VACTERL Association With High Prenatal Lead Exposure: Similarities to Animal Models of Lead Teratogenicity

The VACTERL association is one of the more common patterns of multiple malformations in children, with an incidence of approximately 1.6 cases per 10 000 live births.[1] The pattern of defects consists of vertebral anomalies (found in 70% of patients), anal atresia with or without fistula (80%), cardiac defect (50%) with ventricular septal defect being most common, tracheoesophageal fistula (70%), renal anomalies (53%), and limb anomalies (65% with radial anomalies and 23% with lower extremity defects).[2]

The definition of the VACTERL association as a distinct entity is based on the finding that its constituent anomalies are associated in a nonrandom manner.[1,3,4] The vast majority of cases are sporadic, but there are rare reports of familial recurrence. These may be due to genetic or common environmental factors. For example, there have been conflicting reports about a possible involvement of progestogen and/or estrogen.[5,6] Overall, there are no environmental or genetic factors that have been consistently implicated as causative agents.

There have been a variety of theories put forth to explain the association of the diverse anomalies found in the VACTERL association. These revolve around the possibility that there may be a developmental field common to all of the involved systems.[1] Specifically, defective development of the neural tube and preaxial mesoderm has been postulated to be able to produce the full spectrum of defects found in the VACTERL association.[1,3,7,8] However, there is no direct evidence in support of this hypothesis.

We describe here a patient with the VACTERL association whose mother had high lead levels in the first trimester of pregnancy. The implications of this case for the pathogenesis of the VACTERL association are discussed in the context of animal data demonstrating a toxic effect of lead on the neural tube and preaxial mesoderm.

CASE REPORT

The patient was a 2500-g female product of a full-term gestation born to a gravida 2, para 0, spontaneous aborta 1 23-year-old white woman by normal spontaneous vaginal delivery. Six months prior to becoming pregnant, the patient's mother had taken a job in a factory where she used a blowtorch to cut leaded glass. At 8 weeks' gestation, she was found to have a lead level of 62 μg/dL (2.99 μmol/L) (normal 0 to 20 μg/dL [0 to 0.97 μmol/L]). Her hemoglobin level at that time was 13.2 g/dL (132 g/L); white blood cell count was 11 500 mm^{-3} (11.5 × 10^9/L). She was clinically asymptomatic and had no complaints of neurologic problems. No treatment for the high lead level was undertaken but she did stop working in the glass factory. At 12 weeks' gestation, her lead level was 15 μg/dL (0.72 μmol/L). At 14 weeks' gestation, her lead level was 5 μg/dL (0.24 μmol/L), with a free erythrocyte protoporphyrin (level of 21 μg/dL (0.37 μmol/L) (normal 0 to 35 μg/dL [0 to 0.62 μmol/L] and a hemoglobin level of 12.3 g/dL (123 g/L). Serum α-fetoprotein value at 17 weeks gestation was 50 risk units (normal 50 through 99 risk units). Serum glucose concentration was normal throughout the pregnancy. The infant's father, who also worked in the same factory but at a different job, had a lead level of 11 μg/dL (0.53 μmol/L).

Family history was remarkable only for the mother having had a previous spontaneous abortion at 8 weeks' gestation, occurring before she had any lead exposure. There was no family history of any of the anomalies found in the VACTERL association or of multiple spontaneous abortions.

Physical examination at birth revealed an alert, active newborn with good muscle tone. Birth parameters were as follows: length = 48.5 cm (25th percentile), weight = 2500 kg (3rd percentile), and head circumference = 33.5 cm (25th percentile). There was a hypoplastic left thumb, a right radial clubhand, bilateral clubfeet, a small sacral dimple, anal atresia, and a III/VI holosystolic murmur. External genitalia were normal. Neurologic examination results were normal for a newborn. Results of her physical examination were otherwise normal.

Vaginogram revealed a rectovaginal fistula. Echocardiogram showed a moderate conoventricular septal defect and a dilated coronary sinus with a left superior vena cava draining into the coronary sinus. Skeletal survey showed a sacral segmentation anomaly with absence of S5 vertebra and a midline cleft in S4 (Figure), but the lumbosacral spinal cord appeared normal on ultrasonographic examination. There was no evidence of lead-induced growth arrest lines. Computed tomographic scan of the pelvis was consistent with a high type of imperforate anus. Renal ultrasonography showed no abnormalities but voiding cystourethrogram showed bilateral grade III vesicoureteral reflux. Results of an ophthalmologic examination were normal. Head computed tomographic

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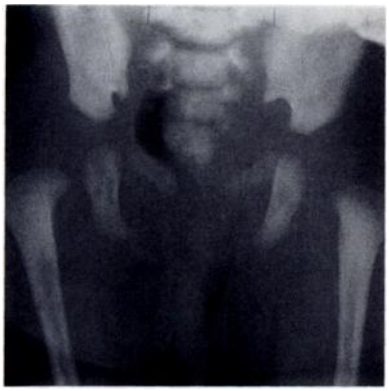

Figure. Radiograph of the sacral vertebrae demonstrating absence of S5 and a midline cleft in S4.

scan, electroencephalogram, electromyelogram, nerve conduction velocities, and brainstem auditory evoked responses were normal. Hemoglobin level at birth was 12.8 g/dL (128 g/L), free erythrocyte protoporphyrin level was 42 μg/dL (0.74 μmol/L), and lead level was 5 μg/dL (0.24 μmol/L). Giemsa-trypsin Giemsa banded karyotype was normal (46, XX).

DISCUSSION

This neonate, whose mother had extremely elevated lead levels during the first trimester of pregnancy, had multiple congenital anomalies consistent with the VACTERL association. Although the VACTERL association is not a true diagnosis, for practical purposes it has been considered to be present when a patient has three of the six major features.[1] Our patient had vertebral anomalies (absent S5), anal atresia, cardiac defect (ventricular septal defect), renal anomaly (vesicoureteral reflux), and a limb anomaly (hypoplastic thumb). She lacked only the tracheoesophageal fistula.

The effect of prenatal lead exposure on the developing human fetus has not been well studied.[9] It is known that lead crosses the human placenta and placental lead levels are close to those in the plasma.[9] Increased placental lead levels have been correlated with an increased incidence of stillbirths,[9] mental retardation,[10] and congenital anomalies.[11]

The best study in humans of the relationship between maternal lead levels and congenital anomalies was done at the time of birth by Needleman et al.[11] Neonates whose mothers had elevated umbilical cord lead levels had an increased incidence of minor congenital anomalies which included hemangiomas, lymphangiomas, hydroceles, skin tags, and undescended testicles. However, they did not find any consistent pattern of anomalies, possibly because the highest lead level in their study was only 35.1 μg/dL (1.69 μmol/L).

In contrast with the data in humans, lead teratogenicity in animals has been studied extensively.[12] Hamsters, chicks, and rats all demonstrate a characteristic pattern of malformations when subjected to prenatal lead exposure. In particular, a urorectocaudal pattern of malformations is seen.[12–14] Prominent malformations include caudal vertebral malformations, imperforate anus, genital anomalies, lower extremity anomalies, and hydrocephalus. Upper extremity anomalies with amelia and deformed radius and ulna are found less frequently.[13]

The pathogenesis of lead teratogenicity in animals has been studied by Carpenter and Ferm.[14] Morphologically, they found that the initial lesion in lead-exposed hamster embryos is caudal edema that in some cases progresses to blistering and hemorrhage. Marked swelling of the neural tube and infiltration of neural crest cells into the surrounding paraxial mesenchyme were seen. This edema caused mechanical disruption of the neural tube and adjacent tissues, including the paraxial presomite mesoderm. Carpenter and Ferm[14] believed that the characteristic pattern of malformations could be entirely explained by the lead-induced neural tube abnormalities. Other teratogenic agents produce a spectrum of anomalies similar to that seen with lead.[8] In many cases, neural tube swelling has also been seen.

The similarity between the lesions induced by prenatal lead exposure and the malformations in our patient is striking, especially because it has been speculated that the VACTERL association is part of a spectrum of anomalies resulting from a disruption of the axial mesoderm.[1,3,4,7] Interestingly, some of the other malformations found in patients with the VACTERL association such as hydrocephalus and genital anomalies are also found in the animal models of lead embryopathy.[13] Cardiac anomalies, which are a major feature of the VACTERL association, are present but not common in animals exposed to lead prenatally. However, conotruncal cardiac anomalies, the type found in our patient, have been produced in chick embryos by ablation of specific regions of the neural fold.[15]

The association between lead exposure and the VACTERL association has not been previously reported despite the many cases of severe lead exposure that have occurred, especially in the earlier part of the 20th century. One possible explanation concerns the pattern of lead exposure, which in the case described here was fairly intense but of short duration early in the pregnancy. This mimics more closely the experimental protocols that produce the urorectocaudal pattern of malformations in animals.[12] Animal studies using low-dose and/or

chronic treatment protocols tend to see an increase in fetal wastage rather than congenital malformations and may more closely resemble earlier industrial exposures where an increase in abortions and stillbirths with high lead levels was evident.[9,12]

It is impossible to establish a causal relationship between prenatal lead exposure and the anomalies of the VACTERL association on the basis of a single report. This can only be done by further epidemiologic studies. However, the clinical manifestations seen in our patient in combination with the animal data on lead embryopathy suggest that such a relationship may in fact exist.

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FOCUS ON DELTA - THE EFFECT SIZE

The sample size required in a randomized trial depends on the alpha (or type I) error and the beta (or type II) error deemed acceptable and on the size of the treatment effect sought (called the delta)...Delta should be set to define a clinical improvement that is great enough that most clinicians or patients would select the new treatment despite its potential unknown hazards... if the delta is set to allow this, there is no reason to set beta larger than alpha. It is better to vary delta than the relative sizes of alpha and beta in determining sample size, because the former makes explicit the extent of trade-offs between known and potential effects of different treatments.

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