CLINICAL REPORT

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Potential Teratogenic Effects of Allopurinol: A Case Report

Mariya Kozenko,[1] David Grynspan,[2] Titi Oluyomi-Obi,[3] Daniel Sitar,[4] Alison M. Elliott,[1] and Bernard N. Chodirker[1]*

[1]Departments of Pediatrics & Child Health and Biochemistry and Medical Genetics, University of Manitoba, Winnipeg, Manitoba, Canada

[2]Department of Pathology, University of Manitoba, Winnipeg, Manitoba, Canada

[3]Department of Obstetrics and Gynecology, University of Manitoba, Winnipeg, Manitoba, Canada

[4]Department of Pharmacology and Therapeutics, Department of Internal Medicine, and Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada

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We report on a case of a multiple congenital anomalies in a newborn infant whose mother was on allopurinol treatment through the pregnancy. The pattern of congenital anomalies that was noted in our patient was similar to the pattern described in a number of published reports following mycophenolate mofetil [CellCept®] treatment during pregnancy. The anomalies present in our patient include: diaphragmatic hernia, unilateral microtia and absence of external auditory canal, micrognathia, microphthalmia, optic nerve hypoplasia, hypoplasia of the corpus callosum, unilateral renal agenesis, pulmonary agenesis, and cleft lip and palate. Since both allopurinol and mycophenolate mofetil act by disrupting purine biosynthesis and given the similarities in anomalies seen after prenatal exposure, we suggest that allopurinol should also be considered a teratogen.

Key words: allopurinol; teratogen; multiple malformations; mycophenolate mofetil

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INTRODUCTION

Allopurinol has been used for many decades as an option for treatment of gout, prophylaxis, and treatment of tumor lysis syndrome after initiation of chemotherapy and kidney stones [Blair nd Fabrizio, 2000; Ozkan et al., 2010]. Recently, it has been tested as an alternative drug treatment for chronic angina and heart failure [Farquharson et al., 2002; Noman et al., 2010]. Little is known about the potential teratogenic properties of this medication, as it is rarely prescribed in pregnancy. Gout is uncommon in pregnancy, as the incidence of gout in women of child-bearing years is estimated to be 1.6 per 10 000 patient-years [Chen et al., 2010].

We observed a number of congenital malformations in a newborn infant born after prenatal exposure to allopurinol. The anomalies were similar to those described after prenatal exposure to mycophenolate mofetil [CellCept®] (Table I). Since both drugs act by disruption of purine biosynthesis [Ransom 1995; Pacher et al., 2006], we postulate that allopurinol is also teratogenic in humans.

CLINICAL REPORT

An infant male was examined at birth with multiple congenital anomalies following a pregnancy where the mother was on allopurinol as prophylaxis against kidney stones. The mother was a 35-year-old G2P0SA1 woman who was referred to the genetics service at 29 weeks gestation due to ultrasound findings consistent with fetal hydrocephalus (ventricular size 16 mm), cleft lip and palate, and diaphragmatic hernia.

The woman had recurrent kidney stones since age 18 and was therefore on allopurinol 300 mg/day for last 12 years. Her other medications included multivitamins and methyldopa for hypertension. The pregnancy was complicated by one episode of bleeding at 8–10 weeks gestation. There was no history of maternal infection, recreational drugs, or alcohol exposure in the pregnancy. She did not have a maternal serum screen. The first fetal ultrasound was performed at 29 weeks gestation. The anomalies noted on prenatal ultrasound were confirmed through fetal MRI (Figs. 1 and 2).

*Correspondence to:
Bernard N. Chodirker, WRHA Program in Genetics 840 Sherbrook Street, Winnipeg, MB R3A 1R9. E-mail: bchodirker@hsc.mb.ca
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TABLE I. Clinical Features in Mycophenolate Mofetil Cases and Our Case Exposed to Allopurinol

	LeRay et al. [2004]	Parisi et al. [2009]	Kallen et al. [2005]	Sifontis et al. [2006]	Tjeertes et al. [2007]	Sebaaly et al. [2007]	Perez-Aytes et al. [2008]	Velinov and Zellers [2008]	Schoner et al. [2008]	Ang et al. [2008]	Vila et al. [2008]	Huang et al. [2008]	Anderka et al. [2009]	Pergola et al. [2001]	Armenti et al. [2004]	Total /17	Our case
Cases	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	17	
Microtia/ Auditory canal atresia	+	+	−	++	+	+	+	+	+	+	+	+	+	−	−	13	+
Cleft lip/palate	+	+	−	+	−	−	+	+	+	−	+	−	−	−	+	8	+
Short fingers/ Hypoplastic nails	−	+	−	+	−	+	+	+	−	−	−	−	−	+	−	6	−
Cardiovascular defect	−	+	+	−	−	+	−	−	+	−	+	−	−	−	−	5	−
Micrognathia	+	−	−	−	−	−	+	+	+	−	−	+	−	−	−	5	+
Hypertelorism	+	+	−	−	−	−	+	+	−	−	−	+	−	−	−	5	+
Urogenital anomalies	+	+	−	−	−	+	−	−	+	−	−	−	−	−	−	4	+
Coloboma of iris or eyelid	−	−	+	−	−	−	+	−	+	+	−	−	−	−	−	4	+
Microphthalmia	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−	1	+
Absent/ hypoplastic corpus callosum	+	−	−	−	−	−	−	−	+	−	−	−	−	−	−	2	+
Diaphragmatic hernia	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	1	+
Esophageal atresia	−	+	+	−	−	−	−	−	+	−	−	−	−	−	−	3	−
Lung defects	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	1	+

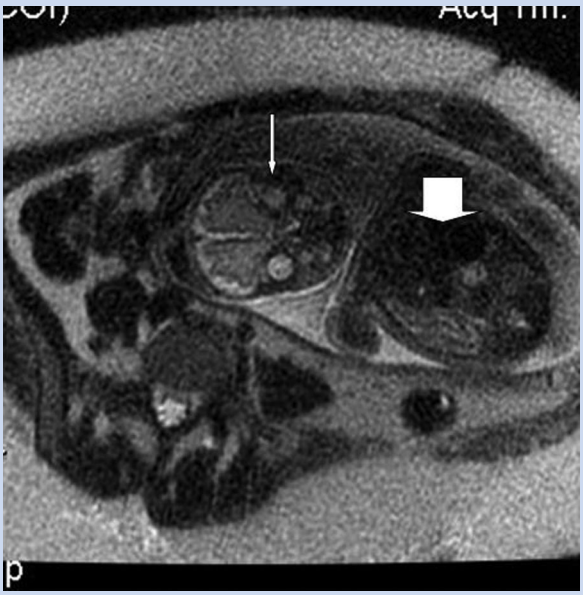

FIG. 1. Fetal MRI, 29 weeks gestation, diaphragmatic hernia (wide arrow), left-sided microphthalmia (thin arrow).

The parents had one previous pregnancy loss at 8–12 weeks gestation. The family history was unremarkable. The infant was of German and Russian descent on the maternal side and of Mennonite descent on the paternal side. There was no consanguinity. After counseling about the potential poor prognosis, the parents declined pregnancy termination. An amniocentesis was performed and the fetal karyotype was reported as 46,XY. The infant was born at 41 weeks gestational via cesarean due to failure to progress. Birth weight was 3.593 kg (25th centile), length was 54 cm (50th centile), and head circumference was 39 cm (90th centile).

The clinical examination at time of delivery documented the presence following of external anomalies: hypertelorism, left-sided microphthalmia, and coloboma involving the upper eyelid, left-sided microtia and absent left external auditory canal, simplified right ear with a preauricular tag, left-sided cleft lip and cleft palate, and undescended testes bilaterally (Figs. 3–5). He had normal palmar and plantar creases. No evidence of distal digital hypoplasia was noted. No other obvious anomalies were noted.

He was intubated and ventilated shortly after birth due to progressive respiratory failure. Despite all efforts, he died on day 8 of life due to cardiac and respiratory failure. An autopsy confirmed the presence of the external anomalies in addition to the following internal anomalies: hypoplasia of the corpus callosum, left optic nerve atrophy, left microphthalmia, small frontal fossa, agenesis of the left diaphragm with intrusion of liver, stomach, and spleen into the diaphragmatic space, mildly enlarged right-sided kidney, absent left kidney, small accessory spleen, and profound left pulmonary hypoplasia. There was a normal cerebellum and gyral pattern with no obvious abnormalities on the external surface of the brain. The examination of cardiovascular system was normal. The skeletal survey was normal.

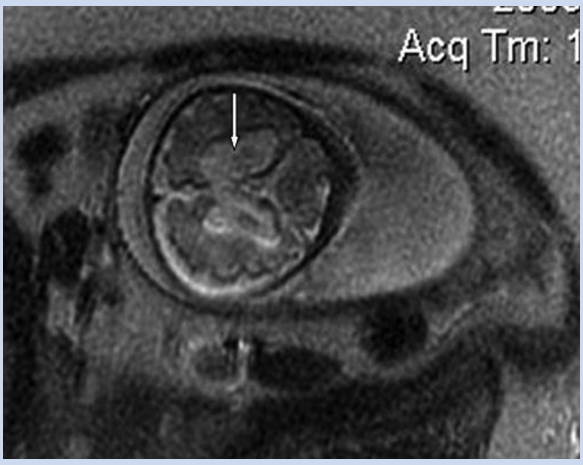

FIG. 2. Fetal MRI, 29 weeks of gestation showing ventriculomegaly (arrow).

DISCUSSION

We have presented a case of multiple anomalies following in-utero exposure to methyldopa and allopurinol. Methyldopa is not considered to be teratogenic [Naden and Redman, 1985]. There is little known about the teratogenic potential of allopurinol as it is rarely prescribed in pregnancy. According to the on-line teratogen database TERIS, the teratogenic risk of allopurinol is undetermined based on very limited data [Friedman and Polifka, 2001]. Gülmezoğlu et al. [1997] studied women treated with allopurinol in addition to vitamins C and E after 24 weeks gestation. No anomalies occurred in the 27 newborns of treated women. Two previous studies

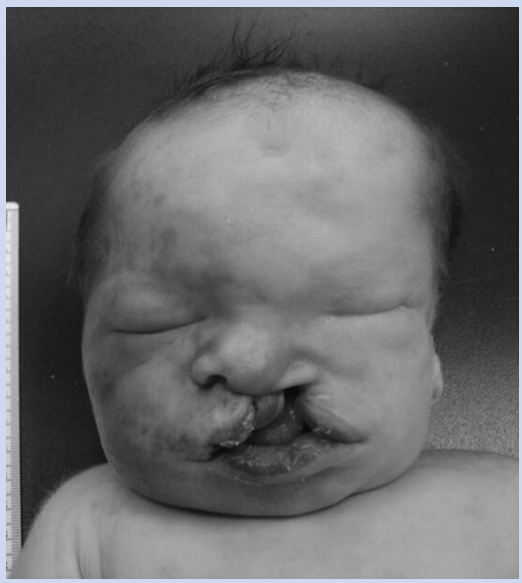

FIG. 3. Frontal view illustrating hypertelorism and unilateral cleft lip and palate.

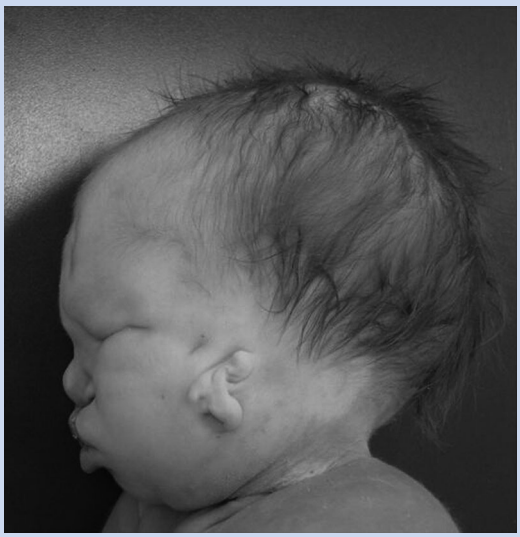

FIG. 4. Left side view illustrating microtia, absence of external auditory canal, micrognathia.

performed on pregnant rats, did not identify any malformations following a single injection of allopurinol at high doses [Bragonier et al., 1964; Chaube et al., 1968]. One mouse study found an increased frequency of cleft palate, growth retardation, and death after first trimester exposure to allopurinol [Fujii and Nishimura, 1972]. A more recent study on rat whole embryo cultures demonstrated teratogenicity and embryolethality after allopurinol exposure [Spézia et al., 1992].

Allopurinol acts on the purine biosynthesis and degradation pathway [Pacher et al., 2006]. It inhibits the enzyme xanthine oxidase, which breaks down purines into uric acid. The lack of xanthine oxidase causes an increase in the concentration of hypoxanthine and xanthine that are converted to adenosine and guanosine monophosphates. Increased levels of these products result in inhibition of amidophosphoribosyltransferase, a key enzyme in purine biosynthesis.

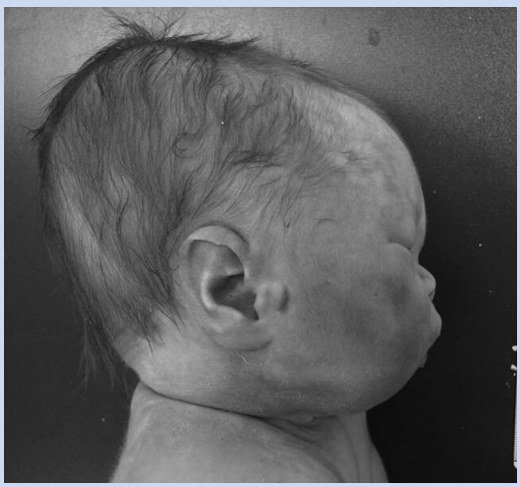

FIG. 5. Right side view illustrating preauricular tag, micrognathia.

The features identified in our case including microtia, auditory canal atresia, eyelid coloboma, microphthalmia, cleft lip and palate, micrognathia, hypertelorism, urogenital anomalies, hypoplasia of the corpus callosum, and diaphragmatic hernia are features that are also seen after mycophenolate mofetil exposure (Table I). Since one of the cases described by Sifontis et al. [2006] was later described in more detail by Parisi et al. [2009], only the later description was used in the Table. The mechanism of action for mycophenolate mofetil also involves interruption in purine biosynthesis [Ransom, 1995]. Mycophenolate mofetil inhibits the enzyme that converts inositol monophosphate to adenosine monophosphate and reversibly inhibits inosine monophosphate dehydrogenase and subsequently de novo synthesis of purine nucleotides [Ransom, 1995]. Interruption in degradation and biosynthesis of purines results in abnormal DNA synthesis, interruption of cell division and possibly DNA methylation. Interestingly, hypertelorism, micrognathia, cleft lip and palate, ear anomalies have been reported due to in-utero methotrexate exposure [Milunsky et al., 1968; Yedlinsky et al., 2005]. The antirheumatic drug, leflunomide in pregnant mice causes limb and craniofacial defects such as exencephaly, cleft palate, and ''open eye'' or failure of eyelid to close [Fukushima et al., 2007]. Both methotrexate and leflunomide act by interruption of purine biosynthesis [Breedveld and Dayer, 2000; Yedlinsky et al., 2005]. Although leflunomide is contraindicated in pregnancy, a study did not find evidence of a substantial teratogenic risk from leflunomide exposure among women who had cholestyramine elimination procedures early in gestation [Chambers et al., 2010].

A number of conditions were considered in the differential diagnosis to explain the pattern of anomalies seen in this infant. As a chromosomal microarray study was not performed, a chromosome microdeletion/duplication syndrome cannot be completely ruled out by a normal karyotype. Hypertelorism-microtia-clefting syndrome has previously been described in the differential diagnosis of anomalies seen following mycophenolate mofetil exposure [Perez-Aytes et al., 2008] and our case shares some features with that condition. Diaphragmatic hernia can be seen in Fryns syndrome [Fryns, 1987], Miller syndrome [Miller et al., 1979], Donnai–Barrow syndrome [Donnai and Barrow, 1993] and Pallister–Killian syndrome [Doray et al., 2002], but microtia is not a feature of these syndromes. Predominately unilateral microtia is a characteristic feature of Goldenhar syndrome, which can be associated with diaphragmatic hernia [Stoll et al., 2008]. Upper eyelid coloboma can also be seen in Goldenhar syndrome [Beck et al., 2005]. Oculo-auriculo-vertebral spectrum is a heterogeneous condition with a broad phenotype which includes Goldenhar syndrome. The etiology of oculo-auriculo-vertebral spectrum can include both genetic and environmental factors [Tasse et al., 2005]. This diagnosis cannot be completely excluded. Even if the diagnosis is oculo-auriculo-vertebral spectrum, the underlying etiology may still be teratogenic We postulate that the presence of facial clefting in combination with serious defects of auricular development in the early embryonal stage may be under strong control of purine biosynthesis and possibly methylation abnormalities secondary to a purine biosynthesis defect.

In summary, we have presented a patient with multiple anomalies consistent with those described after mycophenolate mofetil exposure in an infant exposed prenatally to allopurinol. Both drugs interrupt purine synthesis. We therefore suggest that allopurinol, like mycophenolate mofetil and other drugs which affect purine synthesis be considered potentially teratogenic. We recommend use in pregnancy be avoided if possible. Further clinical reports are however needed to confirm this specific fetal malformation pattern is associated with maternal allopurinol exposure.

EDITOR'S NOTE

In this timely observation Kozenko and colleagues report on an infant with multiple congenital anomalies born after a gestational exposure to allopurinol. Because of the resemblance of the child's pattern of defects to the recently described human teratogen, mycophenolate mofetil (MMF), and because allopurinol and MMF both disrupt purine synthesis, the authors posit that allopurinol may also represent a teratogen. Limited animal studies support the hypothesis. Their line of reasoning is persuasive: Kozenko et al. are inferring causation based on a unique application of the astute clinician model of determining human teratogenicity. Here, the rarity of the exposure (with a similar mechansim of action to MMF) coupled with the distinctive phenotype (overlapping MMF embryopathy) suggest causation. Additional cases of gestational exposure to allopurinol with a similar phenotype will be needed to support the hypothesis.

John C. Carey, MD
Editor-in-chief

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