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Letter to the editor

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Epilepsy of Infancy with Migrating Focal Seizures in a Patient with Nonketotic Hyperglycinemia

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Nonketotic hyperglycinemia (NKH) is an inborn error of glycine metabolism leading to refractory epilepsy and severe developmental delays. It is caused by autosomal recessive inheritance of a defect in the glycine cleavage system in the mitochondrial enzymatic complex pathway [1]. This defect leads to overstimulation of the N-methyl-D-aspartate receptor and neurological damage due to glycine accumulation in all body compartments.

The typical presentation of NKH is progressive encephalopathy, apnea, and seizures during the neonatal period [2]. Those who survive the neonatal period progress into refractory seizures with moderate to severe cognitive impairment. Apart from antiseizure medications, sodium benzoate, dextromethorphan, and a ketogenic diet, no known therapy is effective in treating this condition [3].

Electroencephalography (EEG) is used to assess brain and seizure activity in NKH. The usual patterns seen are burst-suppression, hypsarrhythmia, and multifocal epileptiform activity [4,5]. Epilepsy of infancy with migrating focal seizures (EIMFS) in NKH has never been described in the literature. We report a case of a severe form of NKH presenting during the neonatal period that showed a burst-suppression EEG pattern and evolved into EIMFS.

A female baby was the firstborn child of non-consanguineous Malay parents. She was born at term and weighed 2.78 kg (15th percentile), with a head circumference of 32 cm (10th percentile). The antenatal period was uneventful. She was noted to be lethargic and tachypneic at 14 hours of life, with poor feeding. She required ventilator support at 18 hours of life for progressive lethargy with poor respiratory effort and recurrent apnea. She was treated for neonatal sepsis, as an echocardiogram and chest radiograph had excluded congenital heart disease and respiratory distress syndrome. The infection markers were mildly elevated, and no growth was observed in blood culture. She was noted to be hypotonic with hyporeflexia of the bilateral lower limbs.

Initial investigations showed hypertransaminasemia with aspartate transaminase and alanine transaminase levels of 867 U/L (normal range, < 51) and 119 U/L (normal range, 1 to 25), respectively. The ammonia and lactate levels were normal, but there were high levels of creatine kinase (630 U/L; normal range, < 250 U/L) and lactate dehydrogenase (1,301 U/L; normal range, < 580 U/L). Screening for inborn errors in me-

tabolism showed normal results apart from a high glycine level (1,042 μmol/L; normal range, 102 to 395). The cerebrospinal fluid (CSF) glycine level and CSF plasma/glycine ratio were not obtained due to technical difficulties in obtaining samples despite multiple lumbar puncture attempts on different occasions.

During her first few days on ventilator support, the child showed no spontaneous breathing efforts despite not being on any sedation. She was able to be weaned from the ventilator by day 13 of life. She had her first seizure on day 10 of life, with clonic movement of the left upper and lower limbs and focal eyelid myoclonia. She responded to a combination of phenobarbitone (6 mg/kg/day) and levetiracetam (40 mg/kg/day).

Her first EEG, on day 11 of life, showed a burst-suppression pattern (Fig. 1A). A repeated EEG on day 29 of life showed less burst-suppression, but multifocal spikes/polyspikes and sharp wave discharges, predominantly in the left hemisphere. Magnetic resonance imaging (MRI) of the brain showed hypoplasia of the corpus callosum (Fig. 2). She was discharged home on day 31 of life. For the first 3 months, she had multiple episodes of seizures, with a baseline of up to 10 seizures daily. Three distinct semiologies were observed: eyelid myoclonia, alternating tonic seizures, and focal seizures.

Prolonged video telemetry EEG was done at 3 months of age and showed multiple seizures, including a migrating pattern with an ictal rhythm starting from the left and migrating to the right (Fig. 1B). This reflected an EIMFS pattern of genetic cause. There-

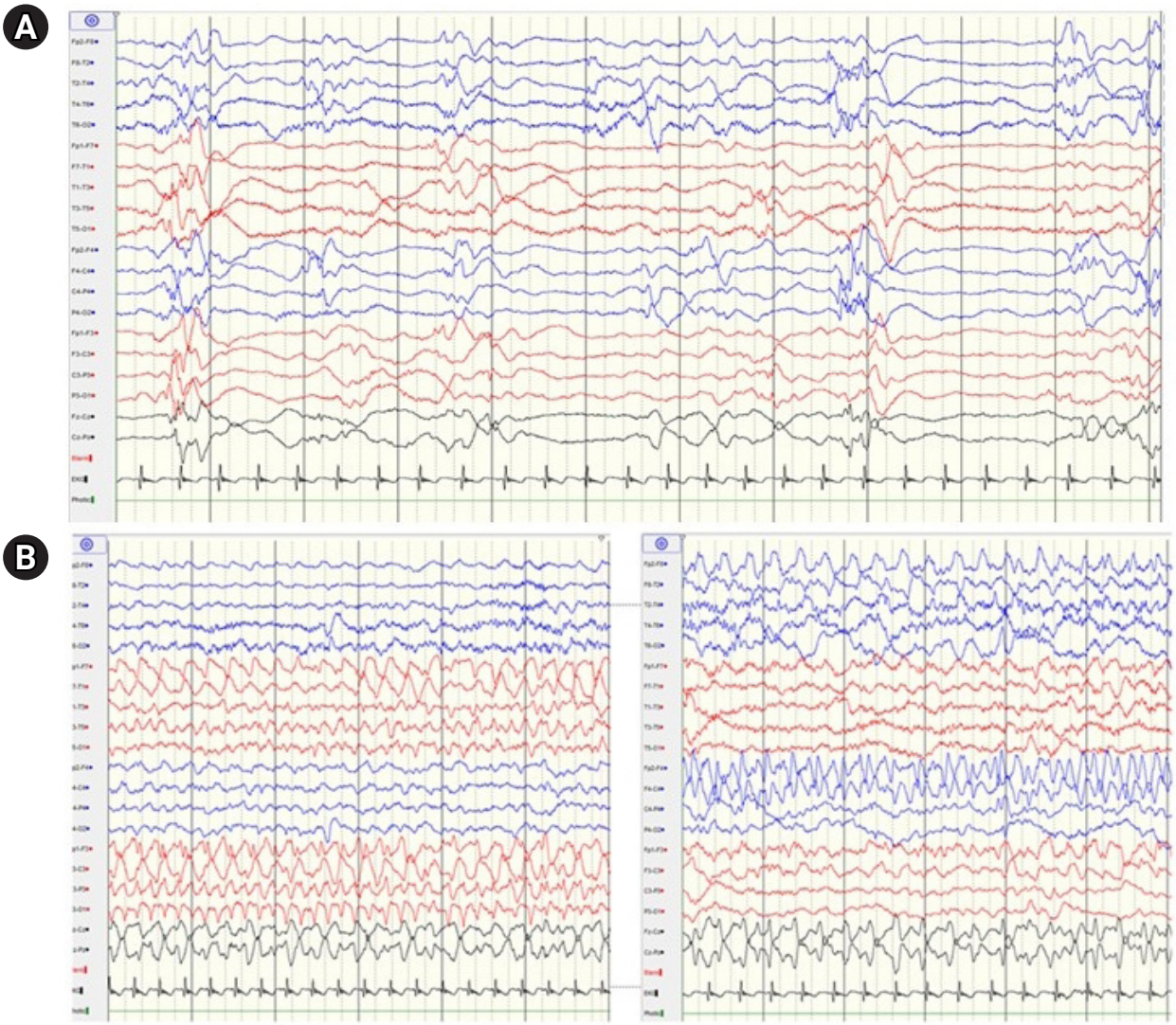

Fig. 1. (A) A bipolar montage showing her background brain activity in keeping with burst-suppression pattern. (B) Two bipolar montages from prolonged electroencephalography telemetry. The left montage shows a seizure over the left hemisphere that correlated with right sided tonic seizure lasted about 80 seconds and the right montage shows a seizure over the right hemisphere that correlated with left sided tonic seizure lasted about 60 seconds.

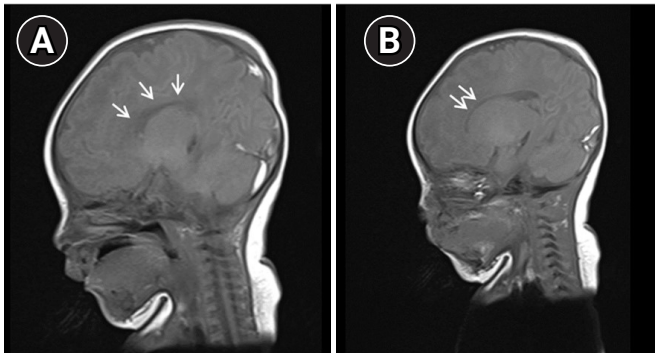

Fig. 2. Two images are T1 sequence of sagittal view of magnetic resonance imaging brain which was performed on day 14 of life that showed very thin or hypoplasia of corpus callosum (as per arrows). (A) image is showing an overall structure of the patient corpus callosum. (B) image is another slice of the same view to show a thin corpus callosum.

fore, hence phenobarbitone was switched to a titrated dose of phenytoin (up to 15 mg/kg/day, with the phenytoin therapeutic level between 155 and 170 μmol/L), but seizure control was unsuccessful. At this time, a workup for EIMFS was conducted, and a genetic study revealed that the child had compound heterozygous mutations of the aminomethyltransferase (*AMT*) gene (c.472-2A > T and c.1033+5G > A), which are associated with glycine encephalopathy, and a missense mutation of sodium voltage-gated channel alpha subunit 3 (*SCN3A*; c.145C > T, p.Pro49Ser), which is associated with developmental and epileptic encephalopathy (DEE). Parental testing confirmed heterozygous inheritance, in which the mother was the carrier of the *SCN3A* c.145C and *AMT* c.1033+5G > A mutations and the father was the carrier of the AMT c. 472.2A mutation. Neither parent was affected by these conditions.

The patient experienced an episode of infantile spasms at 4 months old and was successfully treated with oral prednisolone and vigabatrin (dose, 1,000 mg daily). Standard therapy of dextromethorphan and sodium benzoate was commenced by 6 months of age. Repeated measurements of plasma glycine levels remained high, but the latest reading decreased to 512 μmol/L.

Her seizure burden remains hard to control with multiple semiologies, mainly myoclonic and asymmetric tonic posturing. She is on oral topiramate (25 mg twice a day), dextromethorphan (10 mg thrice daily), sodium benzoate (625 mg thrice daily), phenobarbitone (15 mg thrice daily), and vigabatrin (500 mg twice daily) as well as a ketogenic diet. The child is now 1 year old, and she has remained generally encephalopathic with profound global developmental delays and a persistent burst-suppression EEG pattern.

NKH, also termed glycine encephalopathy, is an inborn error of glycine metabolism that results in the accumulation of large quantities of glycine in all body tissues, including the brain, due to a defect in the glycine cleavage system [6]. It is a rare condition with an incidence of 1 in 200,000 worldwide, but it is more common in Finland, British Columbia (Canada), and the Israeli-Arab population [7].

The clinical presentations of NKH vary with different types of disease. A classical severe form of NKH typically presents in the first week of life, with life-threatening encephalopathy, apnea, and seizures. This initial presentation may mimic typical hypoxic-ischemic encephalopathy or other causes of central nervous system depression, including metabolic and infective causes [8].

The diagnosis of NKH is confirmed by elevated glycine levels in the serum and CSF in the absence of an organic disorder. Common biochemical and baseline investigations, including blood gases, lactate, ammonia, liver function tests, and infection screens, are usually normal [8]. The typical EEG pattern in NKH is a burst-suppression pattern, with cortical atrophy and hypoplasia of the vermis, along with delayed myelination, on MRI [9]. Our patient had transient transaminitis accompanied by elevated creatine kinase and lactate dehydrogenase, which led the neonatologist to manage her in the same way as a patient with hypoxic-ischemic encephalopathy, even though there was no sentinel event during labor.

Seizure semiology varies in NKH, including apnea; hiccups; asymmetric tonic seizures; epileptic spasms; myoclonic, focal, and generalized seizures; and oro-ocular automatisms [5]. This patient's seizure patterns evolved from myoclonic jerks to focal polymorphous seizures that occurred in clusters multiple times a day, asymmetric tonic seizures, and then infantile spasms and generalized tonic-clonic seizures. Based on this seizure pattern, it was not possible to easily distinguish between NKH and EIMFS, as both conditions may have similar and interrelated natural clinical histories.

The typical EEG findings in NKH are a suppression-burst pattern, hypsarrhythmia, and multifocal epileptiform discharges. However, the EIMFS EEG patterns were more commonly seen and reported in DEE, which is characterized by mutations in the *SCN1A, KCNT1, SCN8A, SLC25A22, TBC1D24,* and *QARS* genes [9]. This pattern is usually associated with a poor prognosis and is considered to indicate a complete disconnection within the thalamocortical systems. EIMFS has a natural history of distinct phases of EEG, in which focal EEG discharges typically migrate, starting from a cortical area and remaining localized or expanding to contiguous regions, whereas others independently develop in different areas of the same or the opposite hemisphere [10]. This was observed in our patient when a prolonged EEG at 3 months old showed a migrating pattern. Uncharacteristically, EIMFS has

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not been described in NKH to date. Thus, more studies are needed to review the ever-evolving EEG in patients with early myoclonic epilepsy (e.g., NKH).

Overall, the long-term outcome of NKH concerning seizures, encephalopathy, and psychomotor development remains very severe. Many infants never make any developmental gains; at most, affected children may learn to smile and roll over, but continue to have limited interactions with their environment. Patients sometimes die before the end of the 1st year of life or later in the course of follow-up, mainly because of worsening encephalopathy and respiratory failure.

In conclusion, the typical EEG features in NKH are a suppression-burst pattern, hypsarrhythmia, and multifocal epileptic activity. This case illustrates that EIMFS is a new phenotype in the course of NKH that has not yet been reported in the literature.

This study was approved by the International Islamic University Malaysia (IIUM) Research Ethics Committee (IREC 2022-157). Written informed consent by the patients was waived due to a retrospective nature of our study.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contribution

Conceptualization: MAA. Data curation: SASAA. Writing-original draft: MAA. Writing-review & editing: SM and ARM.

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