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Clinical Report

Infant With Severe Penicillamine Embryopathy Born to a Woman With Wilson Disease

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We report a chromosomally normal infant boy with congenital diffuse cutis laxa, severe micrognathia, contractures of all limbs, and central nervous system abnormalities including agenesis of the corpus callosum, born to a woman taking D-penicillamine (DP) for Wilson disease (WD) throughout her pregnancy. His postnatal course was remarkable for chronic lung disease, profound developmental delays, and probable cortical blindness, as well as resolution of his cutis laxa. Embryopathy is a rare complication in babies born to pregnant women treated with DP, and there have been only seven previous reports of birth defects in exposed infants (three of which had favorable postnatal outcomes). The etiology of the severe outcome in this boy is unclear, but prenatal measurement of maternal copper and zinc levels may be indicated for management.

KEY WORDS: penicillamine embryopathy; cutis laxa; joint contractures; arthrogryposis; corpus callosum agenesis; developmental delay; cortical blindness; Wilson disease

INTRODUCTION

Embryopathy is a rare complication in babies born to women being treated with D-penicillamine (DP). Numerous reports support the safety of prenatal use of DP in pregnancy. Roubenoff et al. [1988] summarized studies of a total of 40 women taking DP for Wilson disease (WD) during pregnancy who had 57 normal babies. Furthermore, they reviewed reports on 93 babies born to mothers exposed to various doses and durations of DP while pregnant, of whom only four had congenital abnormalities. Of these four, two of the mothers had WD, and their babies had reversible cutis laxa and inguinal hernias. To date, there have been 10 reported cases of birth defects in DP-exposed babies. Three of these were not published but were submitted to the United States Food and Drug Administration (FDA) in 1966–1984 [Rosa, 1986]. Details of these cases are summarized in Table I.

Continuing DP therapy in pregnant women with WD has been recommended because stopping therapy has led to clinical deterioration from renewed copper toxicity [Scheinberg and Sternlieb, 1975; Brewer et al., 2000], although Marecek and Graf [1976] offered an alternative view. Untreated maternal WD has been associated with infant hepatomegaly and a persistent hepatic enzyme elevation [Oga et al., 1993]. Of the five cases of congenital anomalies in DP-exposed infants from mothers with WD, only two had adverse outcomes (first-trimester viremia [Rosa, 1986] and maternal hypotension [Gal and Ravenel, 1984]), both of which might be explained by other complicating factors. It is generally accepted that DP is safe to give to pregnant women with WD.

CLINICAL REPORT

The propositus (Figs. 1–3) is a 16-month-old male born after 37 weeks gestation to a 35-year-old G2 P1 woman with WD, who was on DP throughout the pregnancy. Vaginal delivery was induced because of oligohydramnios. She took 1 g/day DP for the first 20 weeks of gestation, but this was reduced to 500 mgm/day after her first fetal ultrasound at 16 weeks showed arthrogryposis, bowed femurs, and a single umbilical artery. Amniotic fluid was normal then, but oligohydramnios developed prior to delivery. His amniocentesis karyotype was 46XY. The pregnancy was otherwise uncomplicated, with no other known maternal exposures. Maternal urine copper excretion was followed, but

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TABLE I. Congenital Malformations With D-Penicillamine Exposure Findings and Outcomes

	Findings						
	Cutis laxa	Joint involvement	Inguinal hernia, males	GI disorders	CNS involvement	Other	Outcome
Maternal Disease							
Proband	+	Arthrogryposis	+	+	Corpus callosum agenesis, probable cortical blindness	Possible pulmonary dysplasia; micrognathia	Severe developmental delay
Wilson disease	+	−	+	−	−	Micrognathia	Hernia repaired, skin normal @ 4 months
	+	−	+	+	−		Hernia repair delayed; skin and GI normal @ 4 months
	−	−	N/A	−	−	Cleft lip and palate	Normal other than CL/P*
	−	Arthrogryposis	N/A	−	Hydrocephalus	Maternal splenic artery rupture 24 weeks gestation	Died @ 18 hours; intraventricular bleed
	−	Neurogenic, clubfeet	?	−	Cerebral palsy, congenital blindness	? Maternal varicella first trimester	Crib death @ 4 months (FDA case report)
Cystinuria	+	Hyperflexible joints	N/A	+	−		Died age 50 days; sepsis, S/P GI surgery
	+	−	N/A	−	−	DiGeorge anomaly	Died DOL 5 cardiac complications
	−	−	?	−	Hydrocephalus		Treated with shunt (FDA case report)
Rheumatoid arthritis	+	Flexion contractures, knees/hips	+	+	−		Died DOL 4, S/P GI surgery
Scleroderma	−	−	?	?	−	Left preaxial polydactyly, syndactyly left fingers, toes (2) bilaterally	? (FDA case report)

N/A, not applicable; GI, gastrointestinal; S/P, status post; CNS, central nervous system; DOL, day of life; FDA, Food and Drug Administration; CL/P, cleft lip/palate.
*Martinez-Frias et al. [1998].

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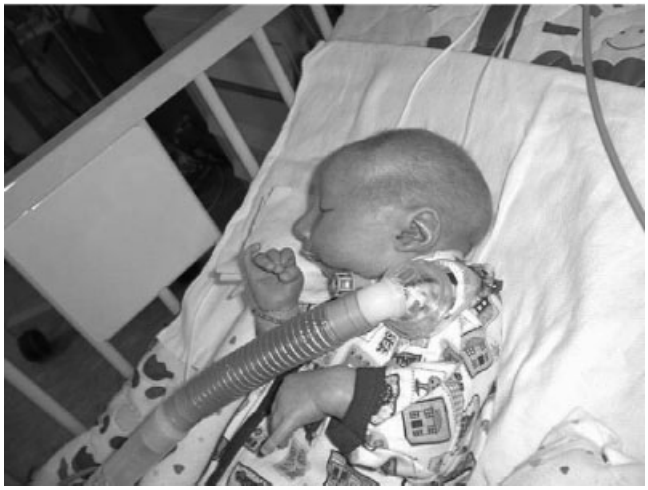

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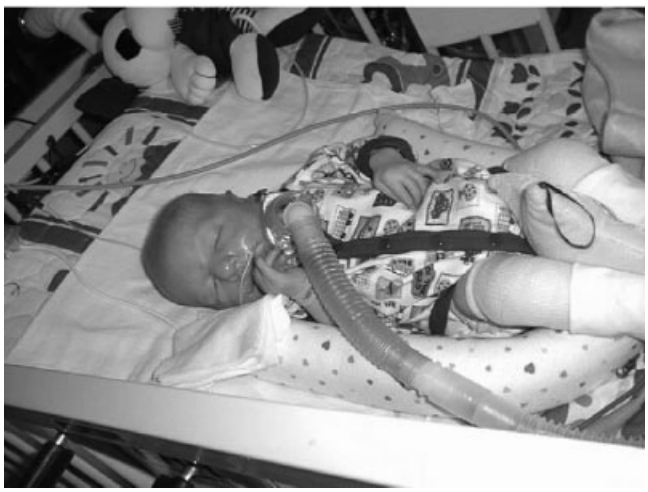

Figs. 1 and 2. The proband at about 2 weeks old. Note contractures and severe micrognathia.

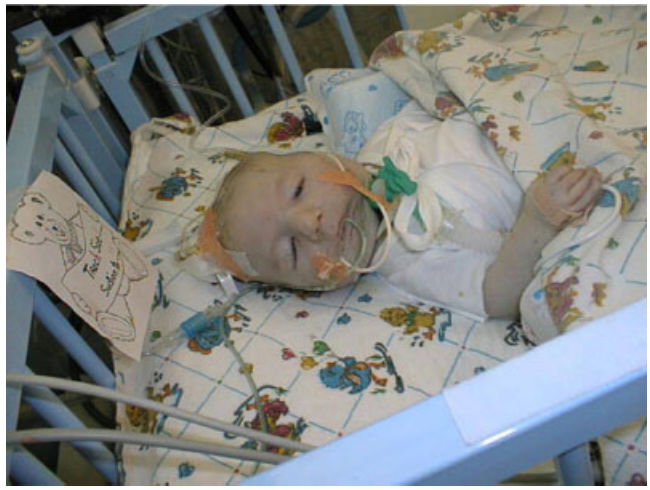

Fig. 3. Cutis laxa evident over the face and neck, giving the impression of ptosis and downslanting palpebral fissures.

maternal serum zinc and copper levels were not determined. At birth he weighed 2,190 g (3%), his head circumference was 31.5 cm (3%), and he had diffuse cutis laxa; severe micrognathia; contractures of all limbs with shoulders internally rotated, elbows/wrists/knees/hips flexed, bowed femurs, camptodactyly, and clubbed feet with normal muscle bulk and tone; flat, posteriorly rotated ears; bridged palmar creases; undescended testes; and brisk reflexes. Otherwise, he was neurologically normal. A chest radiograph demonstrated hooked clavicles and a bell-shaped thorax. A brain MRI showed agenesis of the corpus callosum and colpocephaly. Results of a postnatal echocardiogram and abdominal ultrasound, including renal evaluation, were normal.

A tracheostomy was performed for airway protection on his first day of life because of severe micrognathia. He has no history of significant hypoxia. He has remained ventilator-dependent because of chronic hypoventilation and recurrent pulmonary infections. A copper blood level done at about 24 hr was 40 μgm/dl (normal: 60–190 μgm/dl), but no zinc level was done. Copper and zinc replacement was initiated parenterally the next day at 30 and 300 μgm/kg/d, respectively, and continued for 5 months. A healing right proximal humerus fracture was noted at age 1 month, with no history of trauma. He developed a right inguinal hernia and was found to have pyloric stenosis and gastroesophageal reflux. Mandibular distraction surgery was done at 3 months and was followed shortly thereafter by an inguinal herniorrhaphy, pyloromyotomy, and Nissen fundoplication, all of which were uneventful. He has had bronchopulmonary dysplasia with recurrent pulmonary infections and atelectasis. At age 8 months he had near full resolution of his cutis laxa and marked improvement of joint contractures after casting, but also had profound developmental delays and apparent cortical blindness. His ophthalmology examination was normal aside from a failure to fix and follow (although he responded to light). Auditory brainstem evoked potentials were abnormal at age 5 months. He developed partial complex seizures of undetermined etiology at about 1 year of age. A head CT scan showed decreased brain volume, enlarged ventricles, corpus callosum agenesis, and bilateral subdural hygromas thought to be secondary to brain atrophy.

His 5-year-old maternal half-brother, who was exposed to 1 g/day DP throughout gestation, has congenital partial agenesis of the corpus callosum, but is developmentally normal. He has no history of contractures or cutis laxa.

DISCUSSION

DP (Cuprimine®, Merck and Co., Inc., Whitehouse Station, NJ or Depen®, MedPointe, Inc., Somerset, NJ) or ββdimethyl cysteine-D isomer, is a sulfhydryl-containing amino acid, a derivative of penicillin. It is used as a heavy metal chelating agent for lead, cadmium, and mercury toxicoses, as well as a copper chelator in

WD. It has been used in the treatment of neoplasia, scleroderma, rheumatoid arthritis, and other autoimmune diseases, as well as in cystinuria, because it forms disulfide compounds with cysteine [Keen et al., 1983]. Early reports [Mjolnerod et al., 1971; Solomon et al., 1977] cautioned that DP might be teratogenic, especially when used maternally for disorders other than WD [Solomon et al., 1977]. It was believed that in WD, adverse prenatal effects of DP, which are presumably mediated by copper deficiency, would not occur due to the high level of circulating maternal copper [Keen et al., 1982b]. It was also thought that toxicity resulting directly from DP would not occur because of the increased binding and excretion of the maternal copper/DP complex [Solomon et al., 1977; Lyle, 1978]. However, Linares et al. [1979] reported a case of cutis laxa in a newborn who was prenatally exposed to DP because the mother had WD, and other reports soon followed.

Whether DP is embryotoxic by itself and/or through the action of inadequate levels of copper or zinc is not clear. DP metabolites have been found in the urine of prenatally exposed infants, verifying that it crosses the placenta in humans [Crawhall et al., 1967; Albukerk, 1973]. The actions of DP on connective tissues, including in the lungs, are believed to be mediated through the action of lysyl oxidase, a copper-requiring enzyme active in cross-linking elastin and, to a lesser extent, collagen. DP may also interact with aldehydes to form thiazolidine derivatives, thereby directly affecting collagen crosslinking [Nimni and Bavetta, 1965; Friedman, 1977; Beck et al., 1981; Keen et al., 1983].

DP causes a reduction of maternal plasma copper and zinc, and fetal hepatic zinc and plasma copper in exposed pregnant rats and their fetuses [Keen et al., 1982b, 1983]. DP has been shown to be toxic to the rat embryo in a dose-response fashion, causing loose skin, arthrogryposis, abdominal hernia, spina bifida, and (in high dose) cleft palate [Steffek et al., 1974; Keen et al., 1983]. Abnormalities persist even when copper supplementation is given to bring maternal serum levels to around the normal range, although their frequency decreases dramatically [Mark-Savage et al., 1983]. Maternal copper restriction has also been demonstrated to be teratogenic in developing mammalian embryos. This has been found in lambs, in which it causes ataxia and spasticity due to CNS hypomyelination, and poorly developed, brittle, fracture-prone bones; guinea pigs, with CNS abnormalities similar to the lambs; and rat pups, which were hyperirritable, but lacked nerve fiber degeneration [Keen et al., 1982a; Rosa, 1986]. Rucker and Tinker [1977] reported that young canines and swine fed copper-deficient diets had deformed leg bones thought to be secondary to impairment of osteogenesis. They found a high ratio of soluble-to-insoluble collagen that could have reduced crosslinks needed for normal bone formation [Rosa, 1986]. Bone abnormalities have been found in copper-deficient calves and fowl as well [Keen et al., 1982a]. However, copper deficiency alone may not cause cutis laxa, as rat pups born to dams with copper-deficient diets, and not given DP, did not have this finding [Mark-Savage et al., 1983]. This is consistent with Jaffe et al.'s [1968] study in which young rats fed diets restricted in copper had no discernable dermal collagen abnormalities, but developed marked changes when given DP. The report by Harpey et al. [1983] of a DP-exposed infant with a high level of copper at birth and cutis laxa supports this experimental observation. Dams given triethylentetramine (TETA), another copper chelator, had offspring with copper deficiency, hemorrhages, and micrognathia; however, cutis laxa was not reported [Cohen et al., 1983]. Conversely, cutis laxa was found in mouse fetuses born to dams fed copper-deficient diets but not given DP [Keen et al., 1982a].

In addition to these abnormalities, Kilburn and Hess [1982] reported pulmonary dysplasia as a complication in rats born to dams given DP and a normal copper diet throughout pregnancy. Defects seen with high doses of DP (800–1,600 mgm/kg/day for 6 days (as compared to a typical human dose of 20 mgm/kg/day) not adjusted for metabolic mass differences) include cystic changes of the lungs (~40%), lung underinflation, tracheobronchomegaly (~40%), and pleural hemorrhage (18%). These changes were not seen in rats given copper replacement. Bronchiolitis obliterans has been reported in patients with rheumatoid arthritis who were taking DP chronically [Geddes et al., 1977; Epler et al., 1979]. In our patient, it is unclear whether the chronic lung disease is a direct effect of DP and/or copper deficiency, or merely a consequence of fetal hypokinesia.

In the cases of human DP embryopathy, frequent features include cutis laxa (six of 11 cases), joint abnormalities (five of 11 cases), inguinal hernia (four of seven males), and CNS malformations (four of 11 cases), as shown in Table I. It seems most likely that the infant with cleft lip and palate but with no other anomalies, born to a DP-treated mother with WD, did not truly have DP embryopathy. It is difficult to discern whether the toxic effects of DP contributed to all the anomalies in a previously reported infant with cutis laxa and DiGeorge sequence born to a DP-treated mother with cystinuria [Beck et al., 1981]. Unfortunately, testing for the DiGeorge deletion at chromosome 22q11.2 had not yet been developed when that case was reported. Since thymic hypoplasia has been reported in rat pups exposed to high-dose DP [Kilburn and Hess, 1982] and may occur in association with zinc deficiency [Schaen and Goldsmith, 2002], and since the infant also had cutis laxa, a more typical manifestation of DP embryopathy, it seems more likely that these problems were DP-related.

Zinc deficiency may cause increased susceptibility to infections because of cellular or humoral immunity impairment [Schaen and Goldsmith, 2002], and may have contributed to the demise of the two affected offspring of mothers without WD, who died after surgery (at least one died from sepsis). However, zinc levels were not measured. In a case reported by Harpey et al. [1983], the plasma zinc level was low at birth (85 μgm/dl (normal level at birth: 110–130 μgm/dl)), although that infant had no reported problems with sepsis.

The etiology of the severe neurological outcome in our patient is unclear. Many of his abnormalities (arthrogryposis, micrognathia, humerus fracture, cutis

laxa, inguinal hernia, and pyloric stenosis) are consistent with both experimental animal data and clinical findings in patients with an inability to utilize copper. The allelic human disorders Menkes syndrome and the occipital horn syndrome (OHS; also known as cutis laxa, X-linked or type IX Ehlers-Danlos syndrome) are caused by mutations in the X-linked Menkes gene (MNK), which codes for the intracellular copper transporter Menkes protein [Culotta and Gitlin, 2001]. Menkes syndrome is characterized by hair and collagen abnormalities, including fractures and vascular complications, and cerebral degeneration. Neurological abnormalities are present at birth, implying that copper plays an important role in central nervous system development. OHS patients have mild mental retardation and marked connective tissue abnormalities [Culotta and Gitlin, 2001]. Interestingly, the two reported patients with hydrocephalus (reminiscent of our patient's cerebral atrophy and ventriculomegaly), and the unpublished FDA case report of cerebral palsy, clubbed feet, and congenital blindness (structural eye abnormalities not reported), are similar to the findings in our patient. Our patient's agenesis of the corpus callosum may be another condition entirely, possibly familial, since his half-brother was also affected. Alternatively, since this half-brother was also exposed to DP during gestation, his agenesis of the corpus callosum may be a mild form of DP embryopathy.

This is one of the most severe cases of penicillamine embryopathy reported for an infant born to a woman with WD. Copper deficiency appears to play a large role in birth defects, and there is animal data supporting the idea that replacement during pregnancy decreases congenital anomalies, but copper deficiency and/or prenatal exposure to DP do not explain all of our patient's findings. In women treated with DP during pregnancy, measurements of maternal and neonatal copper and zinc levels may increase our understanding of the mechanisms of embryopathy, and assist with postnatal management.

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