years of age. Also, the patient's elder female sibling, was reported to have had seizures starting at three days of age, reoccurring at six weeks and three months of life. She was given an oral sodium-valproate therapy up to four years of age, with no reoccurring seizures after (Figure1).

The male neonate presented at our clinic with 3200 g, a length of 57 cm and head circumference of 36 cm (97 percentile). The infant presented in a conscious and overall healthy appearance, with normal tolerance of oral feedings and no other pathological signs.

The seizures appeared as tonic-clonic with the limb's involvement, which were reported by the mother to have first occurred on the left leg of the infant, expanding after the first episode with seizing to the right arm. The seizures lasted 5-10 seconds, and would reoccur at 5-10 minutes. The episodes were not accompanied by apnea, and were successfully treated by Pyridoxine amp. IV and Phenobarbital amp. 10 mg/kg IV. We want to emphasize that in this clinical situation Phenobarbital is the drug of choice, and Pyridoxine is given at the possibility of a Pyridoxine dependent epilepsy. Biochemical markers of bilirubin, sodium, potassium, calcium, C-reactive protein and glucose were 265, 2 µmol/L, 146 mmol/L, 4.9 mmol/L, 2.1 mmol/L, 1.9 mg/L and 4.0 mmol/L respectively. The blood type was B positive with negative Coombs test. No infections could be detected at this point, nor any point after. The complete blood count was within normal intervals. Sonography of the CNS and the abdomen showed no pathologic appearances, in addition to normal video EEG findings while awake and spontaneously fall asleep / sleep. Henceforth genetic analysis was needed for diagnosis. DNA samples of the male infant, the elder female sibling and both parents were sent for genetic analysis to the genetic analysis laboratory of the hospital in Lyon, France.
Fig. 1- The Figure describes the autosomal dominant inheritance pattern of the affected patient and the closely related family members, such as parents and one female sibling in a short Pedigree analysis.

SANGER sequencing of exon 13 of the KCNQ2 gene with a 3130XL sequencer (Seq Ref: NM_172107.2) was performed. The substitution c.1342C>T were found at the heterozygous state in the affected male infant patients, the elder female sister and their father´s sample. The mother sample showed in contrary no affection. The gene substitution leads according to our knowledge to the creation of a stop codon (p.Glu130*), which was confirmed by the laboratory and prove therewith the diagnosis of BFNE.

After ten days of observation the male infant was discharged with scheduled follow up visits. In case of reoccurring seizures, the parents of the infant were instructed to bring the patient to the hospitals, or administer appropriated doses of Phenobarbital. Biochemical markers stabilized during the stay at the hospital. No significant situations, such as seizures, occurred any time after. Normal follow up EEG readings were observed, in addition to normal psychomotor development.

Discussion

This Case Report represents a prototypical description of the BFNE disorder, fulfilling all of Miles et. al. proposed criterias of early infancy onset seizures, with otherwise normal neurological examinations, and normal neurodevelopmental progress with no other possible seizure aetiologies, beside BFNE characteristic features, and a positive family history for infantile seizures . However many more severe and more prevalent differential diagnosis, such as; hypoxic-ischaemic encephalopathy (40-60%), intra cranial hemorrhages (7-18%), cerebral infarctions or malformations (6-17%, and 3-17 % respectively), meningitis/septicaemia (2-14%), electrolyte disturbances (1-4%), inborn errors of metabolism (1-4%), maternal drug withdrawal, but also Benign Non-Familial Neonatal Epilepsy have to be excluded before making a definite diagnosis of BFNE . Similar to other etiologies benign neonatal seizures need to be excluded. Genetic testing may be done to confirm the diagnosis.

Table 1

As Q. Zeng et. al. have summarized KCNQ2 to be the most causative gene for BFNE , we would like to highlight the importance of early genetic screening to exclude more harmful disease aetiologies, such as the pathologies mentioned before. However, due to the heterozygous state of the genetic substitution, a frameshift or other forms of mutations of KCNQ2 could be expected, leading to possible pathologic states, such as neonatal seizure encephalopathy . In our case, the
gene sequence analysis showed a stop codon (p.Glu130*) which leads to potassium channel inhibitions. Therefore, it is according to our knowledge, also necessary to work on further investigations of potassium-channel-opening drugs, in addition to more antenatal routine genetic analysis in positive family history of BFNE individuals.

**Conclusion**

BFNE is an autosomal dominant inherited disorder, affecting neonates up to six months of age. Due to the genetic heterozygous mutations of the KCNQ2 gene, M- ligated potassium channel disruption cause hypopolarization of action potentials leading to tonic-clonic seizures. The disorder is treated effectively with anti- epileptic agents, with Phenobarbital as first choice. In our opinion more research about potassium-channel-opening drugs should be performed, with emphasis of how antenatal genotyping could benefit individuals affected by BFNE with preventive treatment during the postnatal period. According to our knowledge, a low rate of BFNE patients may suffer from psychomotor development delay, reoccurring epilepsy or even progress to neonatal seizure encephalopathy. In summary, genetic identification of BFNE has resulted in easier and more specific diagnosis of this rare neonatal seizure disorder and is there with the GOLD standard diagnostic measurement for this disorder.

**Conflicts of Interest Statement**

The authors have no conflict of interest to declare.

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