American Journal of Medical Genetics 76:274–275 (1998)

Letter to the Editor

Prenatal Exposure to Penicillamine and Oral Clefts: Case Report

To the Editor:

We would like to present a patient derived from the Spanish Collaborative Study of Congenital Malformations (ECEMC) [Martínez-Frías, 1994, 1995], who was exposed to penicillamine during the entire pregnancy. The infant, a girl, was born at 41 weeks of gestation to a G3P2, 22-year-old mother and a nonconsanguineous 28-year-old father. The mother has Wilson disease, which was treated daily with therapeutic doses of penicillamine during the entire pregnancy. The pregnancy was complicated only by scant vaginal bleeding. There was no other exposure to known teratogens or risk factors. The girl, who was the first affected individual in the family, had bilateral cleft lip with totally cleft palate, and a birth weight of 3,130 g, which is adequate for gestational age. The child did not have lax skin or flexion contractures of the knees or hips.

Penicillamine, a heavy-metal chelator, is used for treatment of cystinuria, rheumatoid arthritis, Wilson disease, and autoimmune diseases [Harris and Sjordsma, 1966; Briggs et al., 1994]. In experimental studies this drug has a known teratogenic effect, producing cutis laxa, cleft palate, abdominal herniations, wavy and curved ribs, arthrogryposis, and spina bifida occulta [Solomon et al., 1977; Rosa, 1986; Steffek et al., 1972; Mark-Savage et al., 1981; Keen et al., 1982; Myint, 1984]. However, although prenatal exposure to penicillamine has been linked to cutis laxa in the newborn infant [Mjolnerod et al., 1971; Harpey et al., 1983; Rosa, 1986], the teratogenic effect in humans is subject to controversy. There are some case reports [Mjolnerod et al., 1971; Solomon et al., 1977; Harpey et al., 1983; Linares et al., 1979; Beck et al., 1981; Gal and Ravenel, 1984] of infants with congenital anomalies such as fragility of veins, contractures, inguinal hernia, dysplastic ears, micrognathia, DiGeorge anomaly, cardiac anomalies, thymic hypoplasia, and absent parathyroids. Nevertheless, other studies have shown normal infants after prenatal exposure to penicillamine, even from patients with Wilson disease [Folb and Graham Dukes, 1990].

None of the previous case reports showed oral clefts as in our case. Thus, we cannot totally exclude that the oral cleft in this case is a coincidence. However, penicillamine induced cleft palate in mice [Myint, 1984] and rats [Steffek et al., 1972], but in response to very high doses. Animal studies cannot be extrapolated to less severely exposed human pregnancies; however, it is not unreasonable to hypothesize that oral clefts may also be produced in humans, something to be analyzed in further studies. It is generally accepted that one should observe at least 2 cases of associations between a particular malformation and a rare exposure before considering a hypothesis of causal relationship. Nevertheless, we think that isolated case reports are important in drawing the attention to possible associations. Thus, we are presenting this case in order to stimulate the reporting of similar observations generating the hypothesis of a causal relationship to be further analyzed.

Folb and Graham Dukes [1990] think that there are no controlled studies to assess the risks of in utero exposure to penicillamine, because of the relative rarity of the diseases for which this drug is used. This is the situation in our data where, among 24,696 mothers of malformed infants and 24,131 mothers of controls, only one was exposed to penicillamine and had the child whom we are describing here.

The fact that some cases exposed to penicillamine have presented with DiGeorge anomaly, cardiac defects, absent parathyroids, and now oral clefts, suggests that the effect of this drug on prenatal development may also be in early pregnancy.

Although the present evidence, based on a small number of case reports, suggests that a teratogenic risk may exist after prenatal exposure to penicillamine, we agree with Rosa [1986] that treatment with penicillamine in women with Wilson disease should be continued throughout pregnancy, since the benefits outweigh the risks, and that a prudent attitude for conditions other than Wilson disease, for which there are safer alternatives, would be to discontinue penicillamine during pregnancy.

Contract grant sponsor: Dirección General de Farmacia y Productos Sanitarios, Ministerio de Sanidad y Consumo, Madrid, Spain.

*Correspondence to: Dr. M.L. Martínez-Frías, ECEMC, Facultad de Medicina, Universidad Complutense, 28040 Madrid, Spain.

Received 9 October 1997; Accepted 14 November 1997

ACKNOWLEDGMENTS

This work was supported in part by a grant from Dirección General de Farmacia y Productos Sanitarios, Ministerio de Sanidad y Consumo, Madrid, Spain.

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M.L. Martínez-Frías*
ECEMC
Departmento de Farmacología
Universidad Complutense
Madrid, Spain

E. Rodríguez-Pinilla
E. Bermejo
ECEMC
Facultad de Medicina
Universidad Complutense
Madrid, Spain

M. Blanco
Servicio de Pediatría
Hospital Xeral de Vigo
Pontevedra, Spain