Identification and management of birth asphyxia

D.V. Azzopardi A.D Edwards, *Department of Paediatrics, Imperial College, London*

The pathogenesis of brain damage following hypoxic-ischaemic injury in the developing brain is complex and incompletely understood[1]. However noninvasive studies using ^{31}P magnetic resonance spectroscopy (MRS) have shown that hypoxia-ischaemia followed by resuscitation leads not only to *primary* cellular injury during the period of the insult, but to a delayed *secondary* injury 24 to 48 hours later[2]. The degree of later neurodevelopmental impairment is directly related to the severity of the secondary injury[3].

The interval between resuscitation from hypoxia-ischaemia and secondary injury has been investigated by several techniques. In infants suffering a hypoxic-ischaemic insult there is a derangement of cerebral vascular control, but no decrease in global cerebral perfusion. Measurements using the ^{113}Xe clearance technique or near infrared spectroscopy have shown that cerebral blood flow is increased, although the normal response to changes in carbon dioxide is lost[4,5]. Despite the high cerebral blood flow during this period, there is an accumulation of lactate within the brain, and there is a direct correlation between the severity of delayed cerebral injury and the concentration of lactate in the brain soon after birth .

Magnetic resonance imaging has also helped to demonstrate the process of brain injury. Soon after an insult, diffusion weighted images are abnormal, while conventional T1 and T2 images become abnormal some days later. It is also clear that brain injury and repair is a prolonged process: the concentration of Lactate remains high for many weeks in the brains of infants who develop neurodevelopmental impairment, and brain structure shows significant alterations, including both the development of atrophy distant from the original site of injury, and in some cases accelerated growth in areas of focal infarction.

The mechanisms of secondary injury are poorly understood, but probably involve cellular injury mediated by excess concentrations of excitatory neurotransmitters[6], free radical formation and lipid peroxidation[7], activation of immune mechanisms[8] and removal of trophic factors which normally support cell survival[9]. Recent studies have demonstrated that the mechanisms of programmed cell death are activated after hypoxia-ischaemia, and considerable proportion of cells die not by necrosis but by apoptosis[10].

The period between resuscitation from hypoxia-ischaemia and secondary injury offers the potential for therapeutic interventions to ameliorate delayed damage and concomitant neurodevelopmental impairment. Many potential interventions are being investigated, including drugs which block the actions of glutamate in the brain[6], growth factors such as insulin-like growth factor-1 which is a potent anti-apoptotic factor *in vitro*[11], and moderate hypothermia applied following resuscitation [12,13].

References.

1 Vannucci RC. Experimental biology of cerebral hypoxia-ischemia: Relation to perinatal brain damage *Pediatr Res* 1990;27:317-326

2 Wyatt JS, Edwards AD, Azzopardi D, Reynolds EOR. Magnetic resonance and near infrared spectroscopy for investigation of perinatal hypoxic-ischaemic brain injury *Arch Dis Child* 1989;64:953-963

3 Roth SC, Edwards AD, Cady EB, et al Relation between cerebral oxidative metabolism following birth asphyxia and neurodevelopmental outcome and brain growth at one year *Dev Med Child Neurol* 1992;34:285-295

4 Pryds O. Control of cerebral circulation in the high-risk neonate *Ann Neurol* 1991;30:321-329

5 Reynolds EOR, McCormick DC, Roth SC, Edwards AD, Wyatt JS. New non-invasive methods for the investigation of cerebral oxidative metabolism and haemodynamics in newborn infants *Ann Med* 1991;23:681-686

6 Rothman S, Olney JW. Excitotoxicity and the NMDA receptor *TINS* 1987;10:299-302

7 Watson BD, Ginsberg MD. Ischemic injury in the brain. Role of oxygen radical-mediated processes *Ann N Y Acad Sci* 1989;559:269-281

8 Giulian D, Johnson B, Krebs JF, George JK, Tapscott M. Microglial mitogens are produced in the developing and injured mammalian brain *J Cell Biol* 1991;112:323-333

9 Raff MC. Social controls on cell survival and cell death *Nature* 1992;356:397-400

10 Mehmet H, Yue X, Squier M et al. Increased apoptosis in the cingulate sulcus of newborn piglets following transient hypoxia-ischaemia is related to the degree of high energy phosphate depletion during the insult *Neurosci Lett* 1994;181:121-125

11 Gluckman P, Klempt N, Guan J, et al A role for IGF-1 in the rescue of CNS neurons following hypoxic-ischemic injury *Biochem Biophys Res Commun* 1992;182:593-599

12 Sirimanne E, Blumberg RM, Bossano D, Gunning M, Edwards AD, Gluckman PD, Williams CE. The effect of prolonged modification of cerebral temperature on outcome following hypoxic-ischaemic brain injury in the infant rat *Pediatr Res* 1996;39(4):591-597

13 Thoresen M, Penrice J, Lorek Aet al Mild Hypothermia following severe transient hypoxia-ischaemia ameliorates delayed cerebral energy failure in the newborn piglet *Pediatr Res* 1995;37:667-670