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DISCORDANT EXPRESSION OF FETAL HYDANTOIN SYNDROME IN HETEROPATERNAL DIZYGOTIC TWINS

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PRENATAL exposure to hydantoin analogues, including phenytoin, may result in the fetal hydantoin syndrome — a symptom complex characterized by poor growth and development with specific craniofacial and skeletal abnormalities.[1-4] The full syndrome is seen in about 11 per cent of exposed infants, and an additional 31 per cent have partial expression of the teratogenic effects.[1] The resulting dysmorphism is most striking at birth and generally becomes less pronounced with age, although the associated mental deficiency is permanent.[2]

Variability in the clinical manifestations of fetal hydantoin syndrome has been described in fraternal twins[3,4] and triplets[5] who were presumably exposed to the same maternal blood concentration of the drug over the same period, barring placental or vascular inequalities. In this report we describe the discordant expression of phenytoin embryopathy in heteropaternal female twins of different racial heritage, thus providing further evidence for genetic variation in fetal susceptibility to the teratogenic effects of the hydantoins.

CASE REPORT

The probands were four-year-old dizygotic twin girls born to a 21-year-old white epileptic woman (gravida II, para I) who had a family history of twinning and epilepsy (Fig. 1). The mother's seizures had begun at the age of five years; idiopathic epilepsy had been diagnosed, and treatment with phenytoin had been initiated when she was 13 years old. A review of obstetrical records revealed that she had taken 230 mg of phenytoin daily during both pregnancies, but the use of alcohol, tobacco, or other drugs was denied. Her height was 158 cm, her weight 53.7 kg, and her head circumference 52.7 cm. She had somewhat coarse facial features, acne, and mild hirsutism. Her hands and nails were normal.

The first pregnancy, which was complicated by preeclampsia and fetal distress during labor, culminated in the term birth of a 2543-g white boy by cesarean section, with Apgar scores of 8, 9, and 9 at one, three, and five minutes, respectively. He had hypospadias, which was later corrected surgically, and he grew poorly during infancy. At the age of three years he had a febrile seizure, but an electroencephalogram was entirely normal, and he has had no further convulsions. At six years his height was 111.5 cm (25th percentile), his weight 18.5 kg (25th percentile), and his head circumference 50.8 cm (just below the 50th percentile). His intellectual function was in the low-average to average range, and his physical examination was unremarkable.

The probands were born by cesarean section after a 38-week gestation complicated by toxemia. The mother had gained 18 kg, and one seizure had occurred during the third month of pregnancy. The first-born twin (Twin A) weighed 2495 g (above the 25th percentile[6]), was 47.0 cm long (just above the 25th percentile[7]), and had a head circumference of 31.5 cm (10th percentile[7]) and Apgar scores of 6, 7, and 8. She had curly black hair, a broad nose, and Negroid skin pigmentation. The co-twin (Twin B) weighed 2410 g (just above the 25th percentile[6]), was 43 cm long (below the 10th percentile[7]), and had a head circumference of 32.5 cm (just above the 10th percentile[7]) and Apgar scores of 6, 7, and 9. She had sparse brown hair and fair skin. The two separate placentas weighed 478.1 g and 384.1 g, respectively.

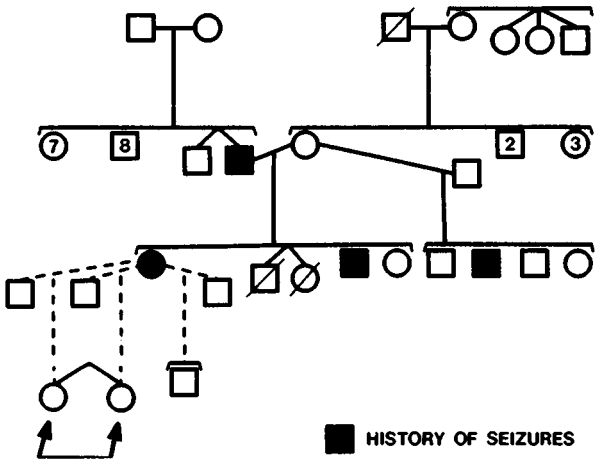

Figure 1. Pedigree of the Probands' Family, Showing Twinning in Four Generations and the Occurrence of Seizures in Their Mother, Two Maternal Uncles, and Their Maternal Grandfather. Broken lines indicate nonmarital relationships. Slashes through symbols indicate deaths. Figures enclosed in symbols denote numbers of unaffected relatives

At four years of age the twins were markedly dissimilar in complexion and physical appearance and were discordant for many features of the fetal hydantoin syndrome (Table 1). Twin A was 98.9 cm tall (below the 50th percentile), weighed 14.2 kg (10th percentile), and had a head circumference of 48.8 cm (below the 50th percentile). Her mother reported that the child had sat up at six months and walked by one year. Evaluation of her functional development with the Stanford–Binet Intelligence Scale, the Peabody Picture Test, and the Vineland Social Maturity Scale placed her intellectual performance within the low-normal range, with an overall IQ of 80. She had coarse black hair, dark skin, and Negroid facial features. Her fingernail and toenail development were normal, and the chest x-ray film was unremarkable.

Twin B had a height of 96.4 cm (below the 25th percentile), a weight of 14.7 kg (below the 25th percentile), and a head circumference of 48.5 cm (below the 50th percentile). Her height had followed the 10th percentile for three years but increased to the 25th percentile during the year before evaluation. She was hyperactive, with aggressive and destructive behavior. Her early development had lagged behind that of her co-twin: She had sat alone at one year, walked at 1½ years, and spoken at four years. Psychological evaluation revealed that her development was mildly retarded in intellectual functioning and delayed in social and self-help skills, with an estimated IQ of 66. She had no history of seizures, and the neurologic examination was normal in all other respects. The facial features were considered highly characteristic of fetal hydantoin syndrome (Table 1). The fingernails were somewhat small, and the nails of the fifth toes were hypoplastic. Chest x-ray studies revealed fusion of the first and second ribs on the left.

The mother acknowledged at the time of the twins' birth and later that they might have been fathered by separate men of different races. The results of genotypic analyses (Table 2) revealed that the twins differed in five of 14 blood groups and in their paternally derived HLA haplotype. An extension of the method of Maynard Smith and Penrose[8] for the diagnosis of twin zygosity was used to

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Table 1. Summary of the Clinical Features of the Fetal Hydantoin Syndrome and Their Presence (+) or Absence (−) in the Probands.

FEATURE	TWIN A	TWIN B
Poor growth	+	+
Mild mental retardation	−	+
Microcephaly	−	−
Brachycephaly	−	+
Metopic sutural ridging	−	+
Characteristic facial appearance	−	+
Mild hypertelorism	−	+
Ptosis	−	−
Epicanthal folds	−	−
Slanted palpebral fissures	−	+
Short nose	−	+
Broad, depressed nasal bridge	+	+
Low-set, abnormal ears	−	−
Broad alveolar ridge	−	+
Wide mouth with prominent lips	−	+
Cleft lip or palate	−	−
Small nails	−	+/−
Hypoplasia of distal phalanges	−	−
Digital thumb	−	−
Delayed bone age	−	−
Rib anomaly	−	+

estimate the likelihood that the twins were fathered by one man, as opposed to the probability that they had race-discordant fathers. On the basis of the blood typing, HLA results, and race-specific estimates of gene frequency among blacks and whites, the odds in favor of superfecundation by separate men of different races were estimated to be 160 to 1. Chromosomal studies of all four family members gave normal results, and dermatoglyphic analyses were uninformative.

DISCUSSION

There have been three previous reports of multiple births after pregnancies during which the mothers took antiepileptic drugs.[3-5] In 1973 Loughnan et al. observed characteristic digital anomalies in one member of a dizygotic twin pair exposed to phenytoin throughout gestation.[3] The co-twin reportedly had normal fingers, as determined both clinically and radiologically. In 1975 Hanson described a second dizygotic pair who had numerous manifestations of fetal hydantoin syndrome, although the concordance for specific defects was not documented.[4] Three years later, coincident fetal hydantoin syndrome was reported in triplets born to a mother who had taken phenytoin and phenobarbital during pregnancy.[5] The severity of the syndrome varied among the triplets, who were assumed to be trizygotic. To our knowledge, no examples of fetal hydantoin syndrome in monozygotic twins have been described.

Phenotypic discordances in twins after prenatal exposure to thalidomide,[9,10] ethanol,[11] and rubella[12] have previously been documented. A lack of concordance for malformations induced by teratogenic agents in dizygotic twins could indicate that fetuses may differ in their susceptibility to the embryopathic effects of teratogenic drugs. Alternatively, Lenz[13] has suggested that apparent variation in fetal sensitivity may be attributable to slightly different rates of organogenesis at the time of exposure — a reasonable hypothesis that could account for discordant expression in either monozygotic or dizygotic pairs. The possibility that genetic predisposition has a role in fetal susceptibility would imply that the variation in the expression of the trait should be greater in dizygotic twins than in monozygotic pairs and greater still in

Table 2. Results of Genotypic Analyses of the Twins and Their Mother.*

SYSTEM	MOTHER	TWIN A	TWIN B
HLA (A,B)	A11, Bw35/A1, B8	A11, Bw35/Aw30, Bw42	A11, Bw35/A2, Bw16
ABO	A	A	A
Rh	cDE/cde	cDe/cde	cDE/cDE
MNSs	Ms/Ms	MS/Ms	Ms/Ns
Kell	kk	kk	kk
Duffy	Fy^a/Fy^a	Fy^a/Fy^a	Fy^a/Fy^b
Kidd	+/−	−/−	+
Haptoglobin	2-2	2-2	2-2
Phosphoglucomutase	2-1	1-1	1-1
Acid phosphatase	B-B	B-B	A-B
Hemoglobin	A	A	A
Glucose-6-phosphate dehydrogenase	B	B	B
6-Phosphogluconate dehydrogenase	A	A	A
Catalase	N	N	N
Lactic dehydrogenase	N	N	N

*Symbols in columns refer to typing results and show that the twins differed in HLA, Rh, MNSs, Duffy, Kidd, and acid phosphatase systems.

heteropaternal dizygotic twins, such as the pair reported here. Despite their rarity, the contrast between heteropaternal and conventional dizygotic twins is of particular value because it is not subject to the biologic biases inherent in conventional comparisons of monozygotic and dizygotic twins.[14]

In our case, Twin B had many of the major characteristics of fetal hydantoin syndrome, including prenatal and postnatal growth deficiency, mental retardation, and a highly characteristic facial appearance. Microcephaly, although often found when mental deficiency is present, was not observed in this twin, whose head circumference was just below the 50th percentile. Although Twin A was small at birth, at the age of four she had no definite evidence of the syndrome. The brother of the twins had some characteristics of prenatal exposure to phenytoin, including mild mental deficiency and hypospadias, but these findings were considered insufficient to permit an unequivocal diagnosis of fetal hydantoin syndrome.

Superfecundation refers to the separate fertilization of multiple ova, released during the same estrous cycle, by sperm from different coitions. In some lower animals superfecundation is a frequent occurrence,[15] and James[16] has suggested that it may also be relatively common in human beings. By leading to the birth of dizygotic twin pairs with slightly different gestational ages, superfecundation may contribute to differences between the birth weights of dizygotic twins. However, superfecundation can be confirmed only in cases involving multiple paternity, and it is seldom suspected in the absence of obvious racial differences between the fathers of the twins. Despite these facts, multiple paternity has been reported in at least 19 pairs of twins and one set of triplets.[17-25] Of these, 11 pairs have involved racially different fathers. When the fathers are available for study, heteropaternity can be proved by blood-marker studies, regardless of the fathers' race. Our case shows that even when the fathers cannot be tested, heteropaternity can be inferred with high probability if the putative fathers come from ethnic groups with different marker-gene frequencies.

Although dizygotic twins are normally assumed to be as similar genetically as ordinary siblings, the members of this set have just one parent in common and are thus related as half siblings. The discordant expression of the fetal hydantoin syndrome in this pair of heteropaternal twins provides further evidence that the genetic sensitivity of the fetus is a relevant factor in the embryopathic effects of hydantoins.

References

1. Hanson JW, Myrianthopoulos NC, Harvey MAS, Smith DW. Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. J Pediatr. 1976; 89:662-8.
2. Smith DW. Recognizable patterns of human malformation: genetic, embryologic, and clinical aspects. Philadelphia: WB Saunders, 1976:346-7.
3. Loughnan PM, Gold H, Vance JC. Phenytoin teratogenicity in man. Lancet. 1973; 1:70-2.
4. Hanson JW, Smith DW. The fetal hydantoin syndrome. J Pediatr. 1975; 87:285-90.
5. Bustamante SA, Stumpff LC. Fetal hydantoin syndrome in triplets: a unique experiment of nature. Am J Dis Child. 1978; 132:978-9.
6. Naeye RL, Benirschke K, Hagstrom JWC, Marcus CC. Intrauterine growth of twins as estimated from liveborn birth-weight data. Pediatrics. 1966; 37:409-16.
7. Lubchenco LO, Hansman C, Boyd E. Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. Pediatrics. 1966; 37:403-8.
8. Maynard Smith S, Penrose LS. Monozygotic and dizygotic twin diagnosis. Ann Hum Genet. 1954-55; 19:273-89.
9. Mellin GW, Katzenstein M. The saga of thalidomide: neuropathy to embryopathy, with case reports of congenital anomalies. N Engl J Med. 1962; 267:1238-44.
10. Schmidt M, Salzano FM. Dissimilar effects of thalidomide in dizygotic twins. Acta Genet Med Gemellol (Roma). 1980; 29:295-7.
11. Christoffel KK, Salafsky I. Fetal alcohol syndrome in dizygotic twins. J Pediatr. 1975; 87:963-7.
12. Nance WE. The use of twins in clinical research. Birth Defects. 1977; 13(6): 19-44.
13. Lenz W. Malformations caused by drugs in pregnancy. Am J Dis Child. 1966; 112:99-106.
14. Nance WE. The role of twin studies in human quantitative genetics. Prog Med Genet. 1979; 3:73-107.
15. Hanken J, Sherman PW. Multiple paternity in Belding's ground squirrel litters. Science. 1981; 212:351-3.
16. James WH. Gestational age in twins. Arch Dis Child. 1980; 55:281-4.
17. Archer J. Facts illustrating a disease peculiar to the female children of Negro slaves. Med Reposit. 1810; 13:319-23.
18. Radasch HE. Superfoetation or superfecundation? Surg Gynecol Obstet. 1921; 32:339-52.
19. von Kries L, Gallasch EH. Ein Fall von Bipaternitat bei Zwillingen. Anthropol Anz. 1967; 30:1-19.
20. Conflicting blood-tests on twins. Br Med J. 1971; 1:183.
21. Sorgo G. Das Problem der Superfoecundatio im Vaterschafsgutachten. Beitr Gerichtl Med. 1973; 30:415-21.
22. Terasaki PI, Gjertson D, Bernoco D, Perdue S, Mickey MR, Bond J. Twins with two different fathers identified by HLA. N Engl J Med. 1978; 299:590-2.
23. Shearer L. Sex sensation. In: Parade Magazine. 1978, September 10.
24. Spielmann W, Kühnl P. The efficacy of modern blood group genetics with regard to a case of probable superfecundation. Haematologia. 1980; 13:75-85.
25. Harris D. J Reprod Med. 1982; 27:39.