CASE REPORT

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The first case of benign familial neonatal epilepsy diagnosed in Serbia

Prvi slučaj benigne familijarne neonatalne epilepsije dijagnostikovan u Srbiji

Katarina Nikolić*, Maja D. Ješić*†, Marko Kojić*, Miloš M. Ješić*†

***University Children's Hospital, Department of Neonatology, Belgrade, Serbia;**
†University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Abstract

Introduction. The exact prevalence of benign familial neonatal epilepsy (BFNE) is unknown due to the likelihood of overlooking the disease and not diagnosing the affected patients correctly. The rare autosomal dominant inherited disorder usually occurs within a few days after birth of 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 the chromosome 20q13.33 which cause voltage-gated potassium channel changes. This clinically rare condition manifests itself in repeated tonic-clonic episodes of focal and generalized convulsions which are effectively treated with antiepileptic therapy. **Case report.** We presented a five-day old affected male infant, with genetically proven KCNQ2 gene mutation, in addition to a positive familial history of epilepsy. Seizures did not reoccur after several episodes in the fifth day of life and further psychomotor development of the child 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 disorder and is therefore the gold standard in its diagnostics.

Key words:
diagnosis; epilepsy, benign neonatal; genetic testing; mutation.

Apstrakt

Uvod. Prevalencija benigne familijarne neonatalne epilepsije (BFNE) je nepoznata zato što mnogi bolesnici ostaju nedijagnostikovani, odnosno bolest se ne prepozna. Ovo retko, autozomno dominantno, nasledno oboljenje, ispoljava se kod novorođenčeta u prvih nekoliko dana posle porođaja, bez drugih tegoba i povlači se posle jedan do četiri meseca. Kod većine bolesnika kasnije se ne javljaju napadi ili drugi psihomotorni poremećaji. Oboljenje je najčešće povezano sa KCNQ2 genom i mutacijama lokalizovanim na hromozomu 20q13.33, što dovodi do voltažno-zavisnih promena kalijumovih kanala. Oboljenje se retko sreće u kliničkom radu i manifestuje se toničko-kloničkim epizodama fokalnih i generalizovanih napada koje se efikasno leče antiepileptičnom terapijom. **Prikaz bolesnika.** Prikazano je muško novorođenče, uzrasta pet dana, sa genetski potvrđenom KCNQ2 mutacijom i pozitivnom porodičnom anamnezom na epilepsiju. Posle nekoliko epizoda u petom danu života, napadi se više nisu ponavljali, a dalji psihomotorni razvoj je bio normalan. **Zaključak.** Epileptični napadi kod novorođenčeta podrazumevaju obimnu diferencijalnu dijagnozu. Na BFNE treba posumnjati kada se isključe česti uzroci ovih napada, a postoji nasledni faktor i klinički tok bolesti koji je sličan BFNE. Identifikacija gena za BFNE doprinela je lakšoj i preciznijoj dijagnostici tog retkog oboljenja i zbog toga danas predstavlja zlatni standard u njegovoj dijagnostici.

Ključne reči:
dijagnoza; epilepsija, benigna, neonatalna; genetičko testiranje; mutacija.

Introduction

Benign familial neonatal epilepsy (BFNE) is a rare autosomal dominant inherited disorder, which manifests itself in sudden and generalized seizures occurring for the first time during the first days of life, in an otherwise healthy newborn [1]. Usually no specific antenatal history is present in BFNE patients, with equal gender distribution. Generally, an Apgar score of minimum 7 is achieved within the first minutes of life [2]. The neonatal seizures are characterized by afebrile, repeated tonic-clonic episodes of focal and generalized seizures, accompanied by hypertonia. The seizures usually disappear within one to four months after the first onset, and thereafter most patients live a seizure-free

Correspondence to: Miloš Ješić, University Children´s Hospital, Department of Neonatology, Tiršova 10, 11 000 Belgrade, Serbia.
E-mail: milos.jesic@udk.bg.ac.rs

life [3]. Due to the spontaneous resolution of BFNE, it is rather controversial if it should be treated. However, to prevent the damage due to seizure attacks, anti-epileptic therapies are advised to be administered for no longer than six months [4].

Most cases have shown no psychomotor development impairment after the seizures, although some studies may suggest otherwise. On the one hand, the risk of 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 from the general population [5]. Reoccurring seizure disorders and developmental delay in BFNE-affected individuals have been described based on molecular analysis cases [6]. The familial analysis of multiple generations has shown expected, clinical heterogeneity in phenotypes expressing KCNQ2 mutations [6, 7]. 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 frequently inherited from the affected parents [8]. For instance, this type of mutations in the KCNQ2 gene, located on the chromosome 20q13.33, has shown to be significantly homogenous with a voltage-dependent delayed reaction of the rectifying potassium channel gene, KCNQ1 [1]. Another relevant gene which was found in BFNE-affected patients, KCNQ3, is mapped on the chromosome 8q24. Both mutations are a part of the KQT-like family and may cause voltage-gated potassium channel changes, which are not only the cause of BFNE, but also of several other epileptic disorders [9].

Studies have shown that recorded electroencephalograph (EEG) changes alone are not specific diagnostic measurements of 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 [10]. Most individuals affected by BFNE present with normal EEG readings, and only a small percentage of individuals may show theta point alternant pattern [11].

Due to the well-established connection of potassium-gated channel dysfunctionality with BFNE, the neurological hyperexcitability is likely a consequence of the impaired repolarization of action potentials. Besides potassium channel, calcium channel and nicotinic acetylcholine receptor subunit defects, and some biochemical markers are known as specific diagnostic parameters of neonatal epilepsy conditions [12]. Besides routine testing for sepsis, serum electrolyte markers such as hyponatremia, hypocalcemia and hypoglycemia have been found to be another possible metabolic causes of these conditions [13, 14]. However, in BFNE, it is important to note that neither infectious, nor metabolic disturbances are the cause of the disease but rather the M-type potassium channel protein disinhibition due to genetic mutation [15].

We presented the first recorded patient in Serbia with clinically and genetically proved BFNE.

Case report

A five-day-old male infant was referred to the University Children's Hospital in Belgrade, Serbia, due to the recurrent episodes of afebrile seizures.

The patient was born to a 32-year-old mother by cesarean 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 newborn 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 that (Figure 1).

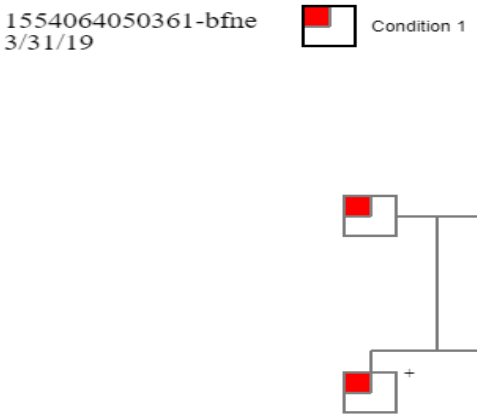

Fig. 1 – Autosomal dominant inheritance pattern of the affected patient and the closely related family members, such as parents and one female sibling in a short pedigree analysis.

The male neonate presented at our clinic with 3,200 g, the length of 57 cm and the 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 sec, and would reoccur at 5–10 min. The episodes were not accompanied by apnea, and were successfully treated by pyridoxine amp i.v. and phenobarbital amp 10 mg/kg i.v. We want to emphasize that in this clinical situation phenobarbital is the drug of choice, and pyridoxine is given at the possibility of pyridoxine-dependent epilepsy [11]. Serum levels 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 infec-

tions could be detected at this point, or at any point later. 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 asleep/sleeping. Henceforth, genetic analysis was needed for the 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.

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 was found at the heterozygous state in the affected male infant patients, the elder female sister and their father´s sample. In contrast, the mother's sample was not affected. To our knowledge, the gene substitution leads to the creation of a stop codon (p.Glu130*), which was confirmed by the laboratory and proved therewith the diagnosis of BFNE.

Ten days after the observation, the male infant was discharged with a scheduled follow-up visits. In case of reoccurring seizures, the parents of the infant were instructed to bring the patient to the hospital, or administer appropriate doses of phenobarbital. Biochemical markers stabilized during the stay in 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 and Holmes [4] proposed criteria of early infancy onset seizures, with otherwise normal neurological examinations, and normal neurodevelopmental progress with no other possible seizure etiologies, besides BFNE characteristic features, and a positive family history for infantile seizures. However, many more severe and more prevalent differential diagnosis, such as hypoxic ischemic encephalopathy (40%–60%), intracranial hemorrhages (7%–18%), cerebral infarctions or malformations (6%–17%, and 3%–17%, respectively), meningitis/septicemia (2%–14%), electrolyte disturbances (1%–4%), inborn errors of metabolism (1%–4%), maternal drug withdrawal, but also non-familial neonatal epilepsy have to be excluded before making a definite diagnosis of BFNE [16]. Similar to other etiologies, benign neonatal seizures need to be excluded. Genetic testing may be done to confirm the diagnosis.

As Zeng et. al. [17] have summarized KCNQ2 to be the most common causative gene for BFNE, we would like to highlight the importance of early genetic screening to exclude more harmful disease etiologies, such as those 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 [17]. In our case, the gene sequence analysis showed a stop codon (p.Glu130*), which leads to potassium channel inhibitions. A small number of BFNE patients may suffer from psychomotor development delay, reoccurring epilepsy or even progress to neonatal seizure encephalopathy [18]. Therefore, in our opinion, it is 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.

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 causes hypopolarization of action potentials leading to tonic-clonic seizures. The disorder is treated effectively with anti-epileptic agents, with phenobarbital as first choice.

In summary, genetic identification of BFNE has resulted in easier and more specific diagnosis of this rare disorder and is therefore the gold standard in its diagnostics.

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Conflicts of interest statement

The authors have no conflict of interest to declare.

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