Antenatal assessment of neurological impairment

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Abstract
An unreactive cardiotocograph late in the mid-trimester led to a sequence of investigations that revealed an appropriately grown fetus, with hepatic calcification, and evidence of intrauterine infection. Ultrasound observation and stimulation of the fetus with vibration and glucose revealed altered neurophysiological responses. The profound neurological impairment was confirmed by detailed neonatal investigations. (Arch Dis Child 1993; 68: 604–605)

The antenatal ultrasound diagnosis and physiological assessment of a neurologically impaired fetus is discussed with relevance to neonatal outcome and prognosis.

Case report
A 23 year old primigravida presented to her local obstetric unit at 27 weeks’ gestation with diminished fetal movements. Cardiotocography demonstrated a normal heart rate but with a non-reactive pattern. She was then transferred to the Liverpool Maternity Hospital. On arrival a repeat cardiotocograph showed little change (figure) and this pattern persisted on continuous monitoring. Ultrasound assessment showed an active fetus, appropriately grown, and with normal liquor volume. The liver was enlarged with diffuse echodense lesions throughout. Fetal anatomy was otherwise normal. Umbilical artery Doppler velocimetry gave normal results. A detailed history revealed maternal varicella zoster infection at 8 weeks’ gestation. In view of the findings, diagnostic amniocentesis and cordocentesis were performed; the results are shown in the table. In the absence of evidence of hypoxaemia and with the suspicion of congenital varicella zoster virus infection, conservative management was pursued.

The karyotype was 46XX. Examination of amniotic fluid for herpes simplex, cytomegalovirus, rubella, and toxoplasma were negative by tissue culture and inoculation. Maternal and fetal blood were negative for antibodies for the same pathogens. However IgM capture (Manchester Public Health Laboratory Service) detected varicella zoster IgM in fetal blood.

While viral serology results were awaited, cardiotocography was performed and remained unaltered; there was poor variability and no response to coincident fetal movements. On subjective assessment liquor volume steadily increased. Isolated fetal breathing movements were noted but sustained fetal breathing (>30 s) was never observed despite prolonged examinations (>30 min).

Although intracranial anatomy was normal on repeated ultrasound examination with no evidence of intracranial calcification, there remained a strong suspicion of neurological dysfunction most likely at brain stem level. To evaluate fully fetal physiology, two manoeuvres known to alter fetal biophysical parameters were performed. Vibroacoustic stimulation produces alteration in fetal behavioural state and a startle reaction

The prenatal diagnosis was of congenital varicella zoster with hepatic and brain stem involvement including derangements of the atrioventricular variability (cardioinhibitor effect of vagus nerve), breathing (phrenic nerve C4), and possibly swallowing (glossopharyngeal and vagus nerves).

The parents were counselled extensively that the prognosis was uncertain. Delivery was performed by elective caesarean section at 39 weeks because of the difficulty of monitoring a fetus with an unvarying heart rate. The infant girl weighed 3426 g at birth (50th centile). She rapidly developed marked inspiratory stridor with pooling of pharyngeal secretions and respiratory distress requiring endotracheal intubation. No other neurological features were present but poor muscle bulk was noted in the limbs.

Bronchoscopy revealed vocal cord paralysis. Contrast swallow and computed tomography of the neck demonstrated marked pooling of contrast in the pharynx indicating significant swallowing problems, leading to the diagnosis of bulbar palsy.

Echocardiography showed a large patent ductus arteriosus with a common origin to the

Antenatal cardiotocograph at 27 weeks’ gestation showing greatly reduced heart rate variability. Arrows indicate fetal activity as noted by the mother.
right innominate and left carotid arteries. Cranial computed tomography suggested early cerebral atrophy; abdominal ultrasound and computed tomography confirmed the presence of calcification in liver and spleen. A skeletal survey and ophthalmic examination were normal.

She required tracheostomy and fundal plication with gastrectomy, as well as surgical ligation of the ductus because of cardiac failure. Despite this she continued to have frequent episodes of aspiration pneumonia often with septicemia, which resulted in obstructive emphysema, cor pulmonale, and severe failure to thrive. No immune deficiency was found.

At 3 months a bilateral keratitis developed from which no virus or organism was isolated, leaving considerable corneal scarring. She died at 10 months from cardiorespiratory failure, by which time there was gross developmental delay with hypoplasia of the muscles in all limbs. Varicella zoster virus was not isolated from the infant after birth but varicella zoster IgG at birth was >200 units. At 1 month it was 193 units.

Postmortem examination revealed cardiocirculatory failure with ventricular hypertrophy, extensive on the right and moderate on the left. There was hepatic engorgement, ascites, bilateral hydrothorax, and patchy pulmonary atelectasis. Mild pancreatic fibrosis was noted.

**Discussion**

The risk of congenital malformation after first trimester primary infection with varicella zoster virus is thought to be very low. However, neurological abnormality could possibly occur towards the end of the first trimester after infection. In the 15 mm fetus (6 weeks' postconception) all of the primordia of the cranial nerves are laid down with their stem nuclei and may then be vulnerable to infection. Intrahepatic calcification was the only abnormality exhibited by this fetus antenatally, as indicative of intrauterine infection, and postnatally there were no skin lesions or contractions. The subsequent neurological dysfunction was anticipated after serial ultrasound assessment of biophysical activities.

Fetal heart rate variability is under the complex control of the developing sympathetic and parasympathetic nervous systems and by chemoreceptors. An animal model has shown that atropine-induced parasympathetic vagal blockade reduces mean beat to beat variability by 65%. In this case variability was markedly reduced with failure to respond to alterations in fetal movement patterns, strongly suggestive of vagal impairment.

Fetal movement is largely under cortical control, and ultrasound demonstrated that this was normal in appearance and in response to vibroacoustic stimulation. Fetal breathing is an important component of respiratory development. A respiratory rhythm generator is well established and active for at least the last trimester. Diaphragmatic movement is an integral part of breathing and requires intact phrenic nerves. Breathing increases after food ingestion and is thought to be mediated via fetal chemoreceptors. Fetal breathing activity is also influenced by the alteration in low voltage electrocortical activity, which parallels alteration in plasma glucose. Thus in this case a glucose load provided a stimulus to fetal breathing movements possibly by both routes. Fetal breathing movements are associated with rapid eye movement sleep, indicating its influence by overall neurological activity. Vibroacoustic stimulation profoundly alters fetal behavioural state causing a shift from 1F state to 4F. In this case such a shift was sufficient to produce sustained fetal breathing movements. Without such additional stimulus, however, sustained fetal breathing was rarely seen despite prolonged observation periods. Normally periods of apnoea are short, but they may extend up to two hours beyond 30 weeks' gestation. Hypoxaemia leads to a cessation of fetal breathing and a slow recovery on returning to a normal arterial oxygen tension. Fetal blood gases and biochemistry in this case excluded factors that are associated with depression of fetal respiration.

The initiation of swallowing is a complex coordinated movement of tongue, pharynx, and larynx mediated through the glossopharyngeal (IX) and vagus (X) nerves. Polymyraminos secondary to neuromuscular disease is well described.

In the absence of an anatomical anomaly the postnatal investigations confirmed the antenatal impression that increased liquor was due to impaired fetal swallowing. This case illustrates the increasing ability of antenatal diagnosticians using invasive and non-invasive examinations and may be a diagnosis but also to examine fetal function in such a way to as to offer insight into the ultimate prognosis. Such information, however incomplete, should be invaluable in the neonatal period to direct investigations and aid prognostic counselling.