

Refractory neonatal seizures caused by hemimegalencephaly

Khuloud Mohamed,¹ Einas Elzubier Elmalik ,² Mohamed Bakry,³ Mohammad A. A. Bayoumi ²

¹Department of medical education, Hamad Medical Corporation (HMC), Doha, Qatar

²Neonatal Intensive Care Unit (NICU), Women's Wellness and Research Center (WWRC), Hamad Medical Corporation (HMC), Doha, Qatar

³Corporate communication department, Hamad Medical Corporation (HMC), Doha, Qatar

Correspondence to

Dr Mohammad A. A. Bayoumi, Neonatal Intensive Care Unit (NICU), Women's Wellness and Research Center (WWRC), Hamad Medical Corporation (HMC), Doha, Qatar; moh.abdelwahab@hotmail.com

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DESCRIPTION

We report a case of a female infant born at term via spontaneous normal vaginal delivery at 38 weeks + 2 days of gestation as a result of an uneventful gestation. The mother was in her early 20s, gravida 2 para 1, with no significant medical history. She did not have any risk factors for early-onset neonatal sepsis, including group B *Streptococcus* colonisation or chorioamnionitis infection. She had a late suboptimal fetal anomaly scan in the third trimester, 2 days before delivery, which showed a small-for-date fetus and a fetal brain with non-visualised cavum septum pellucidum. The preceding ultrasound at the beginning of the third trimester, which was at 30 weeks of gestation, was normal. The antenatal course was unremarkable apart from hyperemesis at 9 weeks of gestation and an episode of self-limited fetal tachycardia at 11 weeks of gestation, for which the mother was reassured. Otherwise, the baby was growing normally, with normal amniotic fluid and Doppler indices. The mother had no further imaging or special follow-up in the fetal medicine unit. On the day of delivery, she presented in labour pain, 5 days ahead of her expected date of delivery, and delivered after 4 hours of leaking liquor. She had an uneventful delivery and perinatal course. The infant was born in good condition and cried immediately after birth. She was found to be small for gestational age, with a weight of 2.495 kg, and was hypoglycaemic with a blood sugar of 2.7 mmol/L. She was given 1 mL of dextrose gel, which normalised her blood sugar. She had no dysmorphic features.

On the second day of life, an ultrasound of the skull was done on the patient to follow the findings of the antenatal ultrasound. The postnatal head ultrasound showed hypoplastic corpus callosum, and linear and fine nodular echogenic shadows at the basal ganglia regions, suggesting mineralizing vasculopathy. It also showed normal ventricles, except for widely separated frontal horns, due to the hypoplastic corpus callosum (figure 1). The patient was admitted to the postnatal ward to arrange brain MRI to further characterise the ultrasound findings. On admission, the baby developed neonatal seizures in the form of clonic movements of the four limbs with deviation of the eyes to the right that lasted for 45–50 s, with no vital instability (video 1). There was a hypoglycaemic reading of 3.1 mmol/L. After 2 min, she had another episode that lasted for less than 10 s. Accordingly, due to the neonatal seizures, the patient was prepared for transfer to the neonatal intensive care unit (NICU)

for close monitoring, further work-up and anticonvulsive drug management.¹

On admission to NICU, the patient received loading and maintenance doses of phenobarbital. In addition, she received one loading dose of phenytoin. The neurology team was consulted and reported no dysmorphic features, normal tone, power and reflexes, and normal back and skin. They recommended the following: load the patient with levetiracetam 40 mg/kg and keep the patient on a maintenance dose of levetiracetam 40 mg/kg/day divided every 12 hours. In case of seizure refractoriness diagnosed if there is no response to the first two lines of anticonvulsive medications, they recommended the following steps in order: give another loading dose of levetiracetam 20 mg/kg, load the patient with phenobarbital 10 mg/kg and start a midazolam drip.² In terms of the underlying diagnosis, they recommended considering central nervous system infection, sending infectious, genetic and metabolic work-up, and proceeding with an MRI of the brain and electroencephalography (EEG). Infectious, metabolic and genetic work-up, in terms of microarray, were unremarkable. Whole exome sequencing (WES) and other brain malformation genetic tests were not performed.

The patient was on first-line antibiotics, ampicillin and amikacin, while a full septic work-up was pending. Antibiotics were stopped after 48 hours of negative blood, urine and cerebrospinal fluid cultures. Blood virology was negative.

EEG showed an abnormal record due to abnormal asymmetric background and frequent right-sided epileptic activity. MRI of the brain showed the following: evidence of right frontoparietal cortical thickening with undersulcation, mild diffusion restriction along with loss of grey-white matter differentiation, thinning of the white matter and abnormal signal intensity compared with the left side. Adjacent multiple linear foci of blooming susceptibility artefacts on susceptibility-weighted imaging were noted, likely representing dysplastic perforator vessels. In addition, it showed asymmetry of the right basal ganglia, especially the caudate head, which appeared indistinct compared with the left side, dilatation of the body of the right lateral ventricle, along with thinned and pointed-up frontal horn. Moreover, it showed thinning of the genu and anterior body of the corpus callosum. The aforementioned features are in keeping with subtotal hemimegalencephaly (HME) (figure 2).



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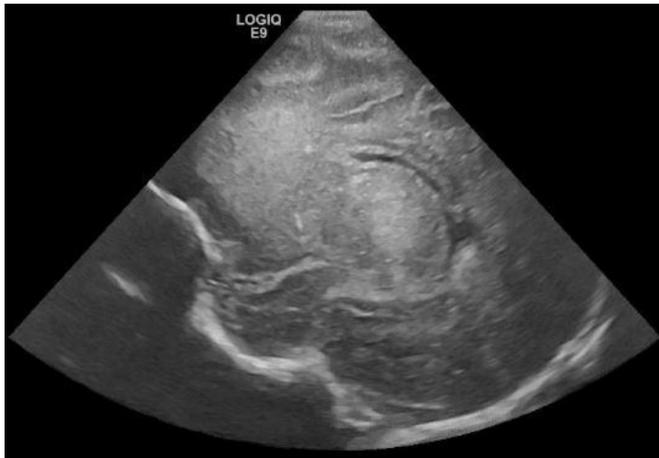


Figure 1 Head ultrasound scan on the second day of life showing hypoplasia of the corpus callosum.

On the third and fourth day of life, the seizure was controlled on levetiracetam and phenobarbital. On the fifth day of life, lip-smacking was noticed. The levetiracetam dose was augmented to 50 mg/kg/day. It was noted on the cerebral function monitor that the patient had convulsions for more than 1 hour, with haemodynamic stability. The baby was loaded with phenobarbital



Figure 2 MRI transverse view of the brain showing findings impressive of right-sided subtotal hemimegalencephaly (arrows).

10 mg/kg. The patient was then kept on phenobarbital at 5 mg/kg/day and levetiracetam 50 mg/kg/day. On the sixth day of life, the patient had recurrent abnormal movement in the form of lip-smacking and uprolling of the eyes, which were associated with tachycardia. The neurology team recommended increasing levetiracetam to 60 mg/kg/day and increasing phenobarbital to 7 mg/kg/day, anticipating further seizures due to the brain condition. In case of frequent seizures, they recommended giving a loading dose of levetiracetam of 20 mg/kg, starting a midazolam drip (loading dose of 0.1 mg/kg/dose followed by a continuous infusion of 0.1 mg/kg/hour) and transferring the patient to a tertiary care hospital for continuous EEG. Seizures became under control after adjustment of medications. The patient was kept on orogastric tube feeding to prevent aspiration. Multidisciplinary meeting was arranged with the parents to discuss long-term management and expected outcomes, including intractable seizures, developmental delay, intellectual ability and swallowing dysfunction. The patient was kept in NICU after seizure control, mainly as a feeder grower and for parental education.

At 2 weeks of life, the patient was discharged home on oral phenobarbital 7 mg/kg/day and levetiracetam 60 mg/kg/day, to be followed by the neurology team in 2 months. A hearing assessment was done before discharge and showed a bilateral pass of otoacoustic emission and auditory brainstem response tests. As per the speech language pathology team assessment, the baby was found to have good sucking and swallowing abilities. Accordingly, she was discharged on oral feeds, with a weight of 2.71 kg, with neurology, physical therapy and occupational therapy follow-up.

Two days after discharge, the patient presented to the emergency department (ED) of the local tertiary hospital with self-limited myoclonic jerks of the upper and lower limbs which were associated with deviation of the eyes. All episodes lasted for 30s and were increasing in frequency, approximately a single episode every 2 hours. Complete blood count (CBC), comprehensive metabolic panel (CMP), venous blood gases (VBG) and phenobarbital level were ordered for the patient and were reassuring apart from transient seizure-related metabolic acidosis. The neurology team was consulted and recommended giving a loading dose of topiramate of 10 mg/kg, then starting a maintenance dose of 3 mg/kg/day after 12 hours, along with the same doses of levetiracetam and phenobarbital. EEG was done and showed the following: severe slow disturbance of cerebral activity over the right hemisphere and frequent focal epileptic abnormality over the right hemisphere. These findings are following the neuroimaging findings that demonstrate the epileptogenic zone to be in the right hemisphere. Accordingly,

Video 1 Neonatal seizures in the infant in the form of clonic movements of the four limbs with deviation of the eyes to the right that lasted for 45–50 s, with no vital instability.

the patient was admitted to neurology for seizure observation and control. The option for ketogenic diet was suggested by the treating team but the parents refused. Antiepileptic drugs (AEDs) were adjusted as follows: phenobarbital was increased to 6.6 mg/kg/day, topiramate 3 mg/kg/day and levetiracetam 53 mg/kg/day.

Seizures improved for 1 day and then increased on the following day to approximately 10 self-limited episodes in 24 hours. The patient was given a phenobarbital loading dose of 5 mg/kg. The topiramate dose was then augmented to 5 mg/kg/day, along with the same maintenance doses of levetiracetam and phenobarbital. The patient continued to have multiple brief seizure episodes, so the topiramate dose was increased to 6 mg/kg/day. On the following day, the topiramate dose was increased to 7.5 mg/kg/day as the patient showed no significant improvement in seizure frequency. She was discharged home on the aforementioned dose for 1 day followed by a topiramate dose of 9 mg/kg/day, with the same maintenance doses of levetiracetam and phenobarbital. The patient presented to the ED 4 days after discharge as she had 41 seizure episodes in 24 hours, increasing in duration to around 70–80 s. CBC, CMP, VBG and phenobarbital levels were reassuring apart from transient seizure-related metabolic acidosis. The phenobarbital dose was increased to 8 mg/kg/day and the family was instructed on the nature of the disease and the unavoidable chance of breakthrough seizures.

The patient presented to the ED the following day with an episode of status epilepticus that lasted for 30 min in the form of generalised tonic-clonic movements with uprolling of the eyes. It aborted spontaneously. In the ED, she was given a loading dose of phenobarbital 10 mg/kg. VBG, CBC and CMP were reassuring apart from transient seizure-related metabolic acidosis. The neurology team started clobazam at 0.75 mg/kg/day in addition to the previous medications. On neurology follow-up in 1 week, the father reported improvement in seizure frequency from every 30 min to every 1–2 hours after adding clobazam. However, she continued to have brief (<1 min) focal seizures in the form of left facial and left hemibody twitching. The clobazam dose was increased to 1 mg/kg/day. The patient was seen 1 week later at 5 weeks of age in the complex epilepsy clinic. The parents reported improvement in the frequency and duration of seizures, with persistence of multiple brief episodes daily. The examination was remarkable for axial hypotonia. The parents also reported no head support at 2 months of age. Otherwise, the patient was doing fine, gaining weight, feeding orally well and developing normally. The levetiracetam dose was increased to 60 mg/kg/day. If the seizure persisted, the parents were instructed to increase the dose of topiramate to 10 mg/kg/day. If seizures continued to increase in frequency, the plan was to start oxcarbazepine and to consider surgical options when the patient is old enough. The parents were recommended following up with physiotherapy for hypotonia.

One week later, the father reported 15 seizure episodes per day that last between 1 and 1.5 min. The clobazam dose was increased to 1.7 mg/kg/day. In the following week, the patient continued to have 15 seizure episodes per day. Oxcarbazepine was started along with a phenobarbital weaning plan as follows: start oxcarbazepine 24 mg two times per day for 1 week, then 30 mg two times per day for 1 week, then 42 mg two times per day for 1 week, then continue on 48 mg two times per day. In addition, the parents were instructed to decrease phenobarbital by 0.1 mL two times per day every week until reaching 0.4 mL two times per day. At 1-week follow-up, the parents reported an increase in the frequency and duration of seizures from 1.5 to 2 min. They were recommended to stop weaning the

phenobarbital until reaching 48 mg of oxcarbazepine, then to start weaning as planned.

At weekly follow-up, the father reported refractory frequent seizures, every 10 min, with episodes that last above 2 min. He was asked to give an oxcarbazepine dose of 60 mg and a midazolam dose of 0.1 mL and to take the patient to the ED. In the ED, the patient was loaded with 60 mg/kg of levetiracetam. VBG, CBC, CMP and phenobarbital levels were reassuring apart from transient seizure-related metabolic acidosis. The oxcarbazepine dose was increased from 16.8 mg/kg/day to 24 mg/kg/day and the patient was discharged home. She only had three seizures in the following 24 hours, but seizure frequency increased to 30 episodes per day afterwards. Most of her seizures occurred out of sleep. The levetiracetam dose was increased to 60 mg/kg/day. The clobazam dose was increased to 1.6 mg/kg/day, with a plan to start weaning off phenobarbital if the seizure improved. The option of a ketogenic diet and the future option of a surgical intervention were discussed with the family.

On the next weekly follow-up, the parents reported around 15–20 seizure episodes per day that last between 1 and 2 min. They were recommended giving one dose of midazolam, increasing the oxcarbazepine dose to 28.8 mg/kg/day and taking the patient to the ED if the seizure did not improve. In the following week, the father reported an increase in seizure frequency from 15–20 to 20–25 episodes per day which were refractory to midazolam. He was asked to take the patient to the ED. VBG was reassuring apart from transient seizure-related metabolic acidosis. Influenza and respiratory syncytial virus panels were taken as the patient had a mild cough and were negative. The patient was given an extra 30 mg/kg dose of levetiracetam. The patient had six seizures in 2 hours afterwards, so she was given a 10 mg/kg dose of phenobarbital. She was observed for 1 hour with no seizures and was discharged home. Ten days later, the patient presented with increased seizure frequency and she had a left ear foul-smelling discharge. She was given a loading dose of phenytoin (27 mg/kg) along with treatment for the ear infection. Admitting the patient for observation was recommended but the parents refused due to travel concerns.

In summary, this is a case of a term female baby with antenatal findings of a small-for-date fetus and non-visualised cavum septum pellucidum. Postnatally, she was found to have intractable focal epilepsy which is refractory to multiple different AEDs. Work-up came remarkable for right HME. Seizures were stabilised at a frequency of daily 15–25 episodes of 1–2 min duration on five AEDs, phenobarbital, topiramate, levetiracetam, clobazam and oxcarbazepine, along with midazolam as needed. Further therapeutic options which are being discussed with the family include ketogenic diet and surgical intervention. The patient is currently 10 months old and is on regular follow-up with the complex epilepsy clinic.

The challenging nature of neonatal seizure, in terms of identification, diagnosis of underlying aetiologies and management, has been repeatedly highlighted in the literature. A thorough history, physical examination, laboratory work-up, and neurophysiological and neuroradiological investigations are all essential in the process of searching for the underlying diagnosis.^{3 4} Neonatal seizure can be triggered by various congenital, infectious, metabolic, hypoxic haematological or syndromic conditions. One of the rare congenital causes of neonatal seizure is HME. HME is a hamartomatous malformation of the brain.³ Kulkarni *et al*⁵ reported a prevalence ranging from 1 to 3 cases per 1000 children with epilepsy and 1%–14% among children with cortical developmental abnormalities. Abnormalities of cortical development can be classified as follows: abnormal neural

proliferation (diffuse cortical dysplasia, microlissencephaly and HME), abnormal neural migration (nodular heterotopia, double cortex, band heterotopia, pachygyria-agyria and lissencephaly) and abnormal postmigrational development (polymicrogyria, focal cortical dysplasia and schizencephaly).⁶

HME is characterised by dysplastic overgrowth of either one of the cerebral hemispheres. The exact aetiology of HME has not been fully established, but involves a disturbance in early brain development and likely involves genes responsible for patterning and symmetry of the brain. It yields a challenging epilepsy syndrome which is featured by early-onset seizures, refractoriness to antiepileptic therapy, and abnormal neurological examination with findings such as contralateral hemiparesis and hemianopia, along with subsequent developmental, cognitive and behavioural disturbances. The intractable seizures in the context of this condition usually necessitate anatomical or functional hemispherectomy to provide effective seizure control. Chandrasekar and colleagues⁷ reported a female newborn who had refractory seizures due to HME. WES analysis revealed a likely pathogenic deletion involving the NPRL3 (nitrogen permease regulator 3-like protein) gene, which is involved in the mammalian target of rapamycin (MTOR) signalling pathway. However, sirolimus, an MTOR inhibitor drug, did not improve her seizure control. Functional hemispherectomy at 3 months of age resulted in total abatement of clinical seizures.⁷

Similarly, Kulkarni *et al*⁵ reported a term infant with HME who had more than 90% reduction in seizures with good developmental outcome on follow-up after hemispherectomy. In addition, Chand and colleagues⁸ reported a neonate who presented with focal seizures. EEG showed excessive spikes predominately over the right hemisphere. MRI of the brain showed asymmetric enlargement of the right cerebral hemisphere, suggestive of HME. Initial treatment with AEDs was successful in controlling her seizures, but later on the seizures became intractable even on polytherapy of AEDs. Ultimately, functional hemispherectomy was performed at 18 months of age and she became seizure-free.⁸ Patients who do not undergo hemispherectomy usually continue to have recurrent seizures that are resistant to AEDs. This has been shown by Ikeda and Mirsattari as they reported a man in his 20s with HME who did not undergo hemispherectomy in childhood and continued to have recurrent focal convulsive or non-convulsive status epilepticus.⁹

Learning points

- ▶ Abnormalities of cortical malformation should be suspected and targeted in the work-up of neonatal seizures, especially when the seizures are refractory or demand multiple antiepileptic drugs.
- ▶ Close follow-up of patients with epilepsy, at least every week, along with complex clinic follow-up involving different subspecialties in the patient care every visit, is an invaluable practice in the provision of adequate care to the infants of concern.
- ▶ It is important to continuously emphasise to the parents the nature of the condition, the natural history, the potential treatment modalities and the prognosis to maintain realistic expectations immediately after the establishment of the diagnosis and to help them set a life plan accordingly.

When surgery is not a viable option, the role of ketogenic diet, which is a high-fat, low-carbohydrate diet, as treatment for drug-resistant epilepsy has been highlighted in the literature. A two-centre study demonstrated that ketogenic diet, when tolerated, in patients with drug-resistant epilepsy secondary to malformations of cortical development can effectively lead to seizure reduction.⁶ Ketogenic diet inhibits phosphatidylinositol-3-kinase-serine/threonine kinase-MTOR signalling, providing a rationale for its use to ameliorate epilepsy caused by overactivation of this pathway in HME.¹⁰ It has been shown that long-term seizure-free outcomes can be expected in patients who become seizure-free 3 months after the diet.¹¹

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Contributors MAAB was the neonatologist involved in the clinical care of the patient, initiated the idea of submission, obtained consent, collected and edited the video, and revised the manuscript. KM performed the literature review, collected the patient's medical data, collected and edited the images, and drafted the manuscript. MB edited the videos. EEE revised the manuscript. All authors read the paper and revised and approved the final manuscript.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iDs

Einas Elzubier Elmalik <http://orcid.org/0000-0003-2518-8161>

Mohammad A. A. Bayoumi <http://orcid.org/0000-0002-2627-4806>

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