Utility of Neonatal Ophthalmologic Examination for Detection of Infectious Etiologies for Symmetric Intrauterine Growth Restriction

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Objective To determine the utility of ophthalmologic examination as part of evaluation for infection in infants with intrauterine growth restriction (IUGR).

Study design This is a single-institution retrospective chart review of neonates diagnosed with symmetric IUGR or small for gestational age (SGA) who underwent complete ophthalmologic consultation to assess for intraocular findings suggestive of congenital infection. Data collected included other factors that may cause IUGR, findings of general and ophthalmologic examinations, and results of investigation for intrauterine infection. Cost minimization analysis was also performed.

Results One hundred neonates met the study's inclusion criteria (IUGR, n = 24; SGA, n = 45; IUGR and SGA, n = 31). The mean gestational age at birth was 34.6 ± 3.0 weeks, and the mean birth weight was 1691 ± 530 g; 74% had an identifiable risk factor for IUGR and 84 patients underwent investigation for intrauterine infection. Two of the 73 patients who had urine culture for cytomegalovirus (CMV) were positive (1 of whom had systemic signs of severe congenital infection without eye involvement, the other who had no clinical signs of congenital CMV); evaluations for infection were negative otherwise. No patients had any ophthalmologic signs of congenital infection.

Conclusions Current literature suggests that routine evaluation of neonates with isolated IUGR for congenital infection may be low-yield and not cost-effective. Our study found that routine ophthalmologic evaluation in newborns with symmetric IUGR who have no systemic signs of intrauterine infection is of little value. *(J Pediatr 2020;226:240-2)*.

Intrauterine growth restriction (IUGR) impairs growth and development of the fetus in utero, affecting 9.2% to 14.4% of neonates.[1] IUGR can result in infants who are small for gestational age (SGA), defined as below the 10th percentile in birth weight. IUGR may be associated with maternal factors, such as hypertension or substance abuse; fetal factors, such as multiparity or chromosomal anomalies; and placental or uterine factors. Infectious etiologies are estimated to account for 5%-15% of cases of IUGR[2] and are typically accompanied by other manifestations, such as purpura, hepatosplenomegaly, jaundice, and cerebral anomalies. Some authors have suggested that screening for intrauterine infection, such as *Toxoplasma gondii*, *Treponema pallidum*, rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV) (together sometimes referred to as TORCH), should be part of the routine evaluation for these neonates,[3] although more recent studies have suggested that this might not be cost-effective.[4-9] In this study, we investigated the utility of routine ophthalmologic examination in assessing for intraocular inflammation as part of the evaluation for infection in neonates with IUGR.

Methods

This was a retrospective chart review of neonates admitted to the neonatal intensive care unit (NICU) and transitional unit at Cooper University Hospital (Camden, New Jersey) between January 1, 2008, and June 1, 2016. Inclusion criteria included a diagnosis of symmetric IUGR or SGA with concurrent ophthalmologic consultation to assess for intraocular inflammation; ophthalmologic evaluation was part of the standard evaluation of infants with symmetric IUGR or SGA during the study period. Institutional Review Board approval was obtained with a waiver of consent, and the work was HIPAA-compliant. Data collected included gestational age, sex, weight, any maternal factors (ie, hypertensive disorders, including chronic hypertension, pregnancy-induced hypertension,

CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
HSV	Herpes simplex virus
IUGR	Intrauterine growth restriction
NICU	Neonatal intensive care unit
SGA	Small for gestational age
TORCH	Toxoplasmosis/other infections/rubella/cytomegalovirus/herpes simplex

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preeclampsia; systemic lupus erythematosus; diabetes; renal disease; medications; and tobacco/drug use), any fetal factors (ie, multiparity, chromosomal anomalies, genetic conditions, and intrauterine infections), and any placental/uterine factors (ie, abnormal placentation, chronic abruption or inflammatory conditions, single umbilical artery, and abnormal umbilical insertion) that may cause IUGR; positive findings on physical or ocular examination (including zone/stage of concurrent retinopathy of prematurity with or without plus disease); and results of an infectious workup. For neonates with symmetric IUGR, standard investigation for infection included urine CMV; serologic tests for toxoplasmosis, HIV, and HSV; *Chlamydia* testing; and blood, urine, and cerebrospinal fluid (CSF) cultures, all done at the discretion of the attending physician. Cost minimization analysis was performed using the Medicare fee schedule for ophthalmologic consultation between 2008 and 2016.

Results

A total of 868 neonates underwent full dilated retinal examinations in the NICU and outpatient clinic between January 1, 2008, and June 1, 2016; 100 of these consultations (11.5%) were done to rule out infectious chorioretinitis, given that congenital infection could offer an etiology for symmetric IUGR or SGA. Twenty-four infants met the criteria for symmetric IUGR, 45 met the criteria for SGA, and 31 met the criteria for both symmetric IUGR and SGA. Fifty-eight females (58%) were examined (**Table**). The mean gestational age at delivery was 34.6 ± 3 weeks, and mean birth weight was 1691 ± 530 g. Thirty-five of these 100 neonates (35%) met screening criteria for retinopathy of prematurity as defined by the American Academy of Ophthalmology and American Academy of Pediatrics (all 35 patients weighed ≤1500 g, and 8 of these patients were also born at ≤30 weeks of gestational age), and 3 patients had type 1 retinopathy of prematurity (stage 2 or less; no patient had plus disease) that resolved without intervention. Twenty-one patients (21%) had no identifiable maternal, fetal, or placental/uterine factors that could account for IUGR. Seventy-four patients (74%) had an identifiable maternal risk factor (49 with multiple risk factors), 22 (22%) had an identifiable fetal risk factor, and 3 had an identifiable placental/uterine risk factor (**Table**).

Eighty-four patients (84%) underwent evaluation for infectious etiology of IUGR. Seventy-three patients (73%) had a urine CMV culture performed; of these, 2 were positive. One of these patients had no clinical signs or symptoms concerning for congenital infection, and the other had microcephaly with cardiac, neurologic, and gastrointestinal findings consistent with congenital CMV. On ophthalmologic examination, this patient did not have any signs of chorioretinitis or other ocular findings consistent with CMV. Fifty-two patients (52%) had blood culture, 4 patients had CSF culture, and 7 patients had urine culture performed, all of which were negative. Four patients had toxoplasmosis titers, all of which were negative. HIV and HSV testing were performed in 2 patients each, all of which were negative. One patient was tested for *Chlamydia* and was negative. Sixty-nine patients (69%) had head ultrasonography. head ultrasonography, none of which showed intracranial calcifications (9 showed cysts of the choroid plexus, 3 showed germinal matrix hemorrhages, and 1 showed an absent corpus callosum). Nine patients had retinal hemorrhages on fundoscopic examination; 8 of these were deemed secondary to birth trauma. One patient who was born via cesarean delivery after fetal cardiac deceleration and who underwent evaluation for sepsis was found to have scattered retinal hemorrhages on fundoscopic examination; otherwise,

Table. Risk factors for IUGR in 74 of the 100 neonates

Risk factors	Number of patients
Maternal	
Substance use	20
Tobacco	8
Alcohol	1
Marijuana	11
Cocaine	7
Amphetamines	2
Opiates	2
Benzodiazepines	1
PCP	1
Heroin	2
Methadone	3
Systemic disease	49
Hypertensive disorder	45
Diabetes	13
Anemia	1
Congestive heart failure	1
Mitral valve prolapse	2
Asthma	1
Crohn's disease	1
SLE	2
Seizure	1
Hypothyroidism	2
Hyponatremia	1
Nephrotic syndrome	1
Infection	24
Herpes	10
HIV	4
HPV	5
Chlamydia	2
Gonorrhea	1
Hepatitis B	1
Hepatitis C	4
UTI	2
CMV	1
Trichomonas	2
Bacterial vaginosis	1
Parvovirus	1
Fetal	
Multiparity	15
Infection	1
Fungal sepsis	1
Genetic abnormalities	8
Trisomy	1
Monosomy	1
Other syndromes	6
Placental/uterine	
Fibroids	1
Abnormal umbilical artery	2

PCP, phenylcyclohexyl piperidine; *SLE*, systemic lupus erythematosus; *HPV*, human papilloma virus; *UTI*, urinary tract infection.

investigation for infection was negative, and the hemorrhages resolved without sequelae. No patient had chorioretinitis on ophthalmologic evaluation.

Based on the Medicare fee schedule between 2008 and 2016, initial ophthalmologic evaluation at our institution costs an average of $193,38; therefore, an additional estimated $19 338.00 was spent in the work-up of these neonates. If only infants with other signs of congenital infection were screened, the cost savings would be $19 144 62. In addition, each of these consults takes an estimated 20 minutes to perform the examination, document findings, and discuss findings with the health care team and family; therefore, these consultations cumulatively used over 30 man-hours of time.

Discussion

Although some authors suggest testing for a number of intrauterine etiologies in infants who meet the criteria for IUGR,[3] much of the literature questions the cost-effectiveness of this approach in the absence of clinical findings suggestive of systemic disease,[4-7] with more recent literature advocating for only CMV testing in otherwise asymptomatic patients. This screening is felt to be warranted given the associated risk of hearing loss, which has important developmental implications, and for which early detection can be beneficial.[8,9]

Although many intrauterine infections can have ocular involvement, rubella rarely presents with ocular inflammation in infancy, possibly due to the availability of vaccination and maternal surveillance in many countries. Because toxoplasmosis and CMV generally are more prevalent entities, particularly in certain endemic areas, they carry a greater risk of neonatal infection and intraocular involvement.

A French study identified 475 neonates with congenital toxoplasmosis who were born to mothers who seroconverted during pregnancy and whose offspring were followed for a mean of 10.5 years. Although 142 of these patients ultimately developed chorioretinal lesions, only 8 were identified in the neonatal period (with 2 peaks identified, at a mean of 7 years and between 11 and 13 years). No patient experienced severe vision loss as a result of chorioretinal involvement; 80.6% of the patients had no vision loss whatsoever.[10]

The Congenital CMV Longitudinal Study Group investigated the ophthalmologic findings of 125 children with congenital CMV infection (42 symptomatic and 83 asymptomatic). Nine patients (22%) in the symptomatic group had moderate to severe visual impairment in 16 eyes (secondary to optic atrophy in 37%, to macular scars in 13%, and to cortical visual impairment in 50%). Only 1 of 83 asymptomatic patients had visual impairment, which was unilateral and mild, secondary to a macular scar. Based on their findings, this group recommended careful screening only of symptomatic patients.[11]

In our retrospective review of 100 ophthalmologic consultations to rule out symmetric IUGR-related chorioretinitis, we found none. Although 9 infants had scattered intraretinal hemorrhages, these were more consistent with birth trauma, and all resolved without retinal sequelae.

Although there is not yet a consensus on when and how to screen neonates with IUGR for infectious etiologies, the growing body of literature described herein suggests that the yield of universal evaluations, such as for TORCH infections, is low and not cost-effective in otherwise asymptomatic patients. Based on our findings and this literature, we believe that an effective strategy that carries low risk and is more economical is to limit ophthalmologic evaluation to infants with other clinical signs of congenital infection.

Our study is limited by its retrospective nature, as well as by the limited enrollment of a small number of patients from a single institution. The low rate of maternal infection with such entities as toxoplasmosis and rubella in the US limits the ability to extrapolate these data to regions where these diseases are endemic, such as South America and Africa, respectively. ■

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