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Epilepsy in Muenke Syndrome: *FGFR3*-Related Craniosynostosis

Nneamaka B. Agochukwu, MD^{a,b}, Benjamin D. Solomon, MD^b, Andrea L. Gropman, MD^{c,d}, and Maximilian Muenke, MD^{b,*}

^aClinical Research Training Program, National Institutes of Health, Bethesda, Maryland ^bMedical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland ^cDepartment of Neurology, Children's National Medical Center, Washington, DC ^dDepartment of Neurology, George Washington University of the Health Sciences, Washington, DC

Abstract

Epilepsy, a neurologic disorder characterized by the predisposition to recurrent unprovoked seizures, is reported in more than 300 genetic syndromes. Muenke syndrome is an autosomal-dominant craniosynostosis syndrome characterized by unilateral or bilateral coronal craniosynostosis, hearing loss, intellectual disability, and relatively subtle limb findings such as carpal bone fusion and tarsal bone fusion. Muenke syndrome is caused by a single defining point mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene. Epilepsy rarely occurs in individuals with Muenke syndrome, and little detail is reported on types of epilepsy, patient characteristics, and long-term outcomes. We present seven patients with Muenke syndrome and seizures. A review of 789 published cases of Muenke syndrome, with a focus on epilepsy and intracranial anomalies in Muenke syndrome, revealed epilepsy in six patients, with intracranial anomalies in five. The occurrence of epilepsy in Muenke syndrome within our cohort of 58 patients, of whom seven manifested epilepsy, and the intracranial anomalies and epilepsy reported in the literature, suggest that patients with Muenke syndrome may be at risk for epilepsy and intracranial anomalies. Furthermore, the impact of Muenke syndrome on the central nervous system may be greater than previously thought.

Introduction

First defined in the mid-1990s, Muenke syndrome constitutes the most common syndromic form of craniosynostosis, with an incidence of 1 in 30,000 births. Of all patients with craniosynostosis, 8% manifest Muenke syndrome. Further, of those patients with craniosynostosis and an identified genetic cause, 24% manifest Muenke syndrome [1]. Muenke syndrome involves an autosomal dominant inheritance pattern, and is clinically characterized by craniosynostosis, most commonly of the coronal suture (bilateral more

often than unilateral), sensorineural hearing loss, developmental delay, and relatively subtle limb anomalies such as carpal bone fusion and tarsal bone fusion [2]. Other typical findings include ocular hypertelorism, ptosis or proptosis (usually mild), recurrent otitis media with effusion, midface hypoplasia, temporal bossing, a highly arched palate, and strabismus. The condition is caused by a single defining point mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene. This mutation is a c.749 C>G transversion that results in p.P250R (a proline to arginine substitution at amino acid position 250) [3].

Because of the inherent variable expressivity and incomplete penetrance of the syndrome, phenotypic variability is considerable, even within the same family. Notably, some individuals with the p.Pro250Arg mutation may exhibit no signs of Muenke syndrome on physical or radiographic examination [4]. Muenke syndrome is unique among the syndromic craniosynostoses, because it is caused by a single defining mutation, whereas most syndromic craniosynostoses can be caused by multiple mutations in multiple different genes, the majority of which are members of the *FGFR* gene family.

The occurrence of epilepsy has been reported in more than 300 genetic syndromes. Well-known conditions include Williams syndrome, Apert syndrome, Saethre-Chotzen syndrome, and 22q11.1 microduplication syndrome [5–9]. Furthermore, there are “epilepsy syndromes”, i.e., syndromes in which seizures comprise the central sign, defined by specific electroencephalogram findings and age/developmental stage dependence. More than 50 such epilepsy syndromes are now recognized [10]. These include Dravet syndrome (severe myoclonic epilepsy of infancy), childhood absence epilepsy, benign rolandic epilepsy, Lennox-Gastaut syndrome, and Landau-Kleffner syndrome, to name a few [11–13].

Historically, epilepsy has not been considered a common clinical feature of Muenke syndrome. However, recent reports described several patients with Muenke syndrome and epilepsy [14,15]. Moreover, a 2003 report described early-onset temporal lobe-related epilepsy in a patient with Muenke syndrome associated with temporal lobe dysgenesis, likely contributory to the seizure focus [16].

Here, we present seven patients, ascertained from our prospective natural history study of Muenke syndrome, with a history of current or past seizures or epilepsy. We also present a literature review of all reported patients with Muenke syndrome involving epilepsy and intracranial anomalies. Because of the association between intracranial anomalies and epilepsy, a literature review with respect to the expression of *FGFR3*, epilepsy, and intracranial anomalies in Muenke syndrome is also presented.

Materials and Methods

Our natural history protocol on Muenke syndrome, as approved by the Institutional Review Boards of the National Human Genome Research Institute and National Institutes of Health (Bethesda, MD), has thus far recruited a cohort of 58 patients, consisting of infants, children, and adults. Participants are referred by clinicians or self-referred. For inclusion, participants require documentation of the defining causative mutation of Muenke syndrome.

From this cohort of 58 patients, seven patients (12% of the total cohort) with a history of seizures or epilepsy were identified. Criteria for determining the presence of seizures or epilepsy for this particular study included documentation of epilepsy by a board-certified pediatric neurologist, based on clinical findings or the results of an electroencephalogram. For those patients meeting these criteria, additional data were collected, including demographic information (age, sex, date of birth, and ethnicity), features of Muenke syndrome (including suture involvement if craniosynostosis was present), hearing loss, otitis media with effusion, limb anomalies, and neurocognitive function. The epilepsy data collected included type of epilepsy, age at diagnosis, antiepileptic medications currently/ previously used, electroencephalogram findings, family history of epilepsy, medical history, surgical history, and neuroimaging (magnetic resonance imaging or computed tomography scans). One of these seven patients was examined in person at the National Institutes of Health (Bethesda, MD). For the six patients who were not examined in person at the National Institutes of Health, available medical records were reviewed, and medical histories with findings of physical examinations were provided by patients, family members, and referring clinicians via telephone and e-mail interviews.

EEG Findings	Use of AEDs	Neuroimaging	Additional Clinical Findings
Right fronto-polar spike waves, bitemporal disorganization	Oxcarbazepine	Periventricular hyperintensity	Hypotonia, sensory processing disorder, obstructive sleep apnea, highly arched palate, neonatal apnea, behavioral issues, recurrent otitis media with effusion
No EEG performed	No AEDs used	No imaging performed	Meniere disease, developmental delay (speech/language), intellectual disability, type II diabetes mellitus, arrhythmia, recurrent otitis media with effusion
Right hemispheric sharp waves, with focal slowing in the right central region	Discontinued as of May 2009 (at 1 year of age); previously on phenobarbital and sodium valproate	Increased diffusion in left hemisphere	Developmental delay (speech/motor), strabismus, temperature dysregulation, torticollis
Generalized spike and wave discharges; independent left frontal, left centroparietal and right centroparietal spikes; mild focal cerebral dysfunction over the right temporal region; intermittent delta polymorphic slowing over the right temporal region	Discontinued; previously on carbamazepine, then gabapentin and clonazepam	Scarring of bilateral frontal lobes	Intellectual disability, strabismus, neonatal apnea, behavioral issues, sensory processing disorder, recurrent otitis media with effusion, carpal bone fusion (capitate-hamate)
No EEG performed	No AEDs used	No imaging performed	Strabismus, developmental delay (speech), recurrent otitis media with effusion
Irregular mixture of delta, theta, alpha, and beta waves, as well as sharp waves over the right central and temporal areas;	Phenobarbital, then levetiracetam; discontinued at 21 months of age	Cortical cyst, white matter hyperintensity adjacent to left frontal horn	Strabismus, highly arched palate, neonatal apnea, moderate developmental delay (speech and motor)

EEG Findings	Use of AEDs	Neuroimaging	Additional Clinical Findings
intermittent sharp waves emanating from the central, right temporal, and left temporal regions			
Rare focal right parietal occipital sharp waves with epileptiform discharges	Previously on phenobarbital, currently on levetiracetam	Normal	Torticollis, strabismus, astigmatism

Literature review

A Medline search was performed to determine all previously reported cases of Muenke syndrome from 1996 (i.e., the time period of the initial description of Muenke syndrome) to the present (2011). The key words and patient terms searched included “Muenke syndrome,” “coronal craniosynostosis,” “*FGFR3* craniosynostosis,” “P250R,” “Pro250Arg,” and “syndromic craniocraniosynostosis.”

Results

Literature review

In total, 789 patients with Muenke syndrome were identified from the literature. Of these patients, epilepsy was reported in six, whereas intracranial anomalies were reported in five. The results of neuroimaging were not reported for five patients with epilepsy. One of these patients was reported with both epilepsy and an intracranial anomaly (temporal lobe dysgenesis). Epilepsy was not documented in the remaining four patients with intracranial anomalies. Notably, none of these patients described in the literature were members of our cohort.

Patients

A total of seven patients (12%) out of our total cohort of 58 demonstrated a history of seizures or epilepsy (see Table 1 for a summary of patient demographics). Included in this group were four females and three males, ranging in age from 4.5 months to 40 years. For all patients, except for patients 2 and 5, who were determined to manifest seizures provoked by fever and febrile seizures, respectively, investigations into seizure etiology, including electrolyte studies, infectious evaluation, and metabolic investigations and blood counts produced negative results, indicating no organic or metabolic etiology. Several patients demonstrated findings on neuroimaging that will be discussed later.

Descriptions of individual patients

Patient 1—Patient 1 is a 3-year-old girl with Muenke syndrome and bilateral coronal synostosis. In addition to Muenke syndrome, this patient also demonstrates behavioral differences, hypotonia, sensory processing disorder (significant problems in sensory motor processing, including tactile, oral, vestibular, and auditory modulation), and obstructive sleep apnea. Pregnancy was complicated by preeclampsia. Birth occurred at term. Her birth

was complicated by neonatal apnea requiring a brief bag and mask resuscitation. Her first seizure was reported at age 1 year. This seizure constituted a staring spell. The seizures have been of two types, i.e., atonic spells and staring spells that occur 1–3 times a day. Electroencephalograms indicated bitemporal disorganization and right fronto-polar spikes. Magnetic resonance imaging indicated periventricular T₂ signal hyperintensity. She was diagnosed with complex partial epilepsy, and is currently managed on oxcarbazepine. On oxcarbazepine, seizures occur about 2–3 times perweek. Her most recent seizure occurred 2 weeks before study ascertainment.

Patient 2—Patient 2 is a 28-year-old woman with Muenke syndrome. The diagnosis of Muenke syndrome was confirmed at age 25 years, after the birth and molecular diagnosis of a child with craniosynostosis attributable to Muenke syndrome. Patient 2 also manifests Meniere disease, type 2 diabetes mellitus, and cardiac arrhythmia (the arrhythmia was diagnosed at age 12 years, and treated with atenolol; the type of arrhythmia is unknown because these records were not available). There were no complications of pregnancy or delivery. At birth, the patient experienced respiratory difficulty because of a collapsed lung. Her first seizure occurred at 1 month of age, concomitant with a fever. Seizures occurred until early childhood, at which point they ceased. These seizures were complex, occasionally focal, and prolonged, and occurred in succession. They were classified as seizures provoked by fever. This patient did not receive antiepileptic medications. In addition, no formal electroencephalogram or magnetic resonance imaging was performed.

Patient 3—Patient 3 is a 3-year-old boy with Muenke syndrome and unilateral coronal synostosis. This patient also manifests torticollis and issues with temperature regulation (his temperature drastically varies from 35°C to 40.5°C within hours) that resolved after cranial vault reconstruction. This patient's previous history included hypotonia, which has improved. There were no complications of pregnancy or delivery. His first seizure was observed on day 8 of life, and was considered generalized tonic-clonic. No triggers were identified. The patient was diagnosed with epilepsy and received an antiepileptic regimen consisting of phenobarbital and sodium valproate. An electroencephalogram revealed right hemispheric sharp waves with focal slowing in the right central region. Diffusion-weighted magnetic resonance imaging revealed increased diffusion in the left hemisphere. He has remained seizure-free since 6 weeks of age. He was weaned off of all antiepileptic medications at age 1 year, and no longer receives an antiepileptic medication regimen. He was discharged from neurology follow-up at age 2 years.

Patient 4—Patient 4 is a 7-year-old girl with Muenke syndrome and unilateral coronal synostosis. This patient was examined in person at the National Institutes of Health. In addition, the patient demonstrates behavioral issues and a sensory processing disorder. No complications of delivery or pregnancy were reported. In the neonatal period, the patient manifested apnea (at day 2 of age), and was hospitalized in the neonatal intensive care unit for 5 days. Her first seizure occurred in the neonatal period during her stay in the neonatal intensive care unit, and the diagnosis of epilepsy was rendered at 1 month of age. Her seizures are mostly complex partial, characterized by a cessation of activity, repetitive head turning, staring, and vomiting. Occasionally, generalized seizures occur. Her most recent

seizure at the time of study ascertainment had occurred 18–24 months earlier. She was initially managed on carbamazepine, and then on a dual regimen of gabapentin and clorazepate. An electroencephalogram indicated generalized spike and wave discharges, independent left frontal, left centro-parietal, and right centro-parietal spikes, mild focal cerebral dysfunction over the right temporal region, and intermittent delta polymorphic slowing over the right temporal region. Magnetic resonance imaging revealed scarring of the frontal lobe. This patient has not manifested a seizure since age 5 years, and was gradually withdrawn from all antiepileptic medications. She continues to be monitored routinely by a neurologist.

Patient 5—Patient 5 is a 40-year-old woman with Muenke syndrome and bilateral coronal synostosis. Features of Muenke syndrome include bilateral coronal craniosynostosis (status post cranial vault reconstruction at age 6 weeks; she underwent additional surgery at age 2 years), bilateral sensorineural hearing loss, developmental delay (expressive speech only), recurrent otitis media with effusion, a highly arched palate, and strabismus. Craniofacial features include mandibular prognathia, a deviated nasal septum, and a broad-shaped head. The diagnosis of Muenke syndrome was confirmed at age 34 years as a result of genetic testing, which was performed as part of prenatal family planning. The inheritance is unknown. No other family members have been tested, although this patient does have a son with recurrent otitis media with effusion. The patient also manifests gastroesophageal reflux disease. Her first seizure was observed at age 3 years, and was classified as febrile. The seizure was not prolonged, and was generalized. No magnetic resonance imaging was performed. Further, this subject did not receive antiepileptic medications.

Patient 6—Patient 6 is a 22-month-old boy with Muenke syndrome and unilateral coronal synostosis. There were no complications of pregnancy or delivery. On day 1 of life, this patient experienced an apneic episode that resolved with free-flow oxygen. Additional apneic episodes occurred on days 2 and 7 of life. This patient's first seizure occurred on day 7 of life. In addition to shallow respiratory effort and apnea, he exhibited posturing and stiffening of his limbs. A physical examination was significant for a wide anterior fontanelle and a large posterior fontanelle, but was otherwise unremarkable. Electrolyte, metabolic, and hematologic evaluations produced normal results. Magnetic resonance imaging revealed a cortical cyst and white matter hyperintensity adjacent to the left frontal horn. An electroencephalogram performed during this period indicated background activity consisting of an irregular mixture of delta, theta, alpha, and beta waves, as well as sharp waves mostly over the right central and temporal areas. Three total electrographic seizures were recorded. All seizures were associated with sharp waves. The clinical correlation during one of these seizures involved a decrease in oxygen saturation. He received phenobarbital, and his seizures were well controlled until about 6 months of age, when he presented with a clustering of tonic-type seizures. His phenobarbital dose was increased. He continued on this antiepileptic regimen of high-dose phenobarbital, and was transitioned to levetiracetam at 21 months of age. He has been seizure-free since his cranial vault reconstruction/fronto-orbital advancement at 10.5 months of age.

Patient 7—Patient 7 is a 7-month-old boy with Muenke syndrome and unilateral coronal synostosis. This patient also manifests astigmatism and torticollis. No complications of pregnancy, delivery, or birth were evident. The maternal history is significant for two previous miscarriages. His first seizure occurred at 2 months of age. His seizures were classified as complex partial. During these episodes, head turning and cessation of breathing occur, and he is unresponsive. The seizures steadily increased in frequency from their first occurrence to the period before cranial vault reconstruction. After the fronto-orbital advancement/cranial vault reconstruction, the seizures began to decrease in frequency. In addition to complex partial seizures, this patient also experiences generalized episodes consisting of full-body tensing, stiffening, unresponsiveness, and whole-body quivering. Initially, his medical management involved phenobarbital. He was later transitioned from phenobarbital to levetiracetam. Significant electroencephalogram findings include rare focal right parietal occipital sharp waves with epileptiform discharges. Magnetic resonance imaging produced normal results. After his cranial vault reconstruction, the frequency of seizures vastly decreased, and as of 1 month before study ascertainment, no seizures had occurred.

Discussion

Several reports described patients with Muenke syndrome and epilepsy. The earliest report of epilepsy in a patient with Muenke syndrome was published in 2003, in which a patient was reported to have manifested early-onset seizures characterized by episodes of staring, facial cyanosis, loss of consciousness, and generalization, with hypertonia of the limbs [16]. Subsequent magnetic resonance imaging in this patient detected temporal lobe dysgenesis. In a recent study by Ridgway et al. [15], 15% of patients (n = 3) demonstrated epilepsy. De Jong et al. [14] reported on two Dutch families with Muenke syndrome, including two patients with epilepsy. These reports did not document whether the epilepsy in these patients was ongoing or transient, nor did it document the results of neuroimaging.

Intracranial anomalies have been reported to date in five patients with Muenke syndrome [16–20]. These anomalies (outlined in Table 2) include agenesis of the corpus callosum, hemimegalencephaly, and porencephaly. Within our National Institutes of Health cohort of patients, one demonstrates a structural anomaly. This anomaly involves a cavum septum pellucidum, which is a normal variant occurring in 35–57% of the population in recent cranial magnetic resonance imaging studies [21,22]. Agenesis and hypoplasia of the corpus callosum are well documented in patients with Apert syndrome, a craniosynostosis syndrome associated with mutations in *FGFR2*. In one series, 23% of patients with Apert syndrome demonstrated abnormalities of the corpus callosum (these abnormalities included agenesis of the corpus callosum, a deficient corpus callosum, and thinning of the corpus callosum) [23,24]. Neuroimaging is not routinely performed during the evaluation of patients with Muenke syndrome, because these individuals are typically less severely affected compared with individuals with more severe syndromic forms of craniosynostosis, such as Apert syndrome. Differences in patterns of the expression, formation, and structure of the central nervous system may also be responsible for the developmental delay and intellectual disability observed in Muenke syndrome. Some of these abnormalities may not be reported because of the lack of central nervous system imaging in Muenke syndrome, or

because microscopic anomalies may not be detectable on routine magnetic resonance or computed tomography imaging. Animal models indicated that *FGFR3*, the gene mutated in Muenke syndrome, is expressed at its highest levels in the developing central nervous system [25]. Moreover, *FGFR3* mRNA is abundantly expressed in the glial cells of the brain [25]. None of these patients have undergone neuropathologic examinations, and the data from surgical brain resections are unavailable. In the future, these data may prove quite useful in determining the etiopathogenesis of epilepsy in Muenke syndrome.

In addition to differences in central nervous system microarchitecture, a plausible etiology of epilepsy in Muenke syndrome involves preoperative intracranial hypertension. Increases in preoperative intracranial pressure may be subclinical and undetectable by a fundoscopic examination or clinical symptoms and signs. Our patients 6 and 7 demonstrated a reduction in seizures or became seizure-free after their cranial vault reconstruction, a procedure that aims to lessen pressures and forces on the growing brain attributable to prematurely fused calvarial sutures.

An additional etiologic consideration, specifically within our cohort of patients, involves anoxic brain injury and a resultant increase in susceptibility to epilepsy (Table 3). Of the seven patients reported with epilepsy in this study, four manifested anoxia during the neonatal period. These cases of anoxia included neonatal apnea requiring a bag and mask resuscitation (patient 1), respiratory difficulty secondary to lung atelectasis (patient 2), neonatal apnea requiring admission to the neonatal intensive care unit (patient 4), and apneic episodes at days 1 and 7 of age, which resolved with free-flow oxygen (patient 6). Of these four patients, three demonstrated positive findings on magnetic resonance imaging, possibly attributable to anoxic brain injury (Table 3). Further, we cannot exclude that the aberrant expression of *FGFR3* may lead to both neonatal apnea and the development of epilepsy through two isolated, distinct mechanisms. Studies of the effects of anoxia on the development of epilepsy present contradictory findings. Animal studies indicate that anoxia alone does not lead to the development of epilepsy, whereas prognostic studies demonstrated that perinatal anoxia constitutes an unfavorable predictive risk factor in the prognosis of patients with epilepsy. Further, hypoxia was revealed as a common cause of neonatal seizures and encephalopathy through the induction of hyperexcitability [26–29]. In addition, apnea may also be caused by structural anomalies of the midface and nasal passages in individuals with Muenke syndrome (e.g., midface hypoplasia, choanal atresia, and narrowed nasal passages). To date, one report described sudden death in a patient with Muenke syndrome [30]. On autopsy, this patient exhibited narrowed airway spaces, although no gross cerebral abnormalities were evident. With more studies on animal models of Muenke syndrome, on individuals with Muenke syndrome, and on the structure and expression patterns of *FGFR3*, clues may accumulate regarding the etiology of these clinical features of the syndrome.

The occurrence of epilepsy in Muenke syndrome within our cohort and the intracranial anomalies and epilepsy reported within the literature on Muenke syndrome suggest that patients with Muenke syndrome are at risk for epilepsy and intracranial anomalies. Patients with Muenke syndrome should be monitored for apnea and seizures, particularly during the neonatal period. Further, all individuals with Muenke syndrome and epilepsy should

undergo neuroimaging. This recommendation extends to individuals with febrile seizures and Muenke syndrome, such as our patients 2 and 5. Because individuals with Muenke syndrome are at risk for intracranial anomalies, individuals with Muenke syndrome who are classified as manifesting febrile seizures should also receive neuroimaging to exclude a structural etiology. Magnetic resonance imaging constitutes the preferred imaging method, because certain anomalies and structural brain differences are not detectable via computed tomography alone (e.g., periventricular hyperintensity and differences in the structure of white and grey matter).

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Table 1

Clinical features of patients with Muenke syndrome and epilepsy

Patient Number	Age at Study Ascertainment (Age Diagnosed With Muenke Syndrome)	Sex	Sporadic or Hereditary	Phenotype of Craniosynostosis	Auditory Phenotype	Age at Onset of Seizures	Type of Epilepsy
1	3 years (7 months)	F	Sporadic	Bilateral coronal	Bilateral mixed hearing loss	1 year	CP
2	28 years (25 years)	F	Unknown	Macrocephaly; no craniosynostosis	Bilateral mixed hearing loss with hearing aid in left ear	1 month	Seizures provoked by fever
3	3 years (16 months)	M	Sporadic	Unilateral coronal (right)	No hearing loss detected by testing	8 days old	GTC
4	7 years (9 months)	F	Sporadic	Unilateral coronal (right)	Conductive hearing loss and hearing aid (left ear)	1 month	CP
5	40 years (34 years)	F	Unknown	Bilateral coronal	Bilateral sensorineural hearing loss	3 years	FC
6	18 months (15 months)	M	Sporadic	Unilateral coronal (right)	Moderate to severe conductive hearing loss	8 days old	CP
7	4.5 months (4.5 months)	M	Unknown	Unilateral coronal (left)	Moderate to severe conductive hearing loss	2 months	GTC

Abbreviations:

AEDs = Antiepileptic drugs

CP = Complex partial

EEG = Electroencephalogram

F = Female

FC = Febrile convulsions

GTC = Generalized tonic clonic

M = Male

Table 2

Cerebral abnormalities reported in patients with Muenke syndrome

Cerebral Abnormality	Reference Number
Temporal lobe dysgenesis	[16]
Agenesis of the corpus callosum, porencephalic cyst in lateral ventricle	[17]
Bilateral lateral ventricle dilatation (ventriculomegaly), small cerebellum	[18]
Left hemimegalencephaly, hypoplasia of the corpus callosum, abnormal hippocampus, abnormal differentiation of grey and white matter	[19]
Grossly dilated lateral, third and fourth ventricles, hematoma within ventricular system, focal hemorrhage in the frontal lobe with porencephaly on the left that extends into the left parasagittal hemisphere	[20]

Table 3

Patients with perinatal anoxia

Subject	Anoxic Event	MRI Finding	Type of Epilepsy
1	Neonatal apnea requiring bag and mask resuscitation	Periventricular T ₂ signal hyperintensity	Complex partial
2	Respiratory difficulty secondary to lung atelectasis	No MRI performed	Seizures provoked by fever
4	Neonatal apnea and subsequent 5-day hospitalization in neonatal intensive care unit	Scarring of the frontal lobe	Complex partial
6	Apneic episodes at days 2 and 7 of age	Cortical cyst and white matter hyperintensity adjacent to the left frontal horn	Complex partial

Abbreviation:

MRI = Magnetic resonance imaging

Refer to Table 1 for more detailed descriptions of patients, including phenotype of craniosynostosis, features of Muenke syndrome, and additional clinical findings.