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TWO SIBLINGS WITH FETAL HYDANTOIN SYNDROME*

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An association between anticonvulsant drugs taken during pregnancy and congenital abnormalities was first identified by Meadow et al. in 1968. Manson and Frederic clarified teratogenic effects of hydantoin in their epidemiological studies in 1973. Varied malformations due to hydantoin intake during pregnancy include digit and nail hypoplasia, growth retardation, typical facial appearance, rib anomalies, abnormal palmar creases, hirsutism, and low hairlines. Ambiguous genitalia is rarely associated with this syndrome. We present two siblings, aged three years and three months, with fetal hydantoin syndrome (FHS). Both were born to an epileptic mother who was given diphenylhydantoin (DPH) and phenobarbital throughout her pregnanies. The patients showed many characteristics of FHS, and ambiguous genitalia. Clinical and laboratory examinations revealed that both have normal female internal genital organs and female karyotypes. *Key words: hydantoin, phenobarbital, pregnancy, craniofacial dysmorphism, genital anomaly.*

The association between anticonvulsant drugs taken during pregnancy and an increased incidence of congenital defects has been documented for nearly four decades. Among these anticonvulsant drugs, phenytoin (DPH), carbamazepine, valproic acid, and various combinations of these three drugs have been proven to have the most potential teratogenic effects[1-4].

The characteristic features of in utero exposure to fetal hydantoin syndrome (FHS) include typical craniofacial anomalies, prenatal and/or postnatal growth deficiency, mental retardation and increased risk of major malformations[5-7]. The risk of congenital malformations for infants exposed to DPH during their fetal lives is about 40 percent[6-9]. The most frequent morphological abnormalities seen in these children are hypoplastic toes or fingernails, while genital abnormalities are relatively rare[5-7].

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Case Reports

The probands were the two siblings born to a 26-year-old woman with epilepsy whose medication included DPH (200 mg/d) and phenobarbital (100 mg/d) for eight years. The mother continued to take the same amount of medication throughout both pregnancies and did not have any seizures. There were no similar cases in the extended family other than the reported ones. The two siblings exhibited the same type of genital abnormality as well as the most common features of FHS.

Case 1

A four-year-old girl (the first child), with genital anomaly identified at birth, was referred to our hospital by a physician for corrective surgery. The delivery had been uncomplicated. At birth her weight was 2700 g and length was 48 cm. Moderate developmental delay was noted in early infancy: she sat at one year old and walked at 2.5 years old. She spoke only seven to eight words at the age of four.

On admission the patient's weight was 14.5 kg (10^{th}-25^{th} percentile), height 96 cm (25^{th} percentile), and head circumference 48 cm (10^{th} percentile). She had ocular hypertelorism; down-slanted palpebral fissures; a low anterior hairline; a broad, depressed nasal bridge; a short nose; long philtrum; broad alveolar ridge; short neck; low posterior hairline; and hirsutism (Fig. 1). Also noted were bilateral simian creases in both hands, broad first toes, and hypoplasia of the toenails, especially the last two toenails of both feet. Nipples were small and widely spaced. Genital examination showed fusion of the labia minora and a prominent clitoris (Fig. 2).

Fig. 1: Case 1. Note low anterior halirline, low and broad nasal bridge, long philtrum.

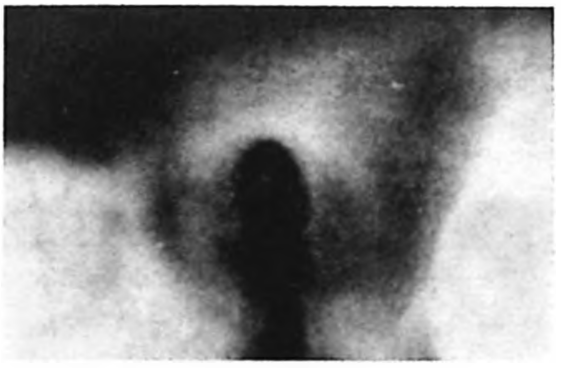

Fig. 2: Case 1, ambiguous genitalia with prominent clitoris and fused labia minora.

There was a single opening at the base of the clitoris. Laboratory tests revealed normal levels of hormones and blood electrolytes. On ultrasonographic examination, the uterus and two ovaries were detected. Cystoscopy showed urogenital sinus where the vagina and urethra opened, and a normal bladder. Roentgenograms revealed hypoplastic distal phalanges (Table I). Chromosomes were normal.

Table I: Clinical Features in Two Affected Siblings

Congenital Anomalies		Case 1	Case 2
Growth deficiency	Prenatal	+	–
	Postnatal	–	–
Developmental problems		+	+
Low anterior hairline		+	+
Low posterior hairline		+	+
Hypertelorism		+	+
Depressed nasal bridge		+	+
Short nose		+	+
Down-slanted palpebral fissures		+	+
Long philtrum		+	–
Broad alveolar ridge		+	–
Widely spaced nipples		+	+
Hypoplastic toenails		+	+
Hypoplastic fingernails		–	+
Broad first toe		+	+
Hypoplastic distal phalanges		+	+
Ambiguous genitalia		+	+

Case 2

A 7-month-old female, the sister of Case 1, was the product of the second pregnancy of the mother. Since, the etiology of the genital anomaly had not been recognized in the first child, the mother was unaware of the potential danger of DPH intake during pregnancy, and continued to take the medication throughout her second pregnancy. This delivery also was normal. Birth weight was 3000 g and length 50 cm. Ambiguous genitalia at birth was also identified in Case 2 and she was brought to hospital with her sister for correction of her genital anomaly.

On admission, her growth was at normal level with a weight of 7100 g (25^{th} percentile), height of 70 cm (50^{th} percentile), and a head circumference of 44 cm (75^{th} percentile). She could not sit without help. Physical examination revealed the same type of craniofacial and limb abnormalities as her sister's with the following exceptions: she had a bowed upper lip instead of the long

philtrum which was seen in Case 1, and the nail hyperplasia was more marked on her fingers (Figs. 3, 4). She also had the same type of genital abnormality (Fig. 5). Her laboratory tests and roentgenograms showed similar findings (Table I).

Fig. 3: Case 2, the sibling of Case 1. Note low anterior hairline, depressed and broad nasal bridge, bowed upper lip.

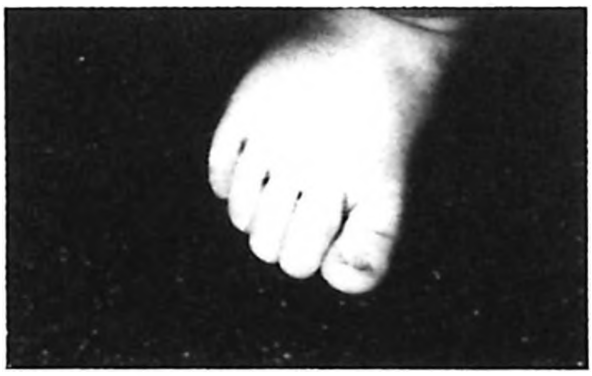

Fig. 4: Case 2, hypoplastic toenails.

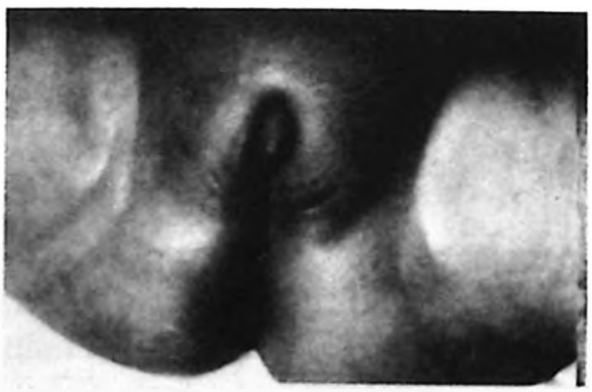

Fig. 5: Case 2, ambiguous genitalia with prominent clitoris and fused labia minora.

Discussion

The majority of minor morphological features seen in patients with FHS are not medically or cosmetically significant and tend to be overlooked unless a very thorough examination is made. Major defects recorded in the literature occur less frequently than minor defects. They include: cleft lip and/or palate, cardiovascular anomalies, renal defects, gastrointestinal anomalies and genital anomalies[9]. The alterations of growth and performance are as important as morphological anomalies in FHS, and are not commonly detected until later in childhood.

The patients presented here possess most of the characteristic features of FHS (Table I), and the genital anomalies which are rarely seen in the syndrome. Dyke et al.[6] recorded no patients with genital anomaly in their study of 62 families having at least two children exposed in utero to DPH. Hanson et al.[5] described only one patient with undescended testes among five patients showing FHS. In a series of 22 patients exposed in utero to DPH, one patient was recorded as having hypospadias[7].

Our cases had been investigated for adrenogenital syndrome before they were seen in our hospital. All laboratory tests for adrenogenital syndrome were found to be normal, as was expected.

Several hypotheses have been proposed to explain the DPH-induced teratogenesis. The most acceptable of these is that the toxic oxidative intermediary metabolites of DPH cannot be detoxified due to an enzyme deficiency in the metabolic pathway of DPH[10, 11]. Whether or not the toxic metabolites have an androgenic effect is not known. Since, all children born to mothers taking DPH during pregnancy do not show FHS, and the clinical findings of FHS differ from case to case, various enzymatic deficiencies may be responsible for causing the syndrome. Oxidative metabolites and their effects may differ in patients, depending on the molecular alterations in enzyme structure.

Unfortunately, the link between DPH intake during pregnancy and the anomalies found in Case 1 was not recognized before the conception of the second child, and genetic counseling was not given to the parents. Perhaps, if this link had been known by the family and doctors, DPH could have been changed to another anticonvulsant drug, or the family might have decided against having a second child.

Van Dyke et al.[6] studied 62 families with DPH exposure and found that, if the first child exposed to DPH in utero is affected, the risk for the second child will be much higher. Our cases support this finding and we would add that not only is the second child affected, but the abnormalities seen in the first child are replicated in the second child.

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