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Developmental Delay in Fetal Aminopterin/Methotrexate Syndrome

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ABSTRACT Maternal exposures to aminopterin and methotrexate have been associated with a pattern of malformation which includes prenatal-onset growth deficiency, severe lack of ossification of the calvarium, hypoplastic supraorbital ridges, small, low-set ears, micrognathia, and limb abnormalities. We report on a patient whose mother received methotrexate during the first trimester of pregnancy and who, in addition to the structural anomalies typical of maternal methotrexate exposure, has significant developmental delay. This is the third patient exposed to folic acid antagonists with mental retardation, providing further evidence that developmental delay is one feature of fetal aminopterin-methotrexate syndrome. Therefore, it is recommended that formal developmental testing be performed in all patients prenatally exposed to methotrexate. *Teratology 60:10–12, 1999.*

Both aminopterin and its methyl derivative, methotrexate, have been associated with a unique pattern of malformation which we refer to as fetal aminopterin/methotrexate syndrome. The principal features of this disorder include prenatal-onset growth deficiency, severe lack of ossification of the calvarium, prominent eyes secondary to hypoplastic supraorbital ridges, small, low-set ears, micrognathia, and limb abnormalities. Although aminopterin is no longer available, methotrexate is increasingly being used , not only as an antineoplastic agent, but also for the treatment of rheumatoid arthritis and psoriasis, and as an abortifacient. Although results of formal developmental testing have not been reported in the majority of children affected with this disorder, mental retardation has been reported only twice: in one patient prenatally exposed to aminopterin (Shaw and Steinbach, '68), and in one patient prenatally exposed to methotrexate (Bawle et al., '98).

The purpose of this report is to present a second case of a child prenatally exposed to methotrexate, who in addition to having the structural abnormalities typical of fetal aminopterin/methotrexate syndrome, is developmentally delayed.

CASE REPORT

The patient, now a 2-year, 10-month-old male, was born by cesarean section for fetal distress, at 40 weeks of gestation, to a 35-year-old G4P3TAB1 woman who received 12.5 mg of methotrexate 3 times per week for chronic severe psoriasis throughout the first 8 weeks postconception. She denied exposures to other drugs. Apgar scores were 2 at 1 min, 5 at 5 min, and 6 at 10 min. The infant was intubated 24 hr, with good progress in weaning ventilatory support after 6 hr of life. He was diagnosed with transient tachypnea of the newborn and mild primary pulmonary hypertension. There was mild oligohydramnios and the placenta was noted to be small. Birth length, weight, and head circumference were 38 cm, 1,645 g, and 29.5 cm, respectively (all less than the 3rd percentile). Physical examination at age 8 days revealed widely separated sutures and large fontanels. The posterior fontanel measured 3.5 cm in diameter. There were bilateral epicanthal folds and sparse eyebrows laterally with hypoplastic supraorbital ridges, a broad nasal bridge, anteverted nares, and a smooth, long philtrum (1.5 cm). The nipples were hypoplastic. There was a small umbilical hernia, diastasis recti, and a shawl scrotum. Decreased extension was noted at the elbows. The proximal phalanges of the third, fourth, and fifth fingers were short bilaterally, and the fingernails were mildly hypoplastic. Neurologic examination was repeatedly normal during the neonatal period. Head ultrasounds at 3 and 15 days of life were normal. A renal ultrasound showed dilatation of the left collecting system, which disappeared on follow-up. Toxoplasma, rubella, cytomegalovirus, herpes simplex (TORCH) titers were normal. A karyotype was normal, 46, XY.

At 20 months, his height was 77.6 cm (height age of 13 months), his weight was 9.5 kg (15th percentile for height age), and his head circumference was 46 cm (−1 SD for height age). He had trigonocephaly with a prominent metopic suture and an open anterior fontanel that finally closed at age 30 months. Although mild

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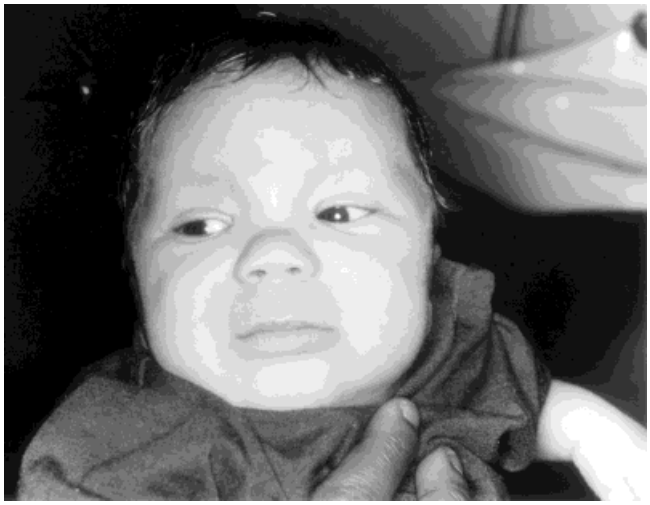

Fig. 1. Face of patient at age 3 months.

hypotonia was noted on the neonatal examination, no specific neurological anomalies were noted until age 1 year, when he had a generalized tonic-clonic seizure associated with fever. A similar episode occurred at age 2 years. No treatment was prescribed. Both of his older sisters have had a single episode of seizure associated with fever during the first 2 years of life.

With respect to developmental milestones, he was delayed in comparison to his sisters. He walked at 17 months, and said his first words at age 2 years. He was involved in an early infant intervention program and is receiving speech therapy. At age 22 months, he performed at the 15-month level on the Bayley Scales of Infant Development, and at age 28 months, his performance was at the 17-month level. In addition, he showed a flat affect with periods of irritability, and a short attention span. The patient is shown in Fig. 1 at age 3 months.

TABLE 1. Structural defects and developmental outcome of children with structural defects exposed to methotrexate

Author/year	Disease treated	Time of exposure	Weekly dosage	Structural anomalies	Development
Powell and Ekert, '71	Psoriasis	0–8 weeks	35 mg/wk	Oxycephaly, fused coronal sutures, wide metopic suture, large anterior fontanel. Hypertelorism, wide depressed nasal bridge. Mild 2–3 hand syndactyly.	Normal at 4 months
Milunski et al., '68	Attempted abortion	About 6–8 weeks	12.5 mg/wk	Oxycephaly, absent coronal and lambdoid sutures, wide posterior fontanel, absent frontal bone. Broad nose, flat midface, hypertelorism, micrognathia. Absent toes 2–5. Dextrocardia.	Normal at 15 months
Diniz et al., '78	Hydatiform mole	8–32 weeks	50 mg/wk	Hydrocephalus, hypoplasia of frontal/orbital bone. Hypertelorism, micrognathia. Short limbs.	Not reported
Bawle et al., '98	Attempted abortion	6 or 8 weeks	?	Growth deficiency, microcephaly, defects in ossification of skull. Hypertelorism, ptosis, short palpebral fissures, prominent nose, low-set ears, widow's peak. Syndactyly, flexion contractures.	Normal at 26 years
Bawle et al., '98	Breast cancer	7½–28 weeks	80 mg/wk	Growth deficiency, microcephaly. Hypertelorism, frontal hair whorl, frontal hair upsweep, low-set ears, micrognathia.	IQ = 70
Bawle et al., '98	Attempted abortion	11 weeks	100 mg/2 weeks	Growth deficiency, bulging forehead, bitemporal narrowing, upslanting palpebral fissures, sparse temporal hair, low-set ears.	Normal at 3½ years

DISCUSSION

The patient set forth in this report represents the second case of a child prenatally exposed to methotrexate in whom formal developmental testing has documented significant early motor and cognitive delays.

As summarized in Table 1 from the literature, developmental follow-up has been documented in 5 of 6 patients prenatally exposed to methotrexate who had the fetal aminopterin/methotrexate syndrome (Milunsky et al., '68; Diniz et al., '78; Powell and Ekert, '71; Bawle et al., '98). Only one, an 8-year-old male born to a 45-year-old woman who received methotrexate for treatment of breast cancer beginning at 7½ weeks postconception, was felt to be in the mentally deficient range. That child was born at 29 weeks of gestation, raising the possibility that complications associated with prematurity might have contributed to his IQ of 70. Although developmental delay was not noted in any of the 18 children prenatally exposed to methotrexate reported to be structurally normal, developmental evaluations were not reported and no follow-up with respect to development was available. (Feldkamp and Carey, '93; Donnenfeld et al., '94).

Although very little reference has been made to formal developmental testing in children prenatally exposed to aminopterin, the majority of them also have been referred to as being of normal intelligence (Reich et al., '78; Jones, '97). However, Shaw and Steinbach ('68) reported an infant exposed during the eighth week of pregnancy to an unknown dose of aminopterin as an abortifacient, who had typical structural abnormalities, a developmental quotient (DQ) at 18 months of 75, and an estimated IQ at 4½ years of 66. In addition, Howard and Rudd ('77) reported on a 10-year-old patient with craniosynostosis, hypertelorism, micrognathia, and shortened forearms, prenatally exposed to an unknown quantity of aminopterin, who had a full-scale IQ of 80, that previously had been estimated to be 64 at age 7 years. Relative to the latter patient, she was prematurely born (27 weeks of gestation, 770 g), which may have contributed to her cognitive deficit.

The patient herein reported was exposed to a standard dose of methotrexate for the treatment of psoriasis (12.5 mg per week), during a period including the first 8 weeks from conception, a dose and timing of exposure which are consistent with those proposed to be necessary for the development of fetal aminopterin/methotrexate syndrome (Feldkamp and Carey, '93), i.e., 6–8 weeks postconception and a minimum dose of 10 mg per week. Although it is impossible to be sure that this child's developmental problems are causally related to prenatal exposure to methotrexate, the fact that prenatal exposure to folic acid antagonists has been associated with developmental delay in at least two additional cases, and the presence in this child of a physical phenotype characteristic of fetal aminopterin/methotrexate syndrome, strongly suggest that his developmental delay is related to the exposure.

Documentation of this patient provides further evidence that developmental delay is one feature of fetal aminopterin-methotrexate syndrome. Furthermore, in that teratogens are known to be associated with a wide spectrum of developmental effects including functional disorders without structural abnormalities, it is recommended that formal developmental testing be performed in all patients prenatally exposed to methotrexate, not only those with fetal aminopterin/methotrexate syndrome, but also those who are structurally normal.

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