

Adult and Two Children With Fetal Methotrexate Syndrome

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ABSTRACT The folic acid antagonists, methotrexate and aminopterin, are known to be teratogenic in humans. The critical period for their teratogenicity is suspected to be between 6 to 8 weeks post-conception. Fetal exposure from 10 to 32 weeks post-conception to methotrexate alone or in combination with other anti-cancer drugs has not resulted in obvious teratogenic effects. Methotrexate is often used to treat cancers but is occasionally used as an abortifacient. The long-term outcome of the fetal aminopterin syndrome has been published in only four adults. We report on a 28-year-old man with fetal methotrexate syndrome and two children with mild manifestations of the syndrome. One child was inadvertently exposed to methotrexate from 7½ through 30 weeks post-conception because his mother was receiving it for treatment of breast cancer. The other was exposed from 11 weeks and 5 days through 25 weeks in an attempt to induce abortion. The 28-year-old man has craniofacial and digital anomalies, growth retardation but normal intelligence as noted in the previously reported cases. These cases remind us of the teratogenicity of methotrexate and should serve as a warning that if methotrexate is used as an abortifacient and an abortion does not ensue, there is a teratogenic risk. *Teratology* 57:51-55, 1998. © 1998 Wiley-Liss, Inc.

Aminopterin and its methyl derivative, methotrexate, are folic acid antagonists used for the treatment of various cancers, rheumatoid arthritis, psoriasis, and occasionally as abortifacients for the management of ectopic or unwanted pregnancies. Prenatal exposure to these drugs during critical periods of embryogenesis is known to cause a multiple malformation syndrome in humans. The critical gestation period has been suggested to be from 6 through 8 weeks post-conception by Feldkamp and Carey ('93) and by Donnenfeld et al. ('94). The threshold dose for teratogenicity of methotrexate is thought to be 10 mg per week. The long-term outcome in fetal aminopterin syndrome has been published in four adults. We report on a 28-year-old man

with fetal methotrexate syndrome and two children with a partial form of the syndrome.

CASE 1

We examined CH at the age of 26 years for multiple anomalies. His parents are African American with no birth defects. His mother had five normal children after him. She attempted to terminate this pregnancy by taking an unknown quantity of methotrexate either 6 weeks post-conception or 6 weeks after the last menstrual period. She gave him up for adoption soon after birth. Some of the birth defects of his hands and feet had been surgically corrected, but since his entire medical record was available, a complete assessment was possible. He has hypertelorism, (interpupillary distance of 6.5 cm, + 2.5 S.D.), ptosis of the eyelids, short palpebral fissures (length 2.5 cm), sparse eyebrows, prominent nose, low-set ears, and a widow's peak at the frontal hairline (Fig. 1). His height was 155 cm (-3 S.D.), weight 39.7 kg (-2.5 S.D.) and head circumference was 51 cms (-3.5 S.D.). He has additional flexion creases on the fingers (Fig. 2A). The "t" triradius is distally placed. A surgical repair of his flexion contractures of the metacarpo-phalangeal joints of both the thumbs and of syndactyly of all the fingers was done at the age of 6 years. Figure 2B is a radiograph of his hands taken at the age of 6 years prior to surgery.

He cannot fully extend his elbows due to subluxation of the radial heads (Fig. 3). His great toes are broad. He had surgical reconstruction of all the toes from a single fused hypoplastic nub of tissue at the forefoot. He has only four metacarpals and severe hypoplasia of phalanges of the toes (see Fig. 4A, B). His genitalia are normal. He developed gynecomastia at puberty for which he had surgery. Radiographs also demonstrated defects in the bones of the skull (Fig. 5). His early psychomotor

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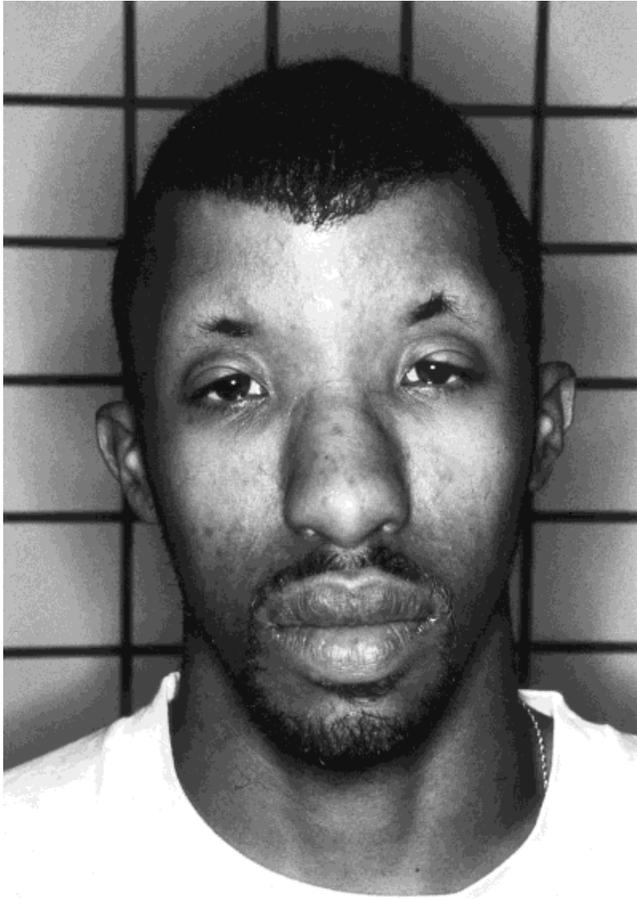


Fig. 1. Case 1 showing hypertelorism, sparse eyebrows, low-set ears, and prominent nose.

development was normal and he passed 11th grade in a regular classroom without any learning difficulties. He is employed as a janitor in the family business. He has a driver's license. He seems well adjusted to his condition. His phenotype is compared to the published reports of adults with this syndrome in Table 1.

CASE 2

Nine-year-old MP was born to a 45-year-old gravida 4 para 4 Caucasian woman at 29 weeks gestation weighing 820 g (small for gestation). His mother's pregnancy was undetected until she went into labor. About 4 weeks after her estimated date of conception (i.e., six weeks after her last menstrual period) she had a lumpectomy for breast cancer. She began chemotherapy with methotrexate at 7½ weeks post-conception. Her chemotherapy schedule was as follows: 80 mg methotrexate weekly at 7.5, 8.5, 11.5, 12.5, 23.5, and 28.5 weeks post-conception. She also received 5-fluorouracil 1,200 mg weekly at 7.5, 8.5, 11.5, 12.5, 15.5, 16.5, 19.5, 20.5, 23.5, and 28.5 weeks post-conception. She received radiation therapy (to the breast and chest

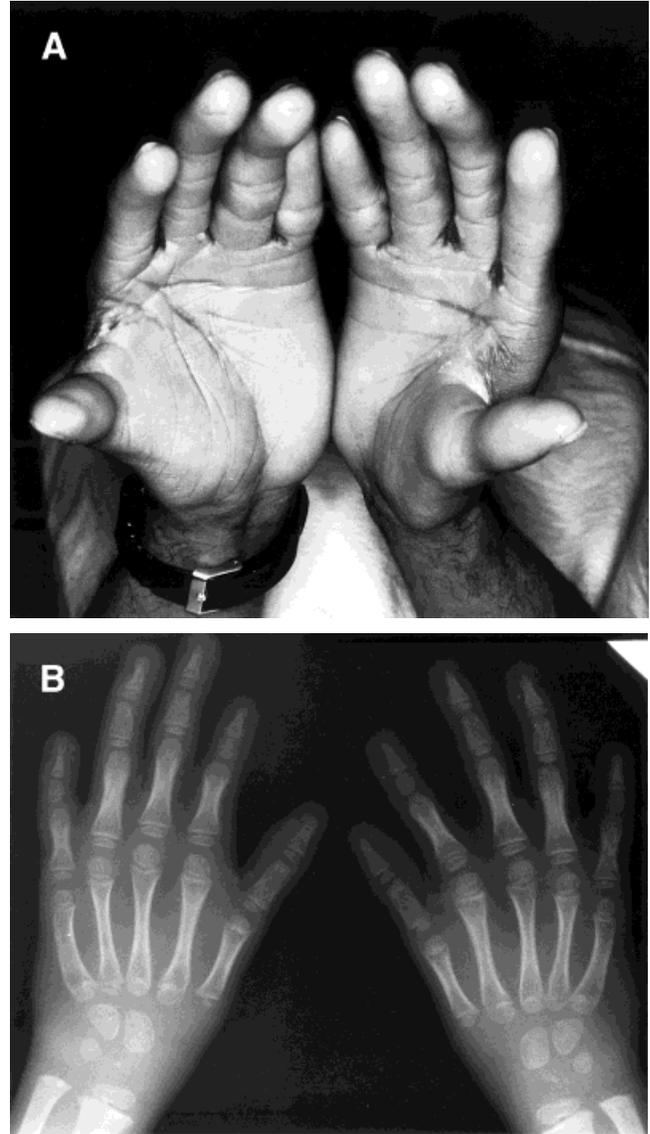


Fig. 2. A: Hands of Case 1 showing excess flexion creases. **B:** Radiographs of hands of Case 1 at age 6 years prior to surgery, showing syndactyly of fingers and hypoplasia of middle phalanges of 2nd and 5th fingers.

wall area) from 15.5 weeks through 25 weeks post-conception. The total fetal radiation dose was estimated to be 14 rads. MP's karyotype was normal.

At 8½ years his height was 107 cm (-4 S.D.), weight 16 kg (-3 to 4 S.D.), and head circumference 47 cms (-4 S.D.). He has hypertelorism, a frontal hair whorl, an upsweep of the frontal hairline, microcephaly, low-set ears, micrognathia (Fig. 6), and a right palmar simean crease. The extremities are normal. On Stanford Binet Intelligence test IV-revised, he earned a composite IQ of 70. This is in the "mentally deficient" to low "borderline" limits of intelligence compared with other students his age. His speech and language skills are in the mildly

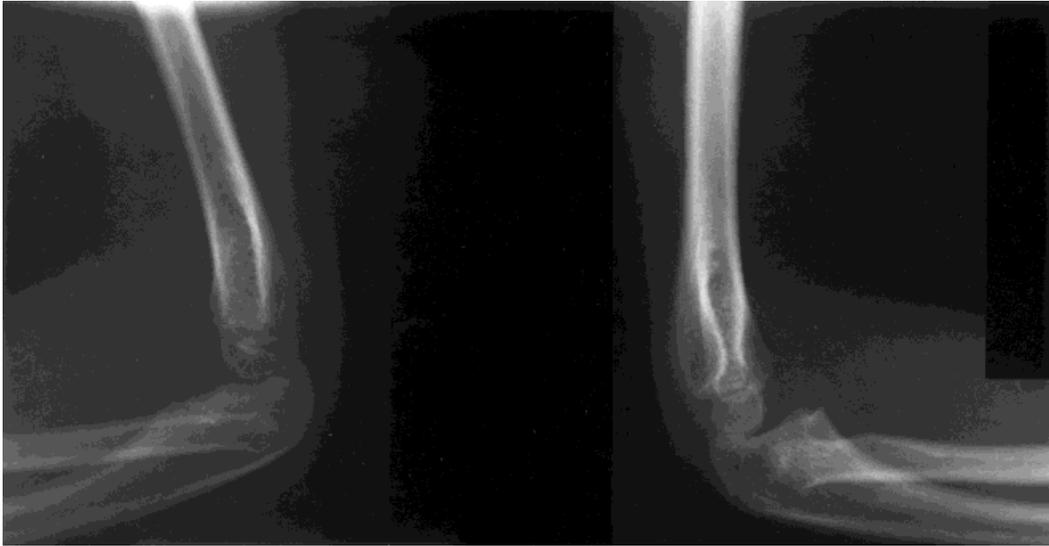


Fig. 3. Case 1 showing subluxation of radial heads.

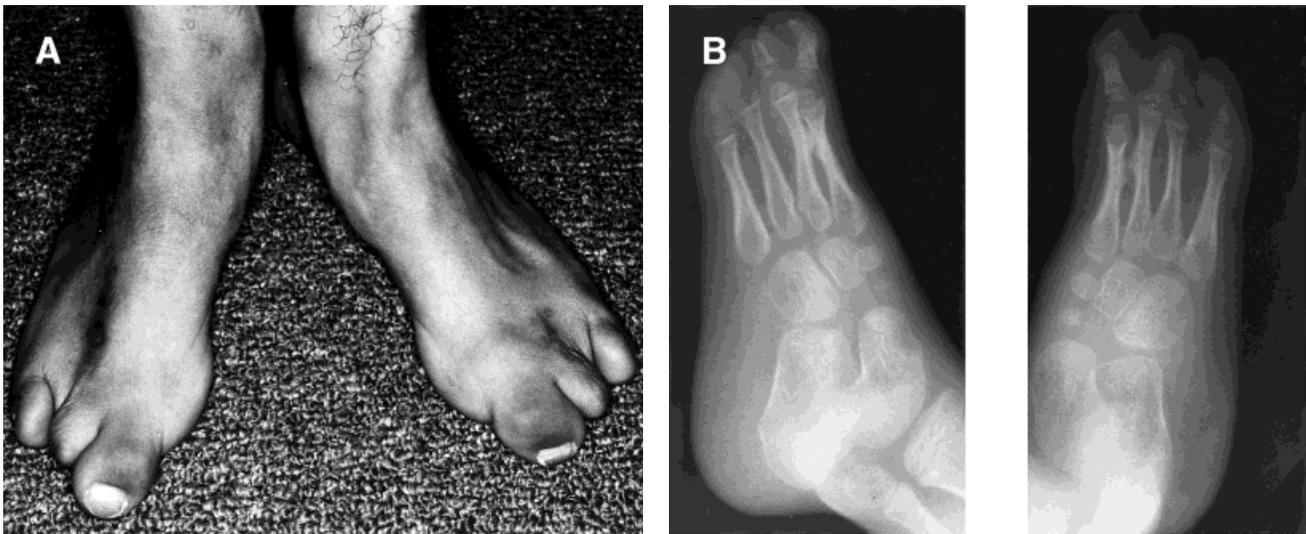


Fig. 4. A,B: Feet of Case 1 with only 4 metacarpals and hypoplasia of toes.

mentally deficient range. He stutters and has verbal expressive difficulties. He does not show any behavioral abnormalities and gets along with classmates.

CASE 3

Three-and-a-half-year-old DC was born at 29 weeks gestation weighing 1,160 g (approximately 50th percentile) to a then 33-year-old gravida 1 para 1 woman of African-American descent. At 9 weeks post-conception (i.e., 11 weeks after her last menstrual period) she underwent dilatation, suction, and curettage in an attempted elective abortion. Two weeks later, being still pregnant, she was offered an abortion via a hysterotomy. The hysterotomy was recommended because of

the risk of hemorrhage from large uterine myomas. Instead, she chose to have a medical abortion with methotrexate. Her methotrexate schedule was 100 mg bi-weekly from 11 weeks and 5 days to 17 weeks post-conception and 200 mg bi-weekly from 17 to 23 weeks post-conception. At 34 months of age his weight was 10 kg (-3.5 S.D.), length 87 cm (-3 S.D.), and his head circumference was 51.5 cm (75th percentile). He has a bulging forehead, bitemporal narrowing, upward slanting palpebral fissures, sparse hair on the temporal areas, low-set ears, broad nasal tip, and a high arched palate. His psychomotor development is normal. The family did not consent for publication of DC's photographs. Chronic diarrhea since the age of 9 months was



Fig. 5. Case 1 with skull defects.

considered the cause of his poor weight gain. Extensive investigations for the diarrhea have not led to a specific diagnosis. An intestinal biopsy initially showed villous atrophy.

DISCUSSION

Thiersch ('52,'56), Meltzer ('56), and Warkany et al. ('59) reported fetal malformations associated with maternal ingestion of aminopterin. Subsequent reports include those by Milunsky et al. ('68), Shaw and Steinbach ('68), Powell and Eckert ('71), Howard and Rudd ('77), Reich et al. ('78), and Shaw and Rees ('80). Many children with aminopterin embryopathy died in infancy. There have been no reported cases since 1980. The risk for malformation is not 100% as shown by the reports of Freedman et al. ('62) and Pizzuto et al. ('80). Feldkamp and Carey ('93) reviewed published cases of fetal aminopterin syndrome and suggested that the critical period for the development of malformations is 6 through 8 weeks post-conception and the minimum dose to be 10 mg per week.

Our Case 2 was initially exposed at 7½ weeks at a much larger dose, but did not develop the digital anomalies. Similarly, the case reported by Shaw and Steinbach ('68), who was exposed from 8–9 weeks, and Howard and Rudd's ('77) patient exposed at 8 weeks showed no digital anomalies. Our Case 2 was also

TABLE 1. Comparison of clinical data of 5 adult patients with fetal aminopterin/methotrexate syndrome

	Our case 1	Reich et al. ('78)			Shaw and Steinbach ('68)
		Case 1	Case 2	Case 3	
Aminopterin exposure	–	?	+	?	+
Methotrexate exposure	+	?	–	?	–
Time of exposure in weeks	6–8	8–12	6–8	?	8–9
Bitemporal flattening, brachycephaly	+	+	+	+	–
Characteristic frontal hairline	+	+	+	+	+
Hypoplastic supraorbital ridges	–	+	+	+	+
Sparse and faint eyebrows, lateral half	+	+	+	+	+
Hypertelorism	+	+	+	+	+
Prominent eyeballs	–	–	+	+	+
Small palpebral fissures	+	+	+	+	+
Prominent nose	+	+	+	+	+
High arched palate	+	+	+	+	+
Micrognathia	–	+	+	+	+
Low-set ears or malformed ears	+	+	+	+	+
Microcephaly	+	–	–	–	+
Distal shortening of limbs	–	+	+	+	+
Limitation of rotation and extension of elbows	+	+	+	+	+
Subluxation of radial heads	+	+	+	+	+
Defects in skull bones	+	+	–	+	+
Brachydactyly/syndactyly/hypoplasia digits	+	+	+	+	–
Abnormal dermatoglyphics	+	+	+	+	–
Short stature	+	+	+	+	+
Normal intelligence	+	+	+	+	+

exposed to 5-fluorouracil from 7.5 weeks post-conception. Experience with 5-fluorouracil during pregnancy is limited but, following systemic therapy in the first trimester, Stephens et al. ('80) reported multiple birth defects in an aborted fetus: radial aplasia, absent fingers, aplasia of the esophagus and duodenum. Our patient does not show these anomalies.

Case 3 in this report was exposed at 11 weeks and 5 days and onward, and showed a different and milder phenotype. This case suggests that the teratogenicity of methotrexate may extend through 11 weeks post-



Fig. 6. Case 2 showing hypertelorism, upsweep of frontal hair line, and micrognathia.

conception but the syndrome then is milder. Methotrexate is useful in the treatment of many types of cancers, rheumatoid arthritis, and psoriasis. It has been shown to be safe and effective in medical treatment of ectopic pregnancy as reviewed by Slaughter and Grimes ('95). Methotrexate followed by misoprostol has been pro-

posed as a means of terminating very early pregnancies. Failed treatment carries the risk of the fetal methotrexate syndrome.

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