RECOGNITION OF THE FETAL ALCOHOL SYNDROME IN EARLY INFANCY

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Summary Historical reports indicate that the observation of an adverse effect on the fetus of chronic maternal alcoholism is not new. Three additional cases of the fetal alcohol syndrome have been recognised in two newborn infants and a 7-month-old baby. The immutable nature of the prenatal-onset growth deficiency was further confirmed. The first necropsy performed on a patient with fetal alcohol syndrome disclosed serious dysmorphogenesis of the brain, which may be responsible for some of the functional abnormalities and the joint malposition seen in this syndrome.

Introduction

A PATTERN of altered growth and morphogenesis has lately been described in eight offspring of chronic alcoholic mothers.[1] We call this disorder the "fetal alcohol syndrome". The purpose of this report is to draw attention to historical evidence which indicates that the observation of fetal malformation associated with maternal alcoholism is not new and to describe three additional cases of the fetal alcohol syndrome, with special reference to recognition of this syndrome in the newborn baby. The main abnormalities of these three new cases and the original eight are summarised in the accompanying table.

ABNORMALITIES IN THE THREE PATIENTS IN THE PRESENT STUDY PLUS THE PREVIOUS EIGHT PATIENTS WITH THE FETAL ALCOHOL SYNDROME

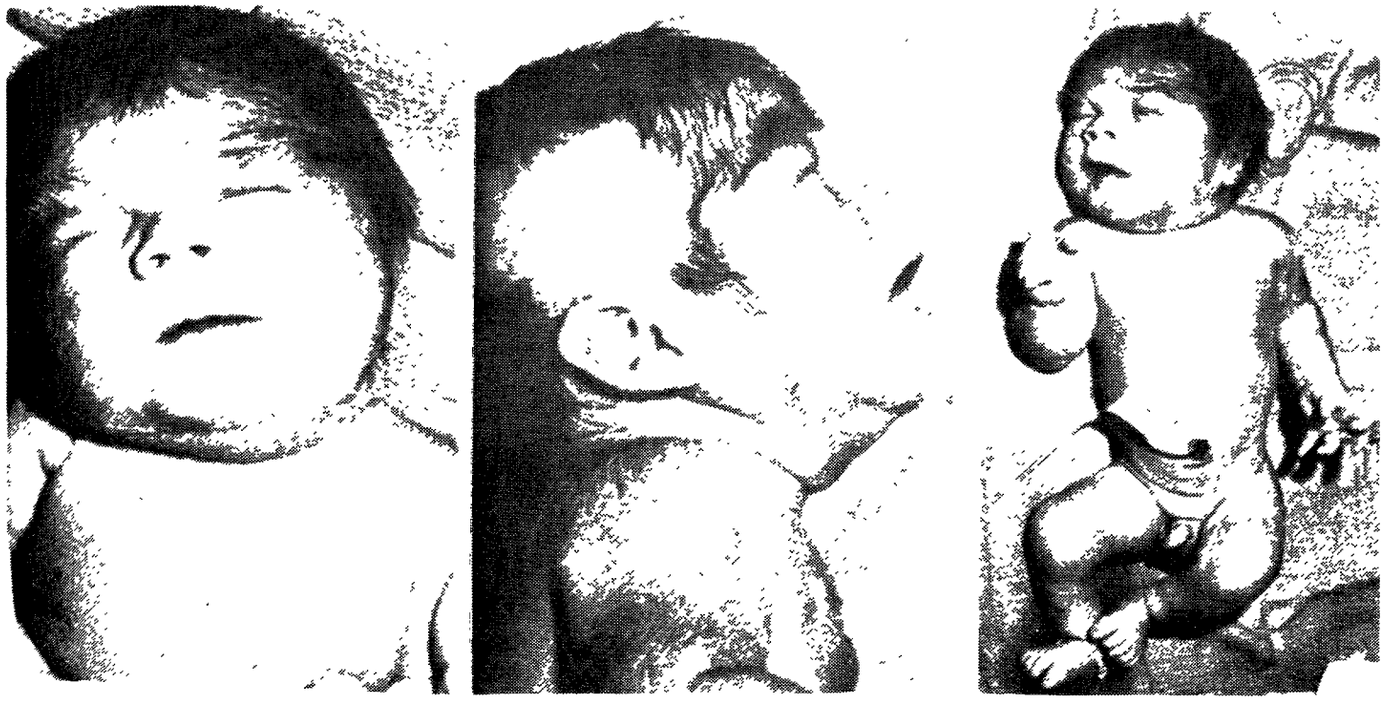
Abnormality	No. affected
Performance :	
Prenatal growth deficiency	11
Postnatal growth deficiency*	10
Developmental delay*	10
Craniofacies :	
Microcephaly	10
Short palpebral fissures	11
Epicanthal folds	4
Maxillary hypoplasia	7
Cleft palate	2
Micrognathia	3
Limbs :	
Joint anomalies	8
Altered palmar crease pattern	8
Other :	
Cardiac anomalies	7
Anomalous external genitalia	4
Capillary hæmangiomata	4
Fine-motor function	9

The number of patients with each abnormality includes only those patients for whom a definite decision could be made. Joint anomalies consist of limitation of motion at elbow, interphalangeal and metacarpal-phalangeal joints, and/or hip dislocation. Fine-motor dysfunction consists of tremulousness, weak grasp, and/or poor eye/hand coordination.

* Not assessed in patient 2, who died 5 days after birth.

Historical Review

An association between maternal alcoholism and faulty development of the offspring is alluded to in early Greek and Roman mythology. In Carthage, the bridal couple was forbidden to drink wine on their wedding night in order that defective children might not be conceived.[2] In 1834 a report to the House of Commons by a select committee investigating drunkenness indicated that infants born to alcoholic mothers sometimes had "a starved, shrivelled and imperfect look".[3] In 1900, Sullivan reported increased abortion and stillbirth rates among chronic alcoholic women and an increased frequency of epilepsy in their surviving offspring.[4] Since then,



Patient 1 at 1 day of age.

Note short palpebral fissures and hirsutism.

sporadic clinical reports have appeared suggesting an association between maternal alcoholism and serious abnormalities in the offspring.[5–8]

The effects of ethanol on early morphogenesis in laboratory animals, reviewed by St. Sandor of Rumania,[9] are variable. St. Sandor demonstrated ethanol-induced dysmorphogenesis in chick as well as albino-rat embryos.[9–11] In the developing chick, deformed brain vesicles and spinal cord, abnormal development of somites, and retardation of general growth and stage of morphogenesis were noted.[9–10] Extrapolating from these animal studies, he warned in 1968 and again in 1971 that there is "a serious danger signal of prenatal risk of ethanol intoxication during early pregnancy in humans".[11]

Case-reports

Patient 1

A newborn American Indian male (see accompanying figure) was ascertained because his 30-year-old mother was a chronic alcoholic. His mother had been an alcoholic for six years before his birth, during this time she also had three first-trimester spontaneous abortions. Her seven other children, all born before she became chronically alcoholic, are living in foster homes and are reported to be of average stature and intelligence. She had cirrhosis and nutritional anæmia, had experienced delirium tremens, and had been admitted to hospital twice with upper-gastrointestinal-tract bleeding secondary to alcoholic gastritis. She drank about two quarts of red wine daily throughout this pregnancy, and her nutritional intake seemed inadequate by history. At the end of the first trimester, she was admitted to hospital with diphtheria and treated with benzathine penicillin, diphtheria antitoxin, and erythromycin. Maternal weight-gain during pregnancy totalled 15 lb. Shortly after delivery, her nutritional status was assessed. Iron deficiency was indicated by a packed-cell volume of 25%, a serum-iron of 52 μg. per 100 ml., a total iron-binding capacity of 500 μg. per 100 ml., and a percentage iron saturation of 10%. Other studies of nutritional status were normal, including serum vitamin A, vitamin C, folic acid, and total protein and albumin. Delivery was from a breech presentation after a 38-week gestation, during which there was limited fetal activity. Endotracheal intubation was performed shortly after birth, because of a 1-minute Apgar score of 1 that rose to 6 after 5 minutes. The attending physician noted "alcohol on his breath". Birth-weight was 2020 g. (50th percentile for 34 weeks' gestation), birth length was 43 cm. (50th percentile for 32·5 weeks' gestation), and head circumference was 29 cm. (below the 3rd percentile).

There was pronounced hirsutism, especially over the forehead. The eyes were small and the palpebral fissures measured 1·1 cm. on the right and 1·2 cm. on the left eye. A grade 2 out of 6 systolic murmur was thought to represent a ventricular septal defect. There was a left congenital hip dislocation and bilateral simian creases. The immediate neonatal period was complicated by the following problems: mild respiratory distress lasting 5 days and requiring 40% ambient oxygen concentration, transient hypoglycæmia in the first 24 hours, and unexplained hypocalcæmia and hyperbilirubinæmia in the second 24 hours. Tremulousness, noted soon after birth, was initially thought to be secondary to alcoholic withdrawal but did not respond to sedation with phenobarbitone and was still present at 4 weeks of age. The infant also had a weak suck. He was discharged to a foster home. Despite an intake of 140 calories per kg., most by nasogastric tube, he gained only 410 g. in the first 4 weeks, at which time his length was 43 cm. and head circumference 31 cm.

Patient 2

A newborn American Indian female was ascertained because her 40-year-old mother had been a chronic alcoholic for an unknown time. Although no complications of alcoholism had been recorded, the mother had a blood-alcohol level of 157 mg. per 100 ml. during an afternoon clinic visit at which she was not obviously drunk. Maternal weight-gain during pregnancy was 11 lb. Delivery at 32 weeks' gestation was from vertex presentation. Apgar score was 5 and rose to 8 at 5 minutes. Birth-weight was 1300 g. (50th percentile for 30 weeks' gestation), birth length was 38·5 cm. (50th percentile for 29 weeks' gestation), and head circumference was 27 cm. She was unusually hirsute, especially over the forehead. She had obvious microphthalmia. There was a cleft of the soft palate. The superior helices of both ears were incompletely developed. The following joint anomalies were present: overlapping of the third fingers over the second fingers; clinodactyly of the left fifth finger; and camptodactyly of the right third finger, with absence of the distal interphalangeal crease. There was a harsh systolic murmur along the left sternal border. The vagina was biseptate. There were only 2 vessels in the umbilical cord. Cyanosis developed at 5 hours of age and multiple apnœic episodes culminated in death at 5 days of age. Necropsy revealed a membranous ventricular septal defect and areas of focal pulmonary atelectasis. The brain weighed only 140 g. Histological examination disclosed extensive developmental anomalies, including aberration of neuronal migration resulting in multiple heterotopias. The anterior superior gyri were fused through infiltration by leptomeningeal hamartomata of glial and neuronal cells. The cerebral cortex was incompletely developed, as shown by relative agyria (lissencephalia) and large lateral ventricles, and there was agenesis of the corpus callosum.

Patient 3

A 7-month-old American Indian female was retrospectively ascertained because her pattern of malformation was that of the fetal alcohol syndrome. Her mother, who was deemed to be a severe alcoholic, was treated in hospital before pregnancy for complications of chronic alcoholism and again 3 weeks post partum for severe alcoholic neuropathy. Gestational timing is unknown. Birth-weight was 964 g. When evaluated at 7 months of age, she weighed only 2260 g. and was 46 cm. long (both measurements are at the 50th percentile for 35 weeks' gestation). She had short palpebral fissures. There was a cleft of the soft palate. A grade 3 out of 6 systolic murmur was thought to be secondary to a ventricular septal defect. The hips abducted poorly, and there was limitation of complete extension at both elbows. The labia majora were hypoplastic. There was a 1×1 cm. capillary hæmangioma on the back. She was hypertonic and exhibited increased motor activity when disturbed, but otherwise there was little spontaneous activity. At 7 months her developmental age was estimated to be at a 2–3 month level.

Her maternal step-brother was evaluated elsewhere by Dr John Opitz and was also judged to have the fetal alcohol syndrome. He was the product of a 32-week pregnancy complicated by maternal gastrointestinal hæmorrhage at 26 weeks' gestation due to chronic severe alcoholism. Delivery was by cæsarean section because of transverse lie. Birth-weight was 1530 g. At 7 weeks of age he was 44 cm. long, weighed 2693 g., and had a head circumference of 29 cm. There was a submucous cleft palate. He had a left simian crease. There was a grade 3 out of 6 systolic murmur. Prominent glabellar

and occipital capillary hæmangiomata were present. Neurological examination revealed decorticate rigidity, hyperacusia, and myoclonic jerk-like seizures.

Chromosome studies were carried out on all three patients evaluated by us and disclosed no abnormality.

Discussion

The pattern of altered growth and morphogenesis in the two newborn babies we describe is strikingly similar to that of the previously reported children with the fetal alcohol syndrome. Pertinent additional findings include the following: both newborn infants had serious problems of respiratory adaptation, and one of them had problems with biochemical adaptation, as shown by hypoglycæmia, hypocalcæmia, and hyperbilirubinæmia. The observation of mild microphthalmia in both newborn babies tends to accord with the suggestion that the consistently short palpebral fissures in this syndrome are secondary to reduced ocular growth.

All three patients were judged to have a cardiac anomaly, further emphasising the frequency of this defect in the fetal alcohol syndrome. Two of them had a cleft soft palate, a new observation in this disorder.

The findings in the brain of patient 2, the first case of the fetal alcohol syndrome on whom a necropsy was performed, are of special relevance. There was serious disorientation of both neuronal and glial elements as well as incomplete development of the brain which must have started before 80 days' gestation, judging from the absence of the corpus callosum. Some of the functional and structural abnormalities in this syndrome may relate to the types of aberration in brain morphogenesis observed in this patient. These secondary features include microcephaly, developmental delay, and fine-motor dysfunction, which showed itself in early infancy by tremulousness. Some of the joint anomalies could be related to neurological impairment of the fetus, including reduced movement.

The most profound degree of prenatal-onset growth deficiency yet noted in the fetal alcohol syndrome occurred in patient 3. The findings in patient 3, who at 7 months of age was still below normal newborn size and showed no growth response to high-caloric feedings, provide further evidence of the immutable nature of the adverse prenatal effect on growth-rate in this disorder. The findings in the two newborn infants accorded with the previous observation that prenatal growth in length is more severely affected than weight gain.

The mother of patient 1 provided us with the first opportunity to study the nutritional status of a chronically alcoholic woman at the time of birth of her affected child, and of investigating the suggestion that a secondary nutritional deficiency could be the cause of the syndrome. Serious iron deficiency was the only abnormality detected. Since neither this degree of growth deficiency nor this pattern of malformation have to our knowledge been noted in offspring of iron-deficient anæmic women who were non-alcoholic, it seems unlikely that iron-deficiency anæmia is the cause of this disorder.

The risk of the initial diagnosis being wrong is high. For example, the 18 trisomy syndrome and Cornelia de Lang syndrome were seriously considered by the physicians who initially evaluated these patients. An incorrect diagnosis could lead to inappropriate advice about the risk of malformation in future children. Risk of fetal alcohol syndrome in future children is potentially high, as indicated by patient 3, unless maternal alcoholism is controlled.

Additional studies are needed to determine the incidence of the fetal alcohol syndrome in offspring of alcoholic mothers. Preliminary data from the collaborative study of the National Institute of Neurologic Disease and Stroke indicate a 32% incidence of this condition in offspring of women whose chronic alcoholism was ascertained during their pregnancy. The results of that study will form the basis of a future report.

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PERSON-TO-PERSON SPREAD OF SALMONELLA: A PROBLEM IN HOSPITALS?

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Summary 8 patients with acute diarrhœa were admitted to hospital and appropriate stool-barrier techniques were not used to avoid secondary spread. These patients later proved to have salmonellosis. Their surroundings were extensively contaminated, exposing 265 patients and staff to infected fæces. No case of symptomatic or asymptomatic salmonellosis was found as a result of person-to-person spread. It is concluded that person-to-person spread of salmonella in hospital is difficult to accomplish without an intermediary common vehicle.