Maternal Intrauterine Herpes Simplex Virus Infection Leading to Persistent Fetal Vasculature

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Herpes simplex virus can cause serious ocular and systemic disease in the neonate. The mode of transmission to the neonate is usually from the maternal birth canal to the fetus intrapartum; but much more rarely, hematogenous transplacental infection can affect the developing fetus months prior to birth. Persistent fetal vasculature occurs when there is persistence of the fetal ocular vasculature, which normally regresses prior to birth. To our knowledge, we report the first case of serologically proven intrauterine herpes simplex virus infection associated with bilateral persistent fetal vasculature in a surviving term infant.


REPORT OF A CASE

The consult service of the Bascom Palmer Eye Institute, Miami, Fla, was asked to evaluate the eyes of a 1-day-old male infant born at 39 weeks' gestation. Prenatal ultrasonography had shown cerebral ventricular dilatation, direct communication of the posterior fossa to the fourth ventricle, and cystic lesions within the brain parenchyma. The patient's mother was a healthy 21-year-old primigravida who had had an upper respiratory tract infection during the late first trimester. The patient's mother denied any history of sexually transmitted diseases or any genital lesion during the pregnancy. She denied any drug or alcohol use and lived in Florida for the entire pregnancy.

The patient had Apgar scores of 7 and 8 at 1 and 5 minutes, respectively. Birth weight was 2725 g (50th percentile) and head circumference was 32 cm (10th percentile). The child was noted to have minimal spontaneous movement but was able to breathe without mechanical ventilation. The patient appeared morphologically normal. Findings from pulmonary, cardiovascular, gastrointestinal, and genitourinary examination were normal. Results of neurologic examination revealed hypotonia and absence of Moro, suckling, and gag reflexes.

Ophthalmologic examination findings revealed 5-mm pupils that were non-reactive in both eyes. External examination findings showed white and quiet conjunctivae and clear corneas. The iris stroma was normal, but multiple fine, radially oriented vessels anterior to the iris converged centrally at an area of plaque on the anterior lens capsule in both eyes (Figure 1). A central plaque was also visible on the posterior lens capsule, but the lens was otherwise clear in both eyes. Findings from fundus examination revealed diffuse chorioretinitis with necrotic-appearing yellow exudates obscuring all normal fundus landmarks. Ocular ultrasonography revealed a thin membrane from the lens to the fundus causing a trac-
tional retinal detachment in both eyes (Figure 2). Axial lengths were decreased (14 mm in both eyes; reference length, 17 mm).

A computed tomographic scan of the head showed marked dilatation of the ventricles, an extremely low-density brain parenchyma, and calcifications surrounding the ventricles and the frontal and occipital horns (Figure 3). Findings from serologic studies for the infant and mother were negative for Toxoplasma gondii IgM and IgG, rubella IgG, and cytomegalovirus IgM. Findings from the infant's and mother's tests for syphilis were both negative. The quantitative findings from an enzyme-linked immunosorbent assay for HSV 1 and 2 IgG were positive in both the mother and infant (2.43 and 2.12 arbitrary units, respectively) (reference range, <0.92 arbitrary units), and both mother and infant tested positive for HSV 1 and 2 IgM. Findings from the infant's cerebrospinal fluid for HSV 1 and 2 IgM were positive. Based on these studies, the diagnosis of intrauterine HSV infection was made. At follow-up 6 months later, the patient's pupils were constricted and nonreactive, and the anterior fetal vessels remained (Figure 4).

COMMENT

Herpes simplex infections in newborn infants are often devastating, leading to high morbidity and mortality.1 Neonatal HSV infections are rare, with an incidence of 1 case per 10000 live births.2 Neonatal HSV infection is usually contracted from the birth canal, and the systemic manifestations occur days to weeks after delivery.2 Transplacental infection of the fetus is even more rare, but histopathologic studies have also confirmed the presence of HSV in maternal uterine, endometrial, and placental tissues.3 The HSV genomic sequences from ocular tissue have been identified by polymerase chain reaction,2 and HSV particles have been identified by electron microscopy in the retinal tissue of eyes from a child who died of a disseminated herpetic infection.4 Maternal genital herpes is asymptomatic or unrecognized in 60% to 80% of women,5 and although our patient's mother did not have any symptoms of a sexually transmitted disease, she was shown serologically to have an acute HSV infection. Since IgM does not cross the placenta, presence of HSV IgM in both the mother and the infant indicates independent infection in each.

Figure 1. Persistence of the pupillary membrane and anterior tunica vasculosa lentis in the right eye of a 1-day-old infant (arrowheads). Note the central lens plaque (arrow). The infant's left eye was similar in appearance.

Figure 2. Ocular ultrasound scan of the left eye. Note the fibrous membrane (arrow) extending from the posterior lens to the posterior pole causing a tractional retinal detachment (arrowheads). This membrane also exerted traction on the equatorial retina, causing it to detach.
individual. High levels of IgG in both mother and child indicate that the infection did not occur during the peripartum period. We hypothesize that the transplacental mode of HSV infection affected the unborn fetus, leading to the ocular and systemic findings described previously.

One unique feature in this case was the arrest of development that occurred in our patient’s eyes as a result of the HSV infection. Goldberg\(^6\) has introduced the term persistent fetal vasculature (PFV) as an encompassing term for the postnatal persistence of the vasculature that would normally regress before birth. During normal growth and development in utero, these intracocular vessels develop during the first month of gestation, reach maximal development during the second and third month, and then begin the process of involution as the mature ocular anatomy becomes better developed. Mann\(^7\) postulated that an arrest of development, for whatever inciting reason, causes the fetal vascular element present at the time of the insult to persist and not to undergo the normal process of involution.

Most cases of PFV are unilateral and sporadic and not associated with other systemic abnormalities.\(^6\) In cases of PFV associated with systemic abnormalities, ocular involvement is often bilateral.\(^8\) The embryogenesis of the fetal ocular vasculature has been studied extensively\(^6\) and has been summarized by Goldberg.\(^6\) In our case, the anterior tunica vasculosa lentis, pupillary membrane, and the iridohyaloid vessels were developed (Figure 1). These vascular structures develop during the first trimester, with maximal development occurring at 8 to 12 weeks’ gestation.

The Cloquet canal, which contains the hyaloid artery and develops during the late first trimester, was present ultrasonographically in our patient (Figure 2). Given the well-developed Cloquet canal, it is unlikely that the arrest of development occurred before 12 weeks’ gestation. The pupillary membrane, which does not begin to show atrophy until 23 weeks’ gestation, and the anterior tunica vasculosa lentis (which regresses even later) had not regressed...
at the time of the inciting event. We therefore hypothesize that the HSV infected our patient transplacentally between 12 and 23 weeks' gestation, leading to the arrest of further vascular development at this stage.

Neonatal HSV infections can lead to a wide spectrum of ocular and systemic findings. Ocular complications can be relatively minor, such as keratoconjunctivitis, or devastating, such as necrotizing retinitis. When disseminated infection is present, infants are severely affected, with high morbidity and mortality. The predilection for HSV for neural tissue in this infant is consistent with other reported cases. However, the arrest of further ocular vascular development in this child because of the intrauterine HSV infection has never been reported in the literature to our knowledge.

Accepted for publication January 12, 2000.

This study was supported in part by Research to Prevent Blindness Inc, New York, NY.

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REFERENCES