Child Neurology: Epilepsy of infancy with migrating focal seizures

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Epilepsy of infancy with migrating focal seizures is a rare, infantile epileptic encephalopathy characterized by normal early development, refractory focal seizures arising independently from both hemispheres, and severe psychomotor retardation. In the revised terminology by the International League Against Epilepsy, it has been classified as an “electro-clinical syndrome” of “unknown cause” with onset in infancy.¹ Affected infants have progressive psychomotor retardation and decline of head circumference percentile. We present a 6-month-old boy diagnosed with this entity and discuss the approach to an infant with unexplained refractory seizures.

CLINICAL CASE, PART I A 6-month-old boy presented with developmental delay and focal seizures. He was the second child born to a third-degree consanguineous couple. His perinatal period had been uneventful and he had attained social smile by the age of 6 weeks. He started having seizures at the age of 2 months. The seizures consisted of deviation of eyes and head along with tonic posturing of arm or leg of either side and associated flushing. The seizures usually lasted for 1–2 minutes. The initial frequency was 2–3 per day but gradually over the next 4 months, it increased to 50–60 per day. He had been treated with phenobarbitone, phenytoin, carbamazepine, topiramate, and levetiracetam without success. He had lost social smile, and not gained any new developmental milestones. Family history was not significant.

Examination revealed a well-thriving baby with head circumference of 40 cm (< -2 SD). There were no neurocutaneous markers or dysmorphic features. The neurologic examination revealed reduced interaction and alertness, normal cranial nerves including fundus, and normal tone with brisk tendon reflexes and extensor plantar responses. Systemic examination was unremarkable.

Differential diagnosis. Important causes for refractory seizures in infancy include malformations of cortical development, acquired structural brain lesions such

as sequelae of intrauterine or perinatal brain injury, pyridoxine dependence, glucose transporter type 1 deficiency syndrome, neurocutaneous syndromes, some metabolic/degenerative disorders, and epileptic syndromes (table). Hence the evaluation begins with a comprehensive history and examination to look for features of perinatal insult, dysmorphism (suggesting a chromosomal abnormality), and neurocutaneous markers. A brain MRI must be obtained to look for structural causes (e.g., malformations, sequelae of previous insults, features of tuberous sclerosis). Metabolic screening tests such as blood ammonia, arterial lactate, blood acylcarnitine profile, and urine organic acid studies are then performed to exclude organic acidemias, aminoacidopathies, and urea cycle defects. If all these investigations are normal, therapeutic trials of pyridoxine, pyridoxal phosphate, and folinic acid must be given sequentially. Another treatable metabolic cause of refractory infantile epilepsy is glucose transporter defect, which is diagnosed by the presence of CSF hypoglycorrhachia (CSF/blood sugar ratio < 0.4). An EEG should be performed to look for localization of seizure focus, and for diagnosis of infantile epileptic encephalopathies such as Ohtahara syndrome and epilepsy of infancy with migrating focal seizures. Other rare causes of refractory infantile seizures include Alpers disease, some chromosomal abnormalities (e.g., ring chromosome 20), and SCN1A mutation-related epilepsy.^{2,3}

CLINICAL CASE, PART II MRI of the brain, arterial blood gas, blood lactate and ammonia levels, urine ketones, plasma acylcarnitine profile, urine gas chromatography–mass spectrometry for organic acids, hair microscopy, serum copper and ceruloplasmin levels, thyroid profile, CSF examination (including glucose and lactate), and the karyotype were normal. The EEG revealed multifocal spikes and ictal rhythms arising variably from the right or left hemispheres (figure). The patient's seizures were uncontrolled despite treatment with sodium valproate, clobazam, pyridoxine, biotin, and folinic

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Table Selected causes of refractory seizures in infancy

Condition	Commonly seen features	Diagnosis
Malformations of cortical development	Seizures, developmental delay, microcephaly	MRI brain
Acquired structural brain lesions	History of perinatal asphyxia, hypoglycemia; neuroinfections, trauma	MRI brain
Neurocutaneous syndromes: tuberous sclerosis and Sturge-Weber syndrome	Tuberous sclerosis: ash leaf macules, adenoma sebaceum; Sturge-Weber syndrome: port wine stain, glaucoma	CT/MRI brain; mutation in <i>TSC1</i> , <i>TSC2</i>
Pyridoxine dependence	Seizures with onset in prenatal or neonatal period, refractory to conventional antiepileptic drugs	Response to therapeutic trial of pyridoxine; elevated α -aminoadipate semialdehyde (AASA) and pipercolic acid in CSF; mutation in <i>ALDH7A1</i> (Antiquitin protein)
Pyridoxal phosphate-dependent seizures	Prematurity, in utero and postnatal seizures, encephalopathy, burst suppression pattern on EEG	Therapeutic trial of oral pyridoxal phosphate (30 mg/kg/d); CSF: elevated glycine, threonine, L-dopa, 3-methoxytyrosine, and decreased homovanillic acid, 5-hydroxyindole acetic acid; <i>PNPO</i> mutation
Glucose transporter 1 (GLUT 1) deficiency syndrome	Infantile onset epilepsy, developmental delay, and acquired microcephaly; treatment of choice: ketogenic diet	CSF hypoglycorrachia (CSF/blood sugar ratio < 0.4); mutation in <i>SLC2A1</i> gene (Glut1 protein)
Folinic acid responsive seizures	Neonatal-onset seizures, variable response to pyridoxine, and rapid response on addition of folinic acid and lysine-restricted diet	Response to therapeutic trial of oral folinic acid (3–5 mg/kg/d); elevated α -aminoadipate semialdehyde and pipercolic acid in CSF
Disorders of biotin metabolism (biotinidase deficiency, holocarboxylase deficiency)	Symptoms within first weeks of life, seizures, breathing abnormalities, hypo/hypertonia, lethargy, vomiting, skin rash, occasionally alopecia; treatment with biotin (10 mg/d) is usually beneficial	Ketoacidosis, organic aciduria, hyperammonemia; <i>BTD</i> and <i>HLCS</i> gene mutations
Sulfite oxidase/molybdenum cofactor deficiency	Seizure onset in first week of life, feeding problems, hypomotility, pyramidal signs, lens dislocation, severe neuromotor impairment	Imaging: cystic cavities in white matter and cortical atrophy; elevated urine sulfite; <i>SUOX</i> , <i>MOC51</i> , <i>MOC52</i> , and <i>GPHN</i> mutations
Glycine encephalopathy	Onset in neonatal period, myoclonic seizures, lethargy/stupor, breathing difficulties, hiccups, rapidly fatal	Glycine levels elevated in urine, plasma, and CSF; <i>GLDC</i> , <i>AMT</i> , <i>GCSH</i> , and other mutations
Disorders of γ-aminobutyric acid (GABA) metabolism	Frequent seizures, diffuse, generally nonprogressive encephalopathy, hypotonia, extrapyramidal signs, ocular abnormalities	MRI may reveal signal changes in globus pallidi, white matter, dentate nuclei; 4-hydroxybutyric acid in urine, plasma, and CSF; free GABA and homocarnosine are usually high in CSF <i>ALDH5A1</i> gene mutation
Menkes disease	X-linked disorder, rapidly progressive neurodegeneration, seizures, hair changes, hypothermia, arterial degeneration, osteoporosis and other skeletal changes	Pili torti on hair microscopy; low serum copper and ceruloplasmin; <i>ATP 7A</i> gene mutation on Xq
Alpers syndrome	Familial rapidly progressive encephalopathy with onset in infancy, intractable seizures, liver disease, progressive cerebral atrophy	Genetic testing for <i>POLG1</i> mutation (DNA polymerase γ)
Early infantile epileptic encephalopathy (Ohtahara syndrome)	Frequent, refractory tonic spasms with onset in first few months of life; frequent association with brain malformations; high mortality and very poor neurodevelopmental outcome in survivors	Suppression-burst pattern on EEG; MRI may demonstrate brain malformations
Early myoclonic encephalopathy	Early-onset, frequent myoclonias and partial seizures; association with genetic and metabolic causes; poor prognosis for psychomotor development	Suppression-burst pattern on EEG
Epilepsy of infancy with migrating focal seizures	See discussion	

acid. The final diagnosis of epilepsy of infancy with migrating focal seizures was concluded based on the electroclinical findings and exclusion of known etiologies. When followed up at 16 months of age, he continued to have 1–2 seizures per week, severe psychomotor retardation, and a head circumference below the first percentile.

DISCUSSION Epilepsy of infancy with migrating focal seizures (earlier known as malignant migrating partial seizures in infancy) was first reported in 1995 by Coppola et al., who described 14 infants with a severe epileptic disorder characterized by refractory multifocal seizures involving both hemispheres and severe psychomotor developmental delay.² The diag-

Figure Ictal EEG during a seizure manifested by gaze deviation to the left

Note seizure onset with α range activity over the right central and temporal leads later evolving into delta activity (A). Ictal EEG after 5 minutes shows seizure onset from the left central and temporal leads (B). The child had tonic posturing of the right upper limb during this period.

nostic criteria include the presence of 1) normal development before seizure onset, 2) onset before 6 months, 3) migrating focal motor seizures at onset, 4) multifocal seizures becoming intractable, 5) intractable to conventional antiepileptic drugs, 6) no identified etiology, and 7) profound psychomotor delay.⁴ It is a rare syndrome and has been reported in approximately 50 patients.

Clinical features. Three distinct phases are described in the natural history of this syndrome.^{4,5} Seizures appear after an uneventful perinatal period and normal early development. The first phase is heralded by seizures beginning in the first few months. The seizures are mainly focal motor with frequent secondary generalization. Autonomic manifestations such as apnea, cyanosis, or flushing are common. This phase usually lasts a few weeks or months. The second phase (also called the stormy phase) starts variably between 1 and 12 months of age. It is characterized by very frequent polymorphous focal seizures. They occur in multiple clusters in a day or nearly continuously. Long-term video EEG recordings frequently reveal subclinical ictal manifestations during this phase. The third phase begins between 1 and 5 years of age. It is a relatively seizure-free period with severe psychomotor retardation. This phase may be frequently complicated by seizure recurrences during intercurrent illnesses and further developmental regression.

Etiology. The exact etiology of this syndrome is not known. A role of channelopathies or metabolic disorders is suspected and is the focus of ongoing research. Neuroimaging has been normal in all reported patients. No familial occurrence or consanguinity has been reported. No metabolic abnormalities have been identified. In those cases that were examined

postmortem, no cortical dysplasia or neuronal migration defects have been found.⁴

Sodium channel (*SCN1A*) mutations have been identified in patients with infantile-onset cryptogenic focal epilepsy with variable intellectual disabilities.³ However, no mutations of potassium (*KCNQ2*, *KCNQ3*), sodium (*SCN1A*, *SCN2A*), or chloride (*CLCN2*) ion channels were identified in a study of 3 patients with epilepsy of infancy with migrating focal seizures.⁶ Recently, a submicroscopic duplication 16p11.2 was found in an infant with this phenotype, raising the possibility that such chromosomal rearrangements may play an etiologic role.⁷

EEG. The EEG patterns in migrating partial seizures in infancy evolve over time.⁸ The interictal EEG initially shows diffuse slowing of background activity and frequent slow waves, which often shift from one hemisphere to the other. Multifocal discharges originating from both hemispheres are also frequently noted. The ictal EEGs display paroxysmal discharges occurring in various regions in consecutive seizures in a given patient. The area of ictal onset shifts from one region to another and from one hemisphere to the other, with occasional overlapping of consecutive seizures. The migratory feature of ictal discharges is not pathognomonic of the disorder and may be seen in benign partial epilepsy of infancy.⁹

Treatment. Therapies including conventional antiepileptic drugs, pyridoxine, biotin, folic acid, ketogenic diet, steroids, and adrenocorticotrophic hormone have proved ineffective. Vigabatrin and carbamazepine may worsen the seizures. Some improvement has been reported with the use of bromides and stiripentol.^{10,11}

Prognosis. The long-term outcome is dismal in most cases. Most children have severe psychomotor retardation and acquired microcephaly along with continuing seizures. A few children whose seizures are controlled may acquire the ability to reach for objects and walk, but do not develop language. A number of patients die before the end of the first year of age or later, mainly because of intercurrent infections and respiratory failure.⁵

AUTHOR CONTRIBUTIONS

All authors contributed to the content of the manuscript. S.S., N.S., and R.K. performed the clinical and diagnostic evaluation of the child, reviewed the literature, and prepared the manuscript. S.G. was in charge of the case and approved the final version of the manuscript.

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