Holoprosencephaly in a fetus with maternal medication of sulfasalazine in early gestation

A case report

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INTRODUCTION

Holoprosencephaly is a malformation of the brain which usually occurs sporadically, and in most cases, its cause is unknown ([1, 2]). This etiology is heterogeneous. Cohen ([2]) reported 66 conditions with either holoprosencephaly or arhinencephaly, in which chromosomal syndromes ([2]), monogenetic disorders ([2]), and maternal diabetes ([3]) have been described. Other suspected, but less established, teratogens include intrauterine infections with viruses including cytomegalovirus (CMV), rubella, and toxoplasmosis; early gestational irradiation; and early exposure to agents such as quinine, salicylates, isotretinoin, chlordiazepoxide, cortisone, estroprogestines, contraceptives, cocaine, phenytoin, and alcohol ([4]).

Sulfasalazine has been widely used as a drug of choice for inflammatory bowel disease such as ulcerative colitis and Crohn's disease, and its use during pregnancy is usually considered to be safe. We have observed a case of a neonate with holoprosencephaly, born to a mother who had been put on a continuous treatment with sulfasalazine before and during pregnancy.

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CASE REPORT

The patient had peritonitis and underwent a laparotomy a the age of 23. Then she had her small intestine partially resected under a diagnosis of Crohn's disease. Since then, she has been treated with sulfasalazine. She visited the infertility clinic of a community hospital for 3 years and successfully became pregnant at the age of 32 by the induction of ovulation with human menopausal gonadotropin and human chorionic gonadotropin and followed by an artificial insemination with her husband's

semen. This primigravid patient was taking sulfasalazine (3 g a day), ferrostatin (Fe) (100 mg a day), kernac (240 mg a day) which was derived from a plant, and a protective drug for gastritis or gastric ulcer to control Crohn's disease for 3 years until 7 weeks of her pregnancy. At 19 weeks of gestation she visited our hospital for the first time. A fetal sonography performed at 27 weeks revealed a suspicious hydrocephalus. The sonography performed a week later also showed the same findings of hydrocephalus. Genetic amniocentesis performed at 29 weeks of gestation revealed normal Q-banded chromosomes (46, XX), and maternal serum and amniotic fluid α-fetoprotein values were 385.1 ng/ml and 1723.7 ng/ml, respectively (they were normal values). The fetal echocardiography performed at the same gestational weeks did not show any congenital heart diseases. However, the coronal MR images revealed a huge dilatation of bilateral ventricles, with a suspicious connection in the frontal region of both ventricles, and a hypoplastic cerebellum (Fig. 1).

Both sonar scan and MRI could not confirm prenatally semilobar holoprosencephaly. The course of her pregnancy was uneventful. There were no signs of infection such as syphilis, toxoplasma, rubella, cytomegalovirus, or herpes simplex virus. An elective cesarean section was performed at 37 weeks of gestation. The infant was a female weighing 2360 g and showed a microcephalus with the head circumference of 30.2 cm and the body height of 48.4 cm. The Apgar score was 3/7 at 1 and 5 minutes, respectively. The child had the following dysmorphic features: microcephaly, a flat nose, median clefts of lip and palate, and hypotelorism (Fig. 2). A postnatal, cranial CT scan showed a partial lobulation of hemisphere (Fig. 3). She was diagnosed as semilobar holoprosencephaly and had no other anomalies elsewhere in her body and was transferred to the NICU in our hospital. For repeated convulsions and hypothermia, she was given anticonvulsants (clonazepam and phenobarbital) and kept in an incubator. Her hydrocephalus gradually became worse (her parents did not want a shunt operation made), and she died 6 months after her birth. An autopsy was not undertaken because of her parents' objection.

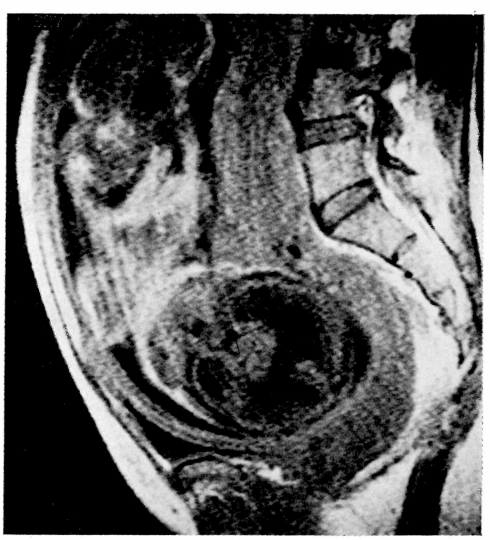

Fig. 1. — The fetal coronal MR image at 30 weeks of gestation showing a huge dilatation of bilateral ventricles.

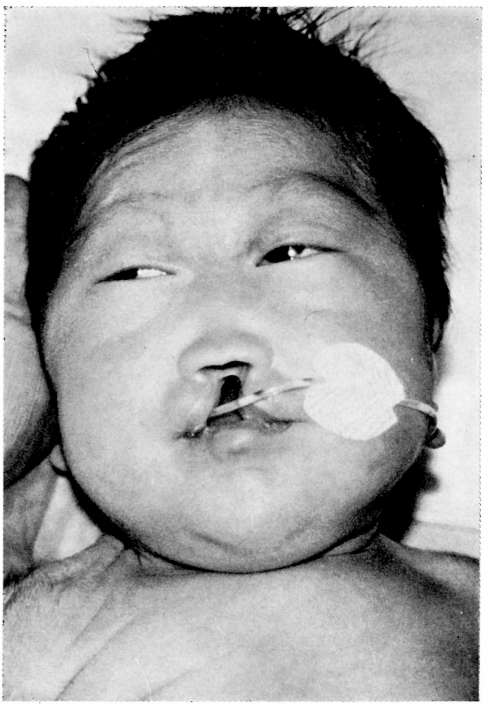

Fig. 2. — Facial structure; a flat nose, median clefts of lip and palate, and hypotelorism.

DISCUSSION

In most studies involving large numbers of patients, no definite association has been made between the use of sul-

fasalazine and fetal malformation even when the drug has been used during pregnancy for the treatment of inflammatory bowel diseases ([5, 6, 7, 8, 9]), except for a few cases of major fetal anomalies, including a disorder of the central nervous system (hydrocephalus) ([10]) and an impairment of the circulatory or urogenital system ([11, 12, 13]).

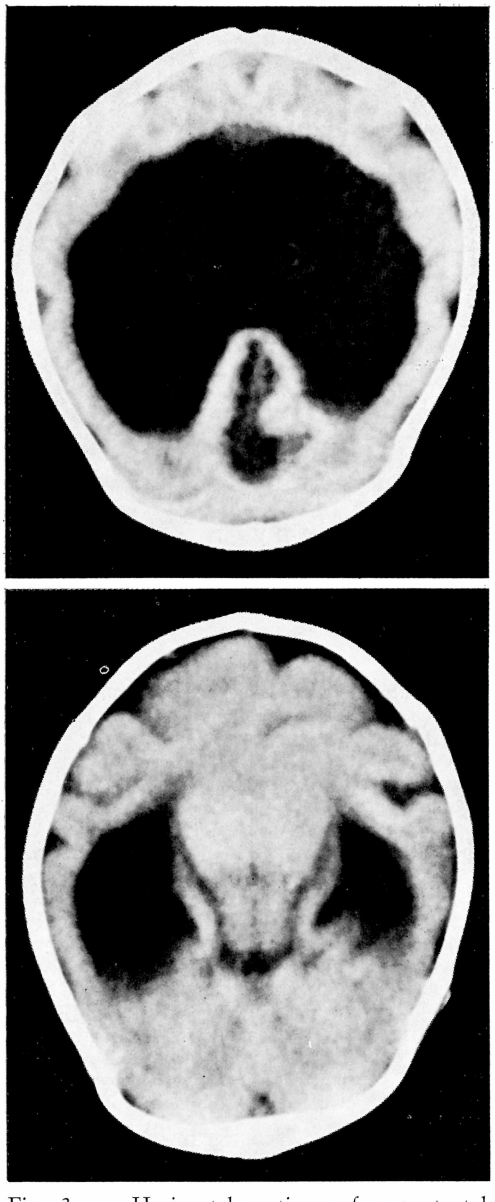

Fig. 3. — Horizontal sections of a postnatal cranial CT scan showing *a*) a large single ventricle with partial sagittal separation and *b*) midline fusion of the basal ganglia and thalami.

Animal studies have shown that other sulfonamides which are classified into the same group as sulfasalazine can produce fetal malformations in mice and rats ([14, 15]). Types of malformation caused by sulfonamides were mainly cleft palates in both species. Our patient had also delivered an infant with a cleft palate. These results seem to suggest that $-SO_2$ NH-R in the structural formula of sulfonamide might be responsible for their teratogenicity. The strength of the teratogenicity might depend on the derivatives of R ([14]).

In our case, the mother took sulfasalazine with iron and kernac during early pregnancy in order to control Crohn's disease. Iron and kernac are reported to have no teratogenicity. As her Crohn's disease was in a remissive state before and during the pregnancy, it was unlikely that the fetus was affected by the disease during pregnancy. Neither parent of the child had any manifestation of an autosomal dominant inherited holoprosencephaly. There was no consanguinity and the chromosomal analysis of the fetus was normal. Therefore, the genetic etiology seems quite unlikely in this case. No infectious diseases were detected during pregnancy and both parents had no history of smoking or drinking.

Holoprosencephaly originates during stages 8-13 of embryonic development (i.e., 18-28 days of gestation) ([16]) and can be described as an incomplete or lack of sagittal cleavage of the prosencephalic vesicle into the two hemispheres. It is considered to be a developmental disturbance of the brain. Normally, the "development of complex structures is coor-

dinated in a spatially ordered, temporally synchronized, and epimorphically hierarchial manner" ([17]). Disturbance in developmen of the brain during this critical period, which is the early stage of gestation, may cause various types of holoprosencephaly. The etiology of holoprosencephaly is regarded as heterogeneous. This malformation is observed in some chromosomal aberrations and with exposure to teratogenic agents as well as in rare autosomal dominant or recessive syndromes. In man, however, maternal diabetes is the only proven teratogen ([3]) though there are some case reports with other heterogenic agents ([18]). Our patient was shown to have a semilobar holoprosencephaly by CT scan. Intake of sulfasalazine during early pregnancy might have delayed the normal sagittal cleavage in the frontal brain.

To our knowledge, this case report is the first of holoprosencephaly with maternal medication of sulfasalazine in early gestation. Although we cannot conclude a proven correlation between sulfasalazine and holoprosencephaly, care should be in the use of sulfasalazine, especially in early gestation.

CONCLUSION

We report a congenital anomalous fetus with holoprosencephaly, prenatally suspected by sonography and MR image at the twenty-sixth week of gestation. Q-band chromosome analysis by amniocentesis revealed no abnormality. Postnatal examination showed semilobar holoprosencephaly associated with a median cleft lip, cleft palate, hypotelorism and a flat nose. The mother had taken sulfasalazine during early gestation for control of Crohn's disease. This is the first case report of holoprosencephaly with maternal exposure to sulfasalazine in early gestation.

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