Prenatal ultrasound and magnetic resonance imaging in fetal varicella syndrome: correlation with pathology findings

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Objectives To assess the diagnostic value of prenatal magnetic resonance imaging (MRI) in addition to prenatal ultrasound in a case of fetal varicella syndrome.

Methods Comparison of prenatal ultrasound and MRI features obtained at 26 and 32 weeks, respectively, with neonatal imaging (ultrasound, MRI and CT) and macroscopic and microscopic pathology findings in a fatal case of varicella embryopathy.

Results Prenatal ultrasound correlated fairly well with neonatal imaging and pathology findings. Most lesions of thoracic, abdominal and retroperitoneal viscera, limb involvement and even dermatologic features were apparent on ultrasonography. Involvement of the CNS, including cerebellar hypoplasia, was not apparent on ultrasound examination, but was clearly demonstrated by prenatal MRI.

Conclusion If maternal seroconversion for the varicella-zoster virus is suspected, combining prenatal ultrasound and magnetic resonance imaging may document the extent of tissue damage in fetal varicella syndrome to a larger extent than has been reported until now and therefore contribute to due counselling following maternal varicella exposure. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS: fetal varicella syndrome; prenatal ultrasound; prenatal magnetic resonance imaging; congenital anomalies

INTRODUCTION

As the vast majority of women of childbearing age has actively acquired immunity for the varicella-zoster virus (VZV), primary varicella infection during pregnancy is uncommon (1–7/10 000 pregnancies) (Pastuzak et al., 1994). If it occurs between the 8th and 20th week of gestation, fetal varicella syndrome (FVS) ensues in 1 to 2% of the cases (Pastuzak et al., 1994; Enders et al., 1994). Pregnant mothers with children attending day care centres or school are at particular risk. Children frequently contract the highly contagious chicken pox virus in an endemic way, in turn exposing other household members, with secondary clinical attack rates of 90% or more (Chapman, 1998).

Despite the rare occurrence of varicella embryopathy, assessing the severity of the condition is a major challenge for prenatal diagnosis (Lecuru et al., 1994). Prenatal counselling has to put a 1 to 2% teratogenic risk (Pastuzak et al., 1994; Enders et al., 1994) in perspective, while lacking reliable means for ascertaining or documenting fetal involvement. Immunological and virological assays correlate rather poorly with FVS. Detection of VZV-DNA in amniotic fluid (Mouly et al., 1997) or trophoblast (Isada et al., 1991) through polymerase-chain-reaction (PCR) does not necessarily indicate fetal affliction, while the absence of viral DNA sequences may not rule out FVS. Similarly, positive VZV-DNA PCR testing and detection of VZV-specific immunoglobulin M (IgM) in cord blood correlate unreliably with FVS (Pons et al., 1992; Dufour et al., 1996). Prenatal ultrasound and magnetic resonance imaging (MRI) may prove to be a superior means in documenting tissue damage in FVS, and to the best of our knowledge combining these techniques in the prenatal diagnosis of varicella embryopathy has not been reported before.

CLINICAL HISTORY

During a routine prenatal visit at 26 weeks’ gestation, a 31-year-old gravida 3, para 1 was diagnosed with a pervasive pattern of fetal compromise, involving diminished gross fetal body movements, decreased fetal heart rate variability, left lower-limb hypoplasia with club-foot deformity, right kidney pyelectasis, echogenic bowels and multiple hyperechogenic foci of the liver and thorax. Amniocentesis showed a normal male karyotype (46,XY) on FISH analysis and a normal amniotic fluid
α-fetoprotein concentration (9.80 µg/mL). PCR analysis for CMV-DNA in the amniotic fluid was negative, while toxoplasmosis and rubella immunity were documented in early pregnancy. Furthermore, none of the parents were carriers of the ΔF508 cystic fibrosis point mutation.

At 31 weeks, the patient was referred to our University hospital. In addition to the above, ultrasonic features included polyhydramnios, symmetric intrauterine growth restriction (<5th percentile), echogenic bowels with ‘multiple bubble sign’ suggestive of meconium ileus and spicular echo reflections surrounding the cranium indicative of cutaneous lesions. The most prominent findings obtained by prenatal MRI of the central nervous system (CNS) were hypoplasia of the right cerebellar hemisphere, inadequate secondary or tertiary sulcal development (pachygyria) and incomplete opercularisation of the Sylvian fissure.

Careful history taking revealed a history of typical chicken pox exanthema of her 1-year-old son, prior to an episode of full-blown (vesicular rash, fever, headache) though non-pneumonia-complicated varicella infection of the mother herself with onset of rash at 12 weeks’ gestation. We found high complement-fixation binding titers and high VZV-specific IgM and IgG levels on enzyme-linked immunosorbent assay (ELISA) at 32 weeks of gestation.

At 37 weeks, the patient went into spontaneous labour and delivered a male baby of 1740 g (<5th percentile).

The baby presented with a throaty, high-pitched cry and rapid and shallow breathing. Gross morphological features included extreme hypoplasia of the left lower limb with club-foot deformity (talipes equinovarus), homolateral fixed flexion contractures of the left lower limb, hand and fingers and cicatricial skin lesions with ‘loose skin’ aspect over the right flank and left lower limb. Diffuse abdominal distension with prominent dilated bowel loops was apparent. Early-onset respiratory distress required intubation and continuous mechanical ventilation. On day 3, vital support was withdrawn following the parent’s informed consent.

Pathological features were documented by macroscopic and microscopic pathology examinations. The presence of VZV-DNA sequences was demonstrated in the cerebrum, fetal lungs, adrenal cortex and bladder with PCR on fixed and embedded tissue specimens, according to Bruder et al. (2000). Imaging and pathology correlates are displayed in Tables 1 and 2 for visceral organ and central nervous systems, respectively.

DISCUSSION

Pretorius et al. found a fairly good correlation between prenatal sonographic findings and fetal outcome at birth in a series of 37 cases of maternal varicella (Pretorius et al., 1992). Consequently, Hofmeyer et al. suggested

| Table 1 — Correlation between prenatal imaging, neonatal imaging and pathology findings of thoracic, abdominal, retroperitoneal and pelvic viscera and limbs |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Thorax Lungs: echogenic spots | — | — | — | Dystrophic calcifications in alveolar septa |
| Retroperitoneum Right kidney hydrourephrosis | Right kidney hydrourephrosis | Right kidney hydrourephrosis | Right kidney hydrourephrosis | — | Right kidney hydrourephrosis |
| Pyelectasis | Pyelectasis | Pyelectasis | Pyelectasis | — | Pyelectasis |
| Abdomen Echogenic bowels with ‘multiple bubble aspect’ | Dilated bowels with echodense lining | Calcinations: — visceral wall — mesenteric | — | — | — |
| Focal echodensities: liver | Focal echodensities: liver | Liver calcifications | — | — | — |
| Pelvis Pelvic mass | — | — | — | Meso-appendix: dystrophic nodule |
| — | Bladder impression | — | Bladder: dystrophic calcifications |
| Limbs Left-sided limb hypoplasia and club-foot deformity | Fixed contracture of the left limb | — | — | — |
| | | | | Muscular atrophy |
| | | | | Epidermolysis |

CT, computerized tomography.
that sonographic examination at five or more weeks after the initial infection should detect most cases of varicella embryopathy (Hofmeyer et al., 1996). Clearly, the sensitivity of ultrasound scanning will herein be enhanced if special attention is paid owing to the number of clinical features that have been associated with FVS (for review see Alkalay et al. (1987) and Birthistle and Carrington (1998)).

In the present case, pervasive fetal involvement was largely documented by prenatal ultrasound in the late second trimester and by magnetic resonance imaging in the mid third trimester, respectively (Tables 1 and 2).

Splanchnic involvement in varicella embryopathy is typically associated with disseminated dystrophic microcalcifications presenting as multiple hyperechogenicities (Table 1). Limb involvement presenting as flexed limbs and limb hypoplasia and occasionally club-foot deformity (Figure 1) has also been considered a clinical hallmark of FVS (Petignat et al., 2001). Dermatological features in FVS have typically been described as punctiform cicatrical skin lesions in a well-described dermatomal distribution. Albeit considered an obligate finding in FVS by (Alkalay et al., 1987), this criterion may be obsolete (Dimova, 2001; Kent and Paes, 2000; Hammad et al., 1989). Conversely, skin lesions may be the sole manifestation of congenital varicella syndrome (Lloyd and Dunne, 1990). Though usually not apparent on prenatal ultrasound, in this particular case, a pericranial halo of spicular echogenicities (Figure 2) suggested the presence of varicella scalp skin lesions, and to the best of our knowledge this finding has not been reported before.

Of all organ systems, the CNS (brain, spinal tract, eye) is most commonly affected in FVS, neurological signs developing in about 80% (Alkalay et al., 1987; Dufour et al., 1996). Hence, CNS involvement is a major determinant of neonatal outcome in FVS. Along with the TORCH infections, congenital varicella has been identified as a cause of cerebral palsy (Gaffney et al., 1994), the most common manifestation of prenatally acquired brain damage. Mustonen et al. recently reviewed neuropathologic findings in reported cases with fatal outcome, and necrotizing encephalitis was present in all (Mustonen et al., 2001). As a matter of fact, Higa et al. postulated that FVS results from both varicella encephalitis together with an intrauterine zoster-like VZV reactivation (Higa et al., 1987). In this particular case, right cerebellar hypoplasia, possibly following an early vascular insult (Table 2), was demonstrated at 32 weeks on both T2-weighted axial and coronal images (Figure 3). Pachygyria and incomplete operculisation of the Sylvian fissure (Table 2), which are thought to be early neuronal migration disorders, were also apparent on prenatal MRI (Figure 3).

In summary, in this case of fetal varicella, most lesions of the thoracic, abdominal and retroperitoneal viscera, limb involvement and even dermatologic features were apparent on thorough ultrasound scanning. Magnetic resonance imaging proved a valuable adjunct to the latter in documenting CNS involvement. We suggest that implementing prenatal ultrasound and MRI may contribute to due counselling following maternal varicella

Table 2—Correlation between prenatal imaging, neonatal imaging and pathology findings of the central nervous system

<table>
<thead>
<tr>
<th>Prenatal</th>
<th>Neonatal</th>
<th>Pathology</th>
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<tbody>
<tr>
<td>Ultrasound</td>
<td>MRI</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Right cerebellar hypoplasia</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Pachygyria</td>
<td>−</td>
<td>+</td>
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<tr>
<td>Incomplete operculisation</td>
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Figure 1—Hypoplastic left lower limb (longitudinal view) with club-foot deformity and axial view of the right lower limb

Figure 2—Transverse (panel B) and oblique transverse (panel A) ultrasonographic images at 32 weeks showing multiple hyperechogenicities at the periphery of the fetal skull as a presentation of varicella scalp skin lesions.

Figure 3—Panel A: In utero axial T2-weighted MRI at the level of the lateral ventricles at 32 weeks: (1) hypoplasia of the right cerebellar hemisphere; (2) incomplete operculisation of the Sylvian fissure. Panel B: In utero axial T2-weighted MRI at 32 weeks: hypoplasia of the right cerebellar hemisphere. Panel C: Neonatal coronal T2-weighted MRI at 37 weeks: intact vermis with hypoplasia of the right cerebellar hemisphere is visible as an ‘asymmetric butterfly sign’. Panel D: Neonatal brain CT imaging at 37 weeks: right cerebellar hypoplasia.

exposure, although larger series are warranted to confirm our findings.

ACKNOWLEDGEMENTS

This work was part of a research project on Prenatal Imaging of Intra-uterine Acquired Brain Damage and was supported through a research grant by the Marguerite-Marie Delacroix Foundation.

REFERENCES


