Fetal alcohol syndrome in dizygotic twins

A pair of fraternal twins with stigmata of the fetal alcohol syndrome are described. Apparently differences in susceptibility to the dysmorphogenic influence of ethanol caused one twin to be more severely affected than the other one. Both infants are growing poorly postnatally, and both are at risk for retarded development. Any evidence of the fetal alcohol syndrome, however subtle, should be considered a warning of possible future developmental delay.

Katherine K. Christoffel, M.D., and Ira Salafsky, M.D.,* *Evanston, Ill.*

THE ABNORMALITIES that characterize some of the offspring of alcoholic mothers have been well described and are considered to constitute the fetal alcohol syndrome.[1, 2] The syndrome includes prenatal and postnatal growth deficiency, developmental delay, microcephaly, and short palpebral fissures as its most consistent components. Other anomalies less consistently found include maxillary hypoplasia, joint anomalies, abnormal palmar creases, cardiac anomalies, hemangiomata, and abnormal external genitals.[1-3] It is sobering that in one study 44% of affected infants were retarded at 7 years of age.[4]

We are reporting nonidentical male twins born to an alcoholic mother; one twin was severely affected at birth with the stigmata of the fetal alcohol syndrome while the other was only minimally affected. The minimally affected infant undoubtedly would not have been recognized in the neonatal period if his twin had not been more severely affected.

CASE REPORT

The twin boys are the product of a 32-week gestation in a 30-year-old A positive, gravida 4, para 3 mother who admits to consuming at least one quart of red wine and an unspecified amount of hard liquor daily throughout pregnancy. During the pregnancy the mother had pedal edema and was treated with hydrochlorthiazide, 125 mg daily, for one month prior to delivery. She also received iron, vitamins, and secobarbital. The pregnancy was otherwise unremarkable. A Kahn test was negative at five months' gestation and again just after delivery. The mother arrived in the delivery corridor imbibing alcohol. She delivered twins, as described below. The placenta was characterized by dichorionic diamniotic twinning. Twin A is blood type A, and twin B is blood type B, establishing dizygotic twinning.

Twin A (Figs. 1 and 2), was born by cephalic presentation with Apgar scores of 7 and 8 at one and five minutes, respectively. He weighed 1,048 gm at birth, which is less than the tenth percentile for twins or singletons at 32 weeks[5, 6]. Head circumference was 27.5 cm, at the tenth percentile for 32 weeks' gestation, and length was 36.5 cm, less than the tenth percentile for 32 weeks' gestation. Physical examination revealed a jittery infant whose development was consistent with 32 weeks' gestation. Repeated examinations over the next month of hospitalization revealed the following morphologic abnormalities: dolichocephaly, prominent occiput, narrow palpebral fissures, anteverted nostrils, hypoplastic nasal bridge, a carp-shaped mouth with a narrow upper lip, low-set posteriorly rotated ears, hypoplastic nipples, a simian crease on the right with a bridged simian crease on the left, a small umbilical hernia, testes in the inguinal canals, a narrow pelvis, marked increase in motor tone with frequent opisthotonic posturing, hemangiomata on the face and abdomen, and a heart murmur. Hospitalization was marked by jitteriness in the first several days of life despite normal calcium and glucose determinations. He developed a systolic murmur in the first week of life consistent with peripheral pulmonic stenosis. Prolonged hyperbilirubinemia occurred with persistence of a high direct fraction for three weeks with no evidence of hepatocellular disease (SGOT 19, SGPT 9 IU, with direct bilirubins of between 2 and 3 mg/dl). He gained weight slowly despite adequate caloric intake of 120 to 175 calories per kilogram on all but a few days (Fig. 3). Analysis of maternal and infant sera revealed: the infant's IgM was 10 mg/dl; the mother's serum was negative for

From the Department of Pediatrics, Northwestern University School of Medicine, and Genetic Service, Department of Pediatrics, Evanston Hospital.

**Reprint address: Genetic Service, Evanston Hospital, 2650 Ridge Ave., Evanston, Ill. 60201.*

Fig. 1. Picture of twin A illustrating some of the features of the fetal alcohol syndrome including hemangioma, anteverted nostrils, and carp-shaped mouth.

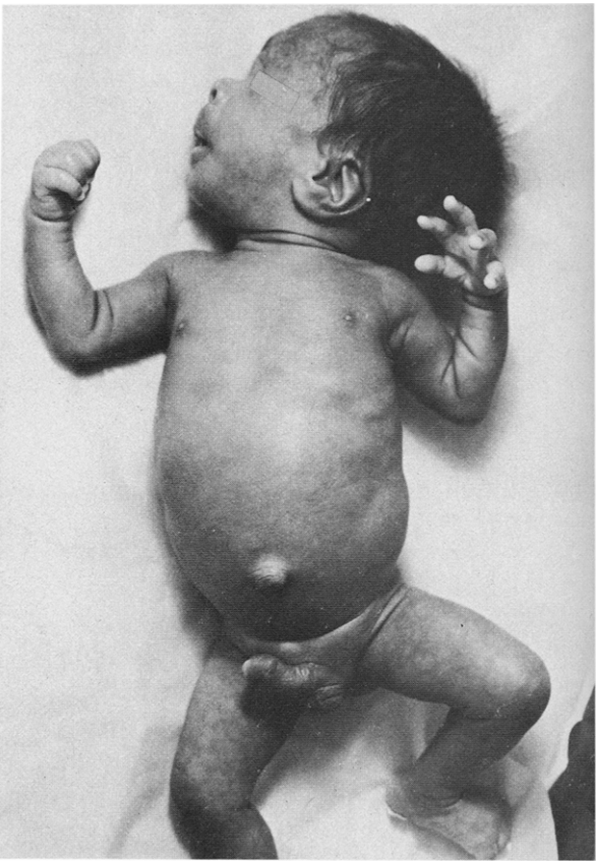

Fig. 2. Lateral view of twin A illustrating prominent occiput, hypoplastic nasal bridge, low-set ears, and narrow pelvis.

Australia antigen; maternal and infant sera were negative for toxoplasmosis antibody; the maternal rubella antibody titer was 1:40 with the infant's titer 1:10. The infant's urine contained no cytomegalovirus on viral culture or inclusion bodies on cytologic examination, and the infant's serum was negative for cytomegalovirus antibody. A chromosome analysis revealed a normal 46 XY karyotype. The baby was hospitalized for one month, and since discharge has continued to grow poorly (Figs. 3 and 4). Bilateral inguinal hernias were noted at 2½ months. On examination at 7 months he smiled, responded to voices, had good head control, and grasped a rattle, but would not sit unsupported. Denver developmental exam at 7 months was consistent with a developmental level of about 5 months.

Twin B (Figs. 5 and 6) was delivered by breech presentation 16 minutes after twin A with the cord wrapped twice around his leg and shoulders. The amniotic fluid was meconium stained. Resuscitation included endotracheal intubation. The Apgar scores were 5 and 7 at one and five minutes, respectively. He weighed 1,540 gm, which is at the thirtieth percentile for his estimated 32 weeks' gestation. Head circumference was 30.5 cm, at the sixtieth percentile for 32 weeks' gestation, and his length was 38.5 cm, at the fifteenth percentile for 32 weeks' gestation. He was extubated shortly after arrival in the intensive care nursery, and after a period of respiratory distress lasting about one hour was comfortable in room air. His physical examination was consistent with 32 weeks' gestation. Examination during hospitalization revealed the following abnormalities: dolichocephaly, a prominent occiput, narrow palpebral fissures, anteverted nostrils, a hypoplastic nasal bridge, a carp-shaped mouth with a narrow upper lip, borderline low-set ears, hypoplastic nipples, a small umbilical hernia, a heart murmur, and somewhat increased motor tone. During his hospitalization some jitteriness was observed in the first few days of life which resolved during treatment for hypocalcemia. He had transient mild hyperbilirubinemia, with the highest direct value 1.2 mg/dl. He was treated with phototherapy for one day. During the second week of life a heart murmur characteristic of peripheral pulmonic stenosis was noted. In the fourth week of life a small umbilical hernia became apparent. In the hospital he ate well and gained weight quickly (Fig. 3). He had a normal 46 XY karyotype. Growth since discharge from the hospital has been poor and at 7 months length and weight are below the third percentile (Figs. 3 and 4). Bilateral inguinal hernias were repaired at two months. On examination at 7 months of age he smiled, rolled over in both directions, grasped a rattle, demonstrated good head control, and turned to the sound of a voice, but could not sit unsupported. Denver developmental exam at 7 months was consistent with about 5 months development.

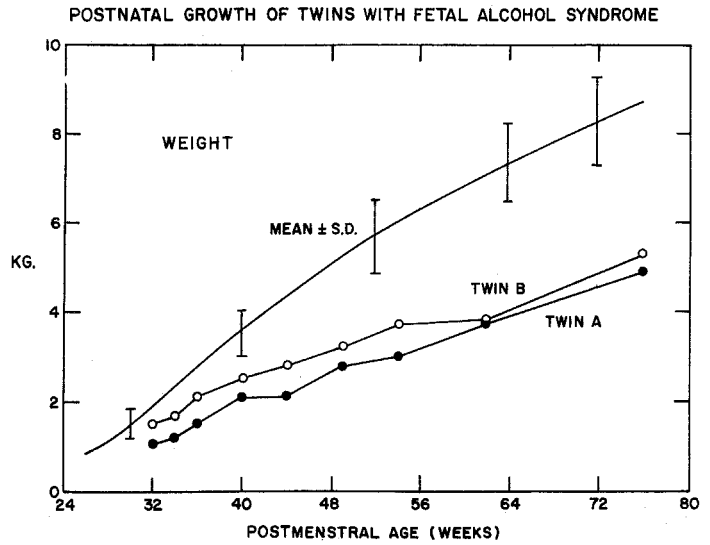

Fig. 3. Chart of the postnatal weight gain of twins A and B illustrating the slow gain in weight. The chart is adapted from data of Babson.[7]

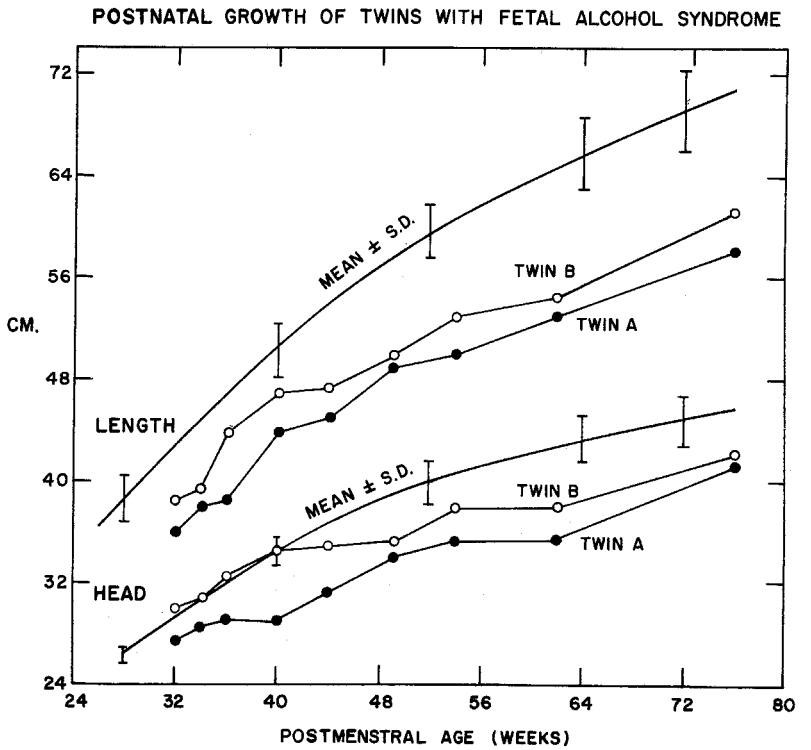

Fig. 4. Chart of postnatal growth and increment in head circumference of twins A and B. The chart is adapted from data of Babson.[7]

DISCUSSION

The dizygotic twins reported here are phenotypically consistent with the fetal alcohol syndrome[1-3] (Table I), as are their transient abnormalities of bilirubin metabolism and their jitteriness.[2] The more severely affected twin, twin A, was abnormally small at birth when compared to singleton or twin intrauterine growth charts. The larger-twin-to-small-twin-birth-weight ratio is abnormally large for dichorionic twins (1.42 as opposed to the expected 1.18 at 32 weeks' gestation[6]). These deviations from normal

Fig. 5. Picture of twin B illustrating some of the features of the fetal alcohol syndrome including anteverted nostrils, carp-shaped mouth, and hypoplastic nipples.

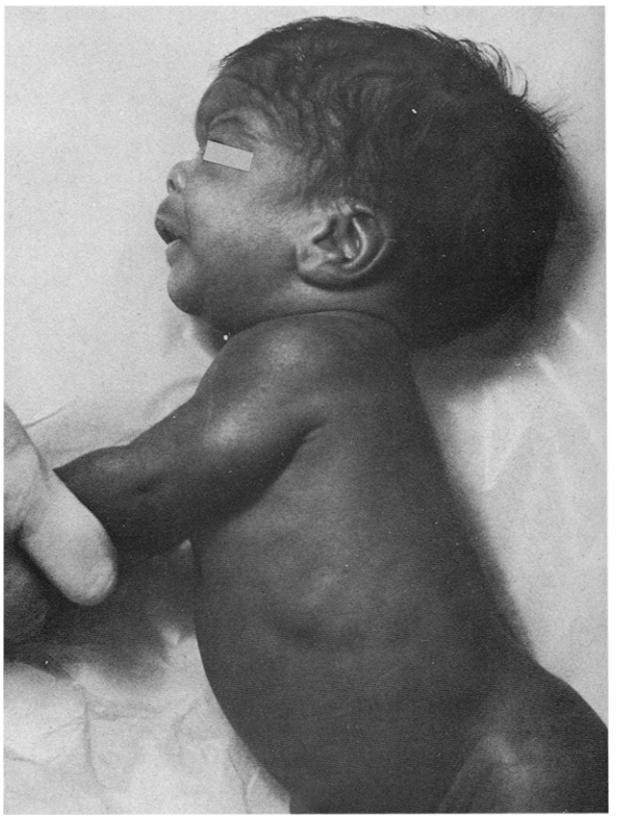

Fig. 6. Lateral view of twin B illustrating hypoplastic nasal bridge and low-set posteriorly rotated ears.

values for dichorionic twins suggest that the twinning alone is not responsible for the abnormalities noted, nor for the discordance of these abnormalities. We therefore speculate that the two fetuses had different susceptibilities to the same dysmorphogenic influence of ethanol in utero.

Discordance of anomalies between dizygotic twins needs little explanation, except when the anomalies are teratogenically induced. In this case a difference in susceptibility to the teratogen must be explained. Several reports of dizygotic twins with discordant teratogenically induced anomalies have appeared in the literature: one of a phenytoin-induced bony abnormality in one twin only,[8] another of only one twin affected by thalidomide,[9] and another of twins exposed to thalidomide and differently affected.[10]

The discordance of thalidomide-induced anomalies has led to the hypothesis that slightly different rates of organogenesis make different fetuses susceptible to teratogenesis at different times.[9] Fogel and associates[11] have proposed possible mechanisms for discordant anomalies in monozygotic twins including discordance of placental and fetal vasculature with resultant discordance of developmental rates and of developmental vascular catastrophes. Such vascular mechanisms could apply equally well to the discordant development of dizygotic twins.

Some work has been done on the specific toxicology and teratogenicity of ethanol in the fetus, stressing the immaturity of the alcohol dehydrogenase system in the fetal and infant liver and the consequent slow fall in neonatal blood ethanol levels when fetuses are exposed acutely in utero,[12] the existence of abnormal brain development in offspring of chronic alcoholic guinea pigs,[13] and the existence of the fetal alcohol syndrome in chronically exposed human fetuses.[1, 2] The mechanisms underlying this difference in susceptibility could involve different rates of organogenesis, different rates of ethanol degradation, and/or differences in placental vasculature.

Palmer and associates[3] have reported their observation of twin girls affected with the fetal alcohol syndrome. They are monozygotic twins because they share a single placenta and umbilical artery. These twins are very close in the degree and detail of their abnormalities, but are not identical: their palmar creases are not identical; only one has a unilateral ptosis; only one has a rudimentary

Table I. Characteristics of fetal alcohol syndrome

	Palmer's series	*Jones' series*	*Twin A*	*Twin B*
Prenatal growth deficiency	3/3*	11/11	+	–
Short palpebral fissures	3/3	11/11	+	+
Postnatal growth deficiency	3/3	10/11	+	+
Developmental delay	3/3	10/11	±	±
Microcephaly	3/3	10/11	+	+
Poor fine motor function	3/3	9/11	Too early to evaluate	
Altered palmar creases	3/3	8/11	+	–
Joint anomalies	?1/3†	8/11	–	–
Maxillary hypoplasia	?2/3†	7/11	–	–
Cardiac anomalies	?1/3†	7/11	+	+
Anomalous external genitals	3/3	4/11	–	–
Capillary hemangiomata	1/3	4/11	+	–
Epicanthal folds	0/3	4/11	–	–
Phalangeal anomalies	1/3	4/11	–	–
Micrognathia	0/3	3/11	–	–
Cleft palate	0/2	2/11	–	–
Accessory nipple	1/3	1/11	–	–
Asymmetric ptosis	1/3	1/11	–	–
Single umbilical artery	2/3	1/11	–	–
Strabismus or myopia	1/3	2/8	Not at 7 months	
Carp-shaped mouth	NA‡	?+§	+	+
Hypoplastic nasal bridge	NA‡	?+§	+	+
Anteverted nostrils	NA‡	?+§	+	+

*Number of affected/total number in series.
†Question mark as noted in Palmer's article.[3]
‡NA: information not available.
§Trait noted in photographs in Jones' article.[2]

accessory nipple; and only one has bilaterally shortened fifth digits.

Differences in fetal susceptibility to ethanol dysmorphogenesis and consequent variations in degree of abnormalities found in the fetal alcohol syndrome may be of some clinical importance: the findings in some cases may be so subtle that they are easily overlooked. We, for example, would not have detected twin B had it not been for twin A's more severe affliction. Since Jones and Smith[2] have reported brain anomalies in one affected child who died and developmental delay in a large proportion of affected infants,[4] we must conclude that the development of children with the fetal alcohol syndrome must be followed unusually closely. This is important so that appropriate educational and remedial action can be instituted early to minimize the difficulties posed by these children in homes already disordered by alcoholism.

Offspring of alcoholic mothers should be carefully examined for stigmata of the fetal alcohol syndrome, and even the presence of a few stigmata should be considered a warning of future developmental delay.

The authors thank Dr. John M. Reichert for referring these patients, Mrs. Verena Salafsky for drawing the graphs, Mr. Christopher DeMuth for taking the photographs, and Mrs. Chrisy Banakis for secretarial assistance.

REFERENCES

1. Jones KL, Smith DW, Ulleland CN, and Streissguth AP: Patterns of malformation in offspring of chronic alcoholic mothers, Lancet **1**:1267, 1973.
2. Jones KL, and Smith DW: Recognition of the fetal alcohol syndrome in early infancy, Lancet **2**:999, 1973.
3. Palmer RH, Ouellette EM, Warner L, and Leichtman SR: Congenital malformations in offspring of a chronic alcoholic mother, Pediatrics **53**:490, 1974.
4. Jones KL, Smith DW, Streissguth AP, and Myrianthopoulos NC: Incidence of the fetal alcohol syndrome in offspring of chronically alcoholic women, Pediatr Res **8**:440/166, 1974 (abstr).
5. Gruenwald P: Environmental influences on twins apparent at birth, Biol Neonate **15**:79, 1970.
6. Naeye RL, Benirschke K, Hagstrom JWC, and Marcus CC: Intrauterine growth of twins as estimated from liveborn birthweight data, Pediatrics **37**:409, 1966.
7. Babson SG. Growth of low-birth-weight infants, J PEDIATR **77**:11, 1970.
8. Loughnan PM, Gold H, and Vance JC: Phenytoin teratogenicity in man, Lancet **1**:70, 1973.
9. Lenz W: Malformations caused by drugs in pregnancy, Am J Dis Child **112**:99, 1966.
10. Mellin GW, and Katzenstein M: The saga of thalidomide, N Engl J Med **267**:1184, 1238, 1962.
11. Fogel BJ, Nitowsky HM, and Gruenwald P: Discordant abnormalities in monozygotic twins, J PEDIATR **66**:64, 1965.
12. Seppala M, Raiha NCR, and Tamminen V: Ethanol elimination in a mother and her premature twins, Lancet **1**:1188, 1971.
13. Papara-Nicholson D, and Telford IR: Effects of alcohol on reproduction and fetal development in the guinea pig, Anat Rec **127**:438, 1957 (abstr)