

Case Report

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Hypoplastic Left Heart Syndrome in a Patient with Fetal Hydantoin Syndrome

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Abstract

We report a patient with fetal hydantoin syndrome and hypoplastic left heart. Only three other cases with this association have been described. This case also highlights the importance genetic variation plays in the phenotypic variability of teratogens and the importance of good prenatal care to minimize risk of teratogenesis.

Keywords: Fetal hydantoin syndrome; Hypoplastic left heart syndrome; Dilantin embryopathy; Phenytoin embryopathy; Teratogen

Introduction

The association between antiepileptic drugs and congenital malformations in the offspring of women with epilepsy was first discussed in the late 1960s. The offspring have a two- to sevenfold increased risk for congenital malformations, a risk that is amplified as the number of pharmaceutical agents increase [1]. In 1975, Hanson and Smith identified the pattern of anomalies including craniofacial features, microcephaly, intellectual disability and hypoplasia of the distal phalanges in the offspring of women taking phenytoin and proposed the name “fetal hydantoin syndrome” (FHS) [2]. This report presents a patient with several classic features of fetal hydantoin syndrome but also with hypoplastic left heart (HLH). Congenital heart disease is seen less frequently with fetal hydantoin syndrome [3]. Hypoplastic left heart has previously been reported in only three other cases of fetal exposure to phenytoin [4-6].

Case Report

The patient is a fraternal twin male who was the result of the first pregnancy in a 20 year old mother with of epilepsy since 10 years of age. During the pregnancy, she was continued on oral antiepileptic therapy of lamotrigine 600 mg twice a day and phenytoin 200 mg in the morning and 400 mg in the evening. At 17 weeks the anatomy ultrasound scan revealed hypoplastic left heart in the male twin B (the subject of this case report). The mother was followed closely by maternal-fetal medicine, and she did not have any additional complications through the remainder of her pregnancy until premature delivery. The family history was negative for congenital heart disease or other congenital anomalies, and the parents were non-consanguineous.

The patient was born at 36 weeks gestation and transferred to our center for congenital heart disease repair. Birth weight, length and head circumference were appropriate for gestational age. He had borderline low set and posteriorly rotated ears, small nose with depressed nasal bridge, mild micrognathia, systolic murmur, hypoplastic nails, mild clinodactyly of the fifth fingers, digitalized

thumbs, a tendency to transverse palmar crease on both hands and long toes with absent toenails (Figures 1-3). Echocardiogram showed mitral and aortic atresia with a diminutive left ventricle and ascending aorta, consistent with hypoplastic left heart. The infant had a hybrid procedure done on day of life 9, subsequently experienced a complicated post-operative course and died on day of life 32.

The patient's twin sister had a similar phenotype including dysmorphic features with hypoplastic nails present on both the fingers and the toes but her cardiac anatomy was normal.

Both twins exhibited the characteristic dysmorphic features associated with in utero exposure to phenytoin. No genetic testing was performed.



Figure 1: Patient with fetal hydantoin syndrome.



Figure 2: Patient with hypoplastic nails.

Discussion

This patient had several classic features of fetal hydantoin syndrome but also had hypoplastic left heart. Although congenital heart disease is seen associated with fetal hydantoin syndrome, the most common reported defects include pulmonary or aortic valvular stenosis, coarctation of the aorta, patent ductus arteriosus, and septal defects, most commonly ventricular septal defects [7-9].

The genetic and teratogenic mechanisms for both hypoplastic left heart and fetal hydantoin syndrome remain unknown. There are several proposed theories for both, but none are universally accepted [10-13]. Animal studies have suggested that hypoxia followed by reperfusion result in production of reactive oxygen species (ROS) which can result in tissue damage [14], proposing the use of antioxidants in the management of pregnant women treated with phenytoin, however studies in pregnant rats do not support a beneficial effect of an antioxidant rich diet in preventing teratogenesis [15].

The risk of developing fetal hydantoin syndrome in an exposed fetus is about 10 percent. A “safe” dose below which there is no increased risk of teratogenicity has not been found, and no dose response curve has been demonstrated. Both twins exhibited features of fetal hydantoin syndrome, but the twin sister did not have congenital heart disease suggesting that individual genetic variation plays a role in the variability of the phenotype.

The presence of two different antiepileptic therapies was also unique to this case. Lamotrigine is considered one of the safest antiepileptic drugs for use during pregnancy, however the role of polytherapy in this association cannot be ruled out [16]. The International lamotrigine pregnancy registry published in 2007 identified 2 cases of HLH in pregnant women exposed to lamotrigine monotherapy [17].



Figure 3: Patient with absent toenails

The etiologies of fetal hydantoin syndrome and hypoplastic left heart syndrome are multifactorial, and there are many modifiers that may play a role in the pathogenesis of each. The possibility that the additional finding of hypoplastic left heart syndrome was related to some factor other than antiepileptic therapy cannot be excluded.

For pregnant women taking antiepileptic therapy, it is recommended to reduce the number and dosage of antiepileptic drugs as low as possible without losing seizure control, to adequately supplement with folic acid and to closely monitor with routine ultrasonography [1]. Early prenatal care and close adherence to standard recommendations aim to continue to reduce the incidence of congenital malformations associated with antiepileptic therapy.

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