Childs Nerv Syst (2003) 19:429–432
DOI 10.1007/s00381-003-0766-5

ORIGINAL PAPER

Stefan Gerber
Patrick Hohlfeld

Screening for infectious diseases

Received: 10 April 2003
Published online: 14 June 2003

S. Gerber (✉) · P. Hohlfeld
Department Gynecology and Obstetrics,
CHUV,
1011 Lausanne, Switzerland
e-mail: Stefan.Gerber@chuv.hospvd.ch
Tel.: +41-21-3143513
Fax: +41-21-3143525

Abstract *Introduction:* Fetal brain injury is an essential cause of lifelong morbidity. Infection appears as a cause of brain damage. Apart from chorioamnionitis, screening for infectious diseases must be considered in pregnancies with a risk of congenital infection or cases with abnormal cerebral ultrasound findings. *Discussion:* Congenital infections include most of the major components of the TORCH complex: toxoplasmosis, rubella, cytomegalovirus, herpes, and varicella. Seronegative mothers can develop primary infection, which carries a risk of vertical transmission. The timing of the infection is a critical point, because fetal damage often depends on the gestational age at which acute maternal infection took place and occurs more likely in the first half of pregnancy. Antenatal ultrasound can detect brain abnormalities, like hydrocephalus, periventricular leukomalacia, calcifications or hemorrhage. Maternal serologic tests must be performed to look for an infectious etiology; the most frequent agents are the components of the TORCH complex. But additional serology must include parvovirus B19, HIV, and coxsackieviruses.

Keywords Ultrasonography · Prenatal diagnosis · Brain damage

Introduction

Fetal brain injury remains an essential cause of lifelong morbidity, which impairs quality of life and social integration, and incurs large health care charges. Cerebral white matter damage or maldevelopment are events that can take place during antenatal life. Although in the majority of cases the cause remains unknown, the different antenatal factors involved can be identified [3, 13]. Antenatal brain anomaly can be caused by genetic diseases, trauma, malformations, cerebral hypoxic-ischemic events, exposure to a toxic agent, preterm delivery, intrauterine growth retardation, and infection. In most developed countries, a policy of general screening has been adopted. This management will offer some information concerning fetal brain development, and is aimed at detecting major malformations or identifying increased risks during pregnancy. Tests performed include various biochemical markers (Pregnancy-associated Plasma Protein A, HCG, AFP, Estriol), genetic tests, and ultrasonographic evaluation (e.g., nuchal translucency, morphology). To evaluate the risk of maternal exposure to infectious agents, serologic tests for cytomegalovirus (CMV), toxoplasmosis, rubella, and syphilis are generally performed during the first antenatal visit.

In recent years, convincing evidence has been published showing a strong link between intrauterine infection and fetal brain injury [1, 10]. Infection appears to be a cause of brain damage through the production of fetal proinflammatory cytokines [7]. In the presence of chorioamnionitis, high levels of cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) can be detected in the amniotic fluid and umbilical blood. They contribute to white matter injury in the offspring, leading to periventricular leukomalacia or other lesions [6]. The elevated cytokine concentration will directly damage the central nervous system, and increased severity or prolonged in utero exposure to

Table 1 Clinical characteristics of TORCH fetal or neonatal infection (*CMV* cytomegalovirus, *AF-PCR* amniotic fluid polymerase chain reaction, *PVL* periventricular leukomalacia, *WG* weeks of gestation)

	Rubella	Toxoplasmosis	CMV	Herpes simplex		Varicella zoster	
Incidence/10^5 births	<0.1	10–30	100–200	100		5	
Maternal clinical picture	Acute exanthema or asymptomatic	Mostly asymptomatic	Mostly asymptomatic	Genital herpes or asymptomatic		Viral exanthema and vesicles	
Fetal transmission	60–90% <12 WG	1–15%, <15 WG	30–40% (cytomegalic inclusion disease 1:10)	Neonatal: 1–50%	Congenital <0.1%	Neonatal: about 30%	Congenital: 1–5% <20 WG
CNS injury							
Meningoencephalitis	+	+	+	++	+	+	+
Microcephaly	+	+	++	−	+	−	+
Hydrocephalus	+	++	+	−	+	−	−
PVL, intracranial calcification	−	++	++	−	+	+	+
Chorioretinitis	++	++	+	++	+	−	+
Hearing loss	+	+	++	−	−	−	−
Mental retardation	+	+	+	++	+	−	+
Other US sign	+[a]	+[b]	+[c]	−	−	−	+[d]
Fetal diagnosis	AF-PCR	AF-PCR	AF-PCR	Culture/PCR	Culture/PCR	Culture/PCR	AF-PCR
Prevention	Vaccine	Spiramycin	−	Acyclovir	−	Vaccine	
Therapy	−	Sulfonamide, pyrimethamine	−	Acyclovir		Acyclovir or/ and IVIgGs	

[a] Cardiovascular defect
[b] Hepatosplenomegaly ascites, liver calcification, pericardial/pleural effusion
[c] Hepatosplenomegaly, liver calcification
[d] Limb hypoplasia, muscular atrophy

infection may be associated with increased severity of neurodevelopment abnormalities. Signs and symptoms of chorioamnionitis must be looked for carefully during pregnancy, particularly when preterm labor or preterm premature rupture of membranes occurs. Unfortunately, the diagnosis of chorioamnionitis is not always clinically evident and additional tests must be performed (e.g., blood test, C-reactive protein, vaginal swab, and eventually amniotic fluid culture). Any evidence of chorioamnionitis requires a quick decision to proceed to delivery.

Apart from chorioamnionitis, screening for infectious diseases must be considered in two different situations: pregnancies with a risk of congenital infectious disease or cases with abnormal ultrasound findings suggesting an infectious etiology.

Screening for pregnancies with a risk of congenital infectious disease

Congenital infections, which may damage the fetal brain, include the major components of the TORCH complex: toxoplasmosis, rubella, cytomegalovirus, herpes, and varicella zoster virus [8]. Currently, prenatal routine serological screening for some TORCH infections is performed during the first trimester. Seronegative patients can develop primary infection, which carries a risk of vertical transmission. In case of congenital infection, fetal damage often depends on the gestational age at which acute maternal infection took place. The timing of maternal infection is thus a critical point. IgG avidity tests are often helpful to exclude primary maternal infection during pregnancy since IgG avidity is directly proportional to the time lapse since the beginning of the maternal infection. Generally, severe fetal damage is more likely to occur in the first half of pregnancy than during the second half. In congenital rubella, for example, maternal infection in the first 12 weeks of gestation leads to congenital rubella syndrome in about 80% of fetuses with a poor outcome, whereas congenital infection acquired during the second half of pregnancy carries no risk to the fetus [8]. Other viruses can cause intrauterine infection or may be acquired at the end of pregnancy or during delivery (e.g., herpes, varicella). Table 1 shows the average rates of fetal infection and the type of injuries to the nervous system.

Congenital CMV is the most common congenital infectious disease responsible for both developmental delay and sensorineural deafness. Fetal infection occurs in 30–40% of cases of primary maternal infection and 10% of infected fetuses will develop cytomegalic inclusion disease. Of the remaining 90% with asymptomatic congenital infection, about 10% will show significant long-term sequelae, e.g., hearing loss. The risk of congenital toxoplasmosis varies according to the gestational age at which acute maternal infection occurred (1% during the first 6 weeks of pregnancy, increasing steadily thereafter to reach 80% at the end of the third trimester) [9]. The risk of severe sequelae is highest during the first trimester whereas severe forms are almost never observed past the 25th week of pregnancy. Once maternal infection is diagnosed, treatment with spiramycin must be initiated. If fetal infection is confirmed, additional treatment with pyrimethamine and sulfonamide should be proposed.

Screening for an infectious cause of fetal brain damage

Antenatal ultrasound examination can detect brain abnormalities like intraventricular hemorrhage, hydrocephalus, porencephalic cysts, hydranencephaly, or intracranial calcifications. When fetal brain damage is demonstrated, other associated malformations must be looked for. Ultrasound remains the gold standard in fetal imaging, but computerized tomography (CT) and, especially, magnetic resonance imaging (MRI) may be useful in in utero fetal nervous system evaluation. CT scans provide some useful information for determining the presence of acute hemorrhage in the late second trimester [4]. With CT scans, the risk of the potentially adverse effect of radiation is considered negligible. No biologic risks are known for MRI. It represents, even in the early mid-trimester, a powerful tool for both anatomic imaging and tissue characterization [5]. MRI is an important adjuvant method in clarifying complex sonographic findings.

Whereas ultrasound normograms have been established for ventricular size throughout the pregnancy, the definition of enlarged ventricles is difficult and subjectively evaluated. Fetal hydrocephalus is associated with CNS malformations or other anomalies in about 80% of cases. Maternal serologic tests must be performed to look for an infectious etiology. Most common infectious agents involved are toxoplasmosis, CMV, HSV, and rubella [8], but in rare situations, treponema pallidum or parainfluenza virus type 3 can induce fetal hydrocephalus. The prognosis is dependent on the severity and duration of progressive hydrocephalus [9]. Rather than the degree of the ventricular enlargement, predictive outcome is largely determined by other associated abnormalities. Some experimental in utero surgical procedures using a ventriculo-amniotic shunt have been attempted, but the results were not convincing.

Intrauterine infection with a neurotropic agent can be associated with brain lesions such as periventricular leukomalacia, intraventricular hemorrhage, or intracranial calcifications [12]. Intracranial calcifications may present with different shapes and topography, but they are strongly suggestive of TORCH intrauterine infection [11]. Meningitis and meningoencephalitis have been associated with viral infections and cerebral perivascular calcification can be observed. Additional maternal serol-

ogy testing must include: parvovirus B19, HIV, and enteroviruses, especially coxsackieviruses B1 to B5 and echoviruses.

Summary

In summary, the prevention of maternal infection is important during the whole pregnancy. Current prenatal screening includes maternal serology to identify seronegative mothers and regular ultrasound to detect early signs of fetal brain damage. The management of seronegative pregnant women must include adequate counseling, careful clinical evaluation, and regular screening during pregnancy. If vaccination is available, it should be performed after delivery (e.g., postpartum rubella vaccination).

References

1. Damman O, Leviton A (2000) Role of the fetus in perinatal infection and neonatal brain damage. Curr Opin Pediatr 12:99–104
2. Gilstrap L, Ramin S (2000) Infection and cerebral palsy. Semin Perinat 24:200–203
3. Hagberg H, Mallars C (2000) Antenatal brain injury: aetiology and possibilities of prevention. Semin Neonatal 5:41–51
4. Hollier L (2000) Can neurological injury be timed? Semin Perinat 24:204–214
5. Jaws T, Jong Y, Shen R et al (1998) Etiology, timing of insult, and neuropathology of cerebral palsy evaluated with magnetic resonance imaging. J Formos Med Assoc 97:239–246
6. Kadhim H, Tabariki B, Verellen G, De Prez C, Rona AM, Sébire G (2001) Inflammatory cytokines in the pathogenesis of periventricular leukomalacia. Neurology 56:1278–1284
7. Nelson K, Willoughby R (2002) Overview. Infection during pregnancy and neurologic outcome in the child. Ment Retard Dev Disabil Res Rev 8:1–2
8. Newton E (1999) Diagnosis of perinatal TORCH infections. Clin Obstet Gynecol 42:59–70
9. Oi S, Honda Y, Hidaka M, Sato O, Matsumoto S (1998) Intrauterine high-resolution magnetic resonance imaging in fetal hydrocephalus and prenatal estimation of postnatal outcomes with ”perspective classification”. J Neurosurg 88:685–694
10. Patrick L, Smith G (2002) Proinflammatory cytokines: a link between chorioamnionitis and fetal brain injury. J Obstet Gynaecol Can 24:705–709
11. Piper J, Wen T (1999) Perinatal cytomegalovirus and toxoplasmosis: challenges of antepartum therapy. Clin Obstet Gynecol 42:81–96
12. Remington J, Klein J (2001) Infectious diseases of the fetus and newborn infant, 5th edn. Saunders, Philadelphia
13. Stanley FJ (1997) Prenatal determinants of motor disorders. Acta Paediatr 422:S48–S52