Tara Benjamin*, Karrie A. Hines, Kareem Khozaim and Frank P. Schubert

Recurrent fetal seizures diagnosed in the offspring of consanguineous parents

Abstract: Fetal seizures are relatively rare and most often associated with anomalies or adverse neonatal outcome. We describe a patient who presented in both her G1 and G2 pregnancies with fetal seizures. The second pregnancy was a twin gestation in which only one twin was affected. The fetal seizures were noted by the patient as “extreme rhythmic movement” and were observed on ultrasound. Both neonates were diagnosed with a seizure disorder within 1 day of life. Currently, the seizures are controlled by medication; however, both children have some developmental delay. Additionally, the patient and her partner are consanguineous, suggesting a likely genetic etiology. In utero diagnosis of fetal seizures warrants a multidisciplinary approach to attempt to further define prognosis and provide appropriate treatment and counseling.

Keywords: Consanguinity; fetal seizures; in utero seizures; recurrent; twins; ultrasound.

DOI 10.1515/crpm-2014-0009
Received February 22, 2014. Accepted April 23, 2014. Previously published online May 22, 2014.

Introduction

Fetal seizures were first reported in 1969 by Badr El-Din [2]. Since then, reports have depicted fetal seizures detected by fetal heart tracings, ultrasound, and maternal awareness, most associated with anomalies, adverse neonatal outcome, or neonatal death. Here we describe a unique case of maternal awareness of fetal seizures in one of a pair of dichorionic-diamniotic twins with a history of fetal and neonatal seizures in a previous singleton gestation. The parents are consanguineous. Our case emphasizes that maternal awareness of fetal seizures alone may justify clinical investigation by a multidisciplinary team. Additionally, there is a risk of recurrence with possible inherited transmission. To our knowledge, there have been no reports of prenatal onset seizure disorders with a likely autosomal recessive etiology or maternal awareness of seizures in one of a set of twins.

Case report

A 29-year-old Caucasian G2P1001 with a dichorionic-diamniotic gestation was referred to our center for delivery because of concern over a genetic seizure disorder. The patient’s history was significant for endometriosis, asthma, two shoulder surgeries, three loop electrosurgical excision procedures, and a laparoscopic abdominal cerclage. Medications included prenatal vitamins, albuterol as needed, aspirin, folate, and nifedipine for symptomatic relief of contractions. She denied a history of viral and environmental exposures. The patient and her partner are of German ancestry. Family history revealed that the patient and her partner are second cousins; her maternal grandmother is the sister of her partner’s paternal grandfather. The coefficient of relationship (R) was calculated and indicated the patient and her partner share approximately 1/32 (3.1%) of their alleles with one another. The patient reported a brother with febrile seizures and a paternal first cousin once removed with epilepsy.

During the first pregnancy, the patient reported odd fetal movements starting at 28 weeks of gestation. The patient stated that the movement felt “extremely rhythmic,” lasted about 30 s in duration and occurred about 5 times daily. Anatomic survey revealed normal intracranial anatomy; however, one seizure episode was reportedly witnessed via ultrasound examination. The patient had an uncomplicated term spontaneous vaginal delivery of a male infant weighing 2920 g. At 12 h of life, the neonate was transferred to the Neonatal Intensive Care Unit for tonic-clonic seizures accompanied by oxygen desaturation.

*Corresponding author: Tara Benjamin, Department of Obstetrics and Gynecology, Indiana University Hospital, 550 North University Blvd, Suite 2405, Indianapolis, IN 46202, USA, Tel.: +1-317-944-8182, E-mail: tarabenj@iupui.edu; and Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, IN, USA
Karrie A. Hines: Maternal Fetal Medicine, Indiana University Health, Indianapolis, IN, USA
Kareem Khozaim and Frank P. Schubert: Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, IN, USA
The neonate was initially treated with four anti-epileptic drugs as well as pyridoxine, coenzyme Q, and carnitine. Magnetic resonance imaging (MRI) of the head showed the possibility of blood in the occipital horn of the lateral ventricle and incomplete gyriform formation. Serial electroencephalograms demonstrated seizure activity originating from the Rolandic region and diffuse encephalopathy. Ammonia was slightly elevated (83 mg/L) and serum free fatty acids were low (0.12 mmol/L). Carnitine (serum plasma 11 μmol/L, ester serum plasma 2 μmol/L, and free serum plasma 11 μmol/L) and coenzyme Q10 (0.379 μg/mL) were decreased. The newborn screen was normal. The karyotype was normal and plasma amino acids were within normal limits. Cerebral spinal fluid (CSF) analysis was sanguineous without malignant cells or microorganisms present and glucose and amino acid concentrations were within normal limits. CSF protein was noted as high (104 mg/dL) and lactate was low (0.6 mmol/L). Tests for several metabolic, genetic and neuromuscular disorders were negative (Prader-Willi methylation, myotonic dystrophy types I and II, spinal muscular atrophy, free fatty acids, and very long chain fatty acids). The neonate was noted to have stridor, laryngomalacia/tracheomalacia, buried penis with chordee, and relative microcephaly. Neurology, medical genetics, and biochemical genetics specialists were consulted with no confirmed diagnosis, but there was a strong suspicion for the presence of a neuromuscular or mitochondrial disorder. Currently the 5-year-old has myoclonic seizures approximately twice yearly, an aversion to oral stimulation, and mild developmental delay. He continues to be hypotonic and receives both occupational and speech therapy. He is currently in a mainstream kindergarten. Present treatment is with levetiracetam.

In the second pregnancy, the patient underwent in vitro fertilization with transfer of two embryos. She declined aneuploidy screening and genetic counseling, and anatomic survey was normal. Her prenatal laboratory panel was normal. At 30 weeks of gestation, she reported fetal movements equivalent to those noted in her previous pregnancy. The patient was able to discern that the movements originated in only one twin. Antepartum surveillance included serial ultrasounds for growth and weekly biophysical profiles starting at 32 weeks of gestation. Ultrasound at 33+6 weeks of gestation detected one of the suspected seizure episodes of fetus A and noted tonic-clonic type movement. The fetus’ heart rate remained normal during this episode. The last ultrasound performed at 37+6 weeks of gestation demonstrated estimated fetal weights of 3007 g (29th percentile) and 2959 g (26th percentile) of fetuses A and B, respectively, with 1.6% discordance. A fetal MRI was not performed during this pregnancy.

A routine cesarean delivery for malpresentation and presence of an abdominal cerclage was performed at term under spinal anesthesia. Infant A was a female delivered in cephalic presentation with APGARs of 1, 4, and 7, and weight of 2820 g; infant B was a female delivered in breech presentation without complication with APGARs 9 and 9, and weight of 2759 g. During delivery, infant A was cyanotic, rigid with clenched fists, and in decerebrate posturing. Immediate resuscitation was performed with continued tonic-clonic seizures, abnormal rhythmic eye movements, and severe bradycardia noted. Initial stabilization was achieved with phenobarbital, lorazepam, and intubation. Newborn screen and serum amino acid profiles were all within normal limits. CSF analysis indicated elevated levels of tyrosine (44.5 μmol/L) and protein (92 mg/dL), with all other parameters within normal limits. An electroencephalogram demonstrated mild to moderate encephalopathy. MRI of the head, limited by motion, exhibited nonspecific basal ganglia abnormalities that could represent hypoxic ischemic encephalopathy. Maternal postpartum course was uncomplicated and she was discharged on the third post-operative day. Pathological exam of the placenta revealed a normal dichorionic-diamniotic placenta with a fused disc.

The infant (twin A) was subsequently found to have laryngomalacia and organic feeding dysfunction with aspiration and stridor. The infant was evaluated at 1 and 5 months by neurogenetics and was diagnosed with neonatal encephalopathy with seizures. She has hypotonia, but normal strength. She has no abnormal movements, tremor, or dystaxia, but does have tongue fasciculations. Her condition was reported to have been improving, although she remains developmentally delayed. Based on clinical exam and family history, a genetic cause for her seizures was suspected, however, a lack of interest by the family precluded aggressive genetic testing. Present treatment is with levetiracetam, topiramate, and phenobarbital.

Discussion

Neonatal seizures are associated with a 50% rate of morbidity and mortality, a prognosis found to be even poorer for fetal seizures [5, 6]. In the most recent review (2007), Usta et al. reported 22 cases, most resulted in death or stillbirth and were associated with fetal anomalies or neonatal abnormalities [8]. The few reported cases without
structural abnormalities or other risk factors that actually survived were subsequently diagnosed with benign familial seizures, motor delay, and/or mental delay [3, 6, 8]. In our case, outcomes were more optimistic in the first pregnancy and are pending but guarded in the second. Our case suggests that the prognosis for fetal seizures may not be uniformly poor.

Prospective maternal recognition of antepartum seizures was reported in a subgroup of the Western Australian Newborn Encephalopathy Study [3]. There were eight neonatal diagnoses of encephalopathy in the study that prompted chart review and retrospective identification of maternal report of fetal seizures in the antepartum period. In our case, the patient sought maternal fetal medicine and neonatology consultation during her second pregnancy because of fetal movement in one twin that was reminiscent of that in her previous pregnancy. Maternal awareness was consistent with diagnosis as seizures were noted at delivery and in the immediate neonatal period.

Fetal seizures can recur, particularly in the setting of consanguineous couples. Offspring of consanguineous unions are at increased risk for genetic syndromes, including seizure disorders, due to the presence of deleterious autosomal recessive genes inherited from a common ancestor or the inheritance of polygenic disorders. Several previous studies have shown that consanguinity may be an important risk factor for developing seizures, including prenatal, perinatal, and infantile epilepsy [1, 4, 9]. In the present case, two affected siblings were born to consanguineous parents, suggesting that autosomal recessive inheritance is likely. Epilepsy is sometimes the presenting feature of mitochondrial disease and could also be considered as an underlying etiology in this family. Mitochondrial disease can be caused by mutations in the mitochondria (maternal inheritance) or nuclear DNA (autosomal dominant or autosomal recessive inheritance). This case highlights the importance of family history evaluation and genetic counseling as the risk for recurrence for this couple is significant.

This case provides several salient teaching points. Fetal seizures may not carry a uniformly poor prognosis as previously described. Maternal awareness of fetal seizures alone may justify clinical investigation. There is a risk of recurrence with possible inherited transmission. This case is unique because, to date, there have been very few reports of apparent autosomal recessive neonatal seizure disorders, no reports of prenatal onset recessive seizure disorders, or maternal awareness of seizures in one of a set of twins [7]. Patients presenting with evidence of fetal seizures, including maternal account of seizure-like fetal activity, warrant consideration of attempts to further define prognosis with assessment for risk factors, referral for genetic counseling, and detailed anatomic survey.

References


The authors stated that there are no conflicts of interest regarding the publication of this article.