FETAL BEHAVIOURAL STATES AND PHYSIOLOGICAL FUNCTION

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The use of ultrasound techniques in obstetric practice have introduced possibilities to study the human fetus non-invasively, and in its natural environment. Direct assessment of the condition of its most important organ, the Central Nervous System (CNS), is not yet possible, but fetal behaviour can be studied and is a direct expression of CNS activity. In a longitudinal study in low risk pregnancies, two real-time ultrasound scanners (eye and body movements) and a cardiotocograph (fetal heart rate pattern, FHRP) were used simultaneously to record fetal behaviour from 32 weeks onward. Observation sessions lasted 2 hours and were repeated at 2-weekly intervals. From 36-38 weeks it was possible to define four behavioural states which resembled those in the neonate as described by Prechtl (3). They were therefore designated 1F to 4F ("F" for fetal), although somewhat different criteria had to be used (1).

STATE 1F: quiescence, sometimes interrupted by a brief body movement, mostly a startle. Eye movements absent. Stable FHRP with a small bandwidth, and isolated accelerations may occur, strictly related to movements (FHRP A).

STATE 2F: frequent and periodic gross body and extremity movements. Eye movements continually present. The FHRP B shows a wider oscillation bandwidth than FHRP A, with frequent accelerations in association with movements.

STATE 3F: gross body movements absent, eye movements present. FHRP C is stable, but with a wider bandwidth than FHRP A.

STATE 4F: vigorous activity with many trunk rotations eye movements present. FHRP D is unstable with many longlasting accelerations, sometimes fused into a sustained tachycardia. It must be emphasized that the existence of states can only be accepted if three criteria have been fulfilled: the combinations must be specific, must be stable over time (at least 3 min), and clear state-transitions must be present. Before 36 weeks periods of "coincidence" of parameters do occur and may mimic a state, but the other requirements are not satisfied. Fetal breathing is not continuously present in the human fetus and cannot be used as a state-criterion. However, fetal breathing is much more regular in 1F than in 2F, and regularity can be used as a state-concomitant (2). Furthermore, fetal breathing incidence is much higher in 2F (5). Other phenomena such as fetal micturition, are also related to states (4).

A study of behaviour in growth-retarded fetuses (6) demonstrated a reduction of time spent in state 1F and some disorganization of the states as reflected in less stable combinations and in the fact that many transitions lasted longer than 3 min. These preliminary results indicate that the study of behavioural states may be of value in detecting neurological dysfunction in utero. If so, it could be the beginning of an "intra-uterine" neurological examination, which is essential for the precise evaluation of the condition of the human fetus.

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BRAIN DAMAGE

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CLINICAL APPLICATIONS OF POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) has provided the capability of obtaining in vivo regional biochemical and physiological information about human brain in health and disease. This capability, not long ago considered an unattainable fantasy, is the product of four major developments in the necessary technology; specifically, the apparatus for nuclear bombardment, i.e., the cyclotron, to produce positron-emitting isotopes, the techniques for rapid synthesis of radiopharmaceuticals necessary for biochemical and physiological studies, the mathematical models and practical algorithms to obtain the critical information from the data, and the PET instrumentation to detect safely the radiopharmaceuticals in vivo in a regional and quantitative manner.

The only extensive appearance with PET in pediatrics has been in the study of the newborn, specifically the premature infant with intraventricular hemorrhage (IVH) and hemorrhage intracerebral involvement, and the asphyxiated term infant with hypoxic-ischemic encephalopathy (HIE). These studies are reviewed briefly next.

IVH WITH HEMORRHAGIC INTRACEREBRAL INVOLVEMENT

The magnitude of the problem of IVH with hemorrhagic intracerebral involvement is emphasized by our study of 460 premature infants by cranial ultrasonography; thus, IVH occurred in 38% (n=177), and of these, 20% (n=34) had the lesion under discussion. IVH with hemorrhagic intracerebral involvement accounts for the vast majority of the deaths and subsequent neurological morbidity in all infants with IVH. To define the basic nature and probable pathogenesis of the critical intracerebral involvement, we have measured regional CBF by PET in 12 premature infants with the lesion.

The clinical features of the infants have been generally similar. All have had severe respiratory distress syndrome; approximately 50% have experienced perinatal asphyxia. Cranial ultrasonography consistently has demonstrated IVH and a globular collection of blood within the frontal white matter, i.e., the hemorrhagic intracerebral involvement. The lesion has occurred on the left in two-thirds of the cases.

Regional CBF has been determined by PET after intravenous injection of $H_2^{15}O$. The findings have been similar and dramatic. First, anteriorly, in the region of the hemorrhagic intracerebral involvement, CBF is reduced markedly (as expected). Second, and unexpectedly, markedly diminished CBF is observed in posterior cerebral (parieto-occipital) white matter in the same hemisphere. Third, CBF is reduced, albeit to a lesser extent, in cortical regions, including posterior parietal and Sylvian cortex. Thus, the impairment of CBF in the hemisphere containing the intracerebral blood is much more extensive than could be accounted for by the locus of the intraparenchymal blood. This larger lesion presumably accounts for the serious neurologic deficits nearly uniformly observed in the survivors.

We have concluded that the extensive abnormality of CBF demonstrated by PET is indicative of a fixed structural lesion for two reasons. First, the PET lesion was irreversible in the one patient studied a second time (at 90 days). Second, neuropathological correlation demonstrated extensive infarction in the affected hemisphere in the six infants studied post-mortem. We believe the structural lesion to be ischemic in basic nature, primarily because the topography of the lesion, as defined by PET, resides in periventricular vascular border zone regions. Future work will attempt to identify the timing of the ischemia and its precise cause(s) to make possible the ultimate goal, i.e., prevention of the extensive intracerebral involvement.

HIE IN THE TERM ASPHYXIATED INFANT

Hie in the term newborn is the most frequent, recognized cause of the subsequent nonprogressive motor deficits often grouped under the rubric "cerebral palsy". The magnitude of the problem of HIE relates to the essential gravity of the disorder and to its relatively high and unchanging prevalence. Thus, concerning the gravity, approximately 10-20% of infants die in the neonatal period and approximately one-half of the survivors exhibit neurologic deficits. Concerning the prevalence, as many as 1.5/1000 live births exhibit subsequent neurologic deficit secondary to perinatal asphyxia with HIE. To obtain insight into the basic nature and probable pathogenesis of the encephalopathy, we have measured regional CBF in 25 term infants with the disorder.

The clinical features of the infants have been similar. Thus, all have exhibited markedly depressed Apgar scores, presumably secondary to intrauterine asphyxia, which, in fact, was documented in those patients monitored during labor. All infants exhibited the neonatal neurological syndrome that we have described previously as characteristic of HIE in the term infant.

Regional CBF was determined by PET after intravenous injection of $H_2^{15}O$. The major findings were as follows. In the two least affected infants, a distinct outer ribbon of relatively higher CBF was discernible and presumably reflected flow to cerebral cortex. These cortical flows were 50-100% higher than those in cerebral white matter (CBF comparable to that in cortex was also apparent in deep nuclear structures, i.e., thalamus and basal ganglia). In contrast to this apparently normal or near normal pattern of regional CBF, in the remaining patients the pattern of regional CBF was different and quite consistent. The uniform abnormality was a diminution in CBF to parasagittal regions of cerebrum, bilateral and generally symmetric, more marked in posterior than in anterior cerebrum.

We have concluded that at least the major portion of the parasagittal impairment in CBF in these infant represents a fixed structural lesion for three major reasons. First, the PET lesion was irreversible in the one patient who had a second scan (at 20 days). Second, technetium brain scans in five infants showed increased uptake of the radionuclide in the parasagittal regions, bilateral and more marked posteriorly, correlating closely with the PET abnormality. Third, in the one infant who had a postmortem examination, neuropathologic study confirmed softening of cerebral cortex and subcortical white matter in the parasagittal regions, posteriorly more than anteriorly. We believe the structural lesion to be ischemic in basic nature, primarily because of the topography of the lesions, as defined clearly by PET. The particular

vulnerability of parasagittal vascular border zones to systemic hypotension has been shown in experimental models and in adult patients.

CONCLUSIONS

PET scanning provides the capability for determining in vivo critical information about the metabolism and perfusion of small regions of brain. No other technique, currently available or on the horizon, can provide the rapid, serial regional information attainable with this technique. Enormous insight has been gained with PET in adult patients with cerebrovascular disease, epilepsy, dementia, brain tumors and disorders of neurotransmitters and neuroreceptors. Similar insight should be attainable by study of the pediatric counterparts of these adult disorders. Initial studies of the most complex pediatric patients, i.e. critically ill newborns, indicate the feasibility and great value of PET in the study of pediatric disease. We appear to be on the edge of a new frontier in the study of pediatric disease.

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REGENERATION OF THE NERVOUS SYSTEM

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A question of key importance for neurobiology, cell biology and developmental biology as well as clinical medicine, concerns the ability of the nervous system to repair itself after injury. Unlike the peripheral nervous system where considerable regeneration and repair are possible and where function can be restored, the central nervous system is less successful in repairing itself. Recent experiments have shown that given the right conditions neurons within the brain can sprout over considerable distances. One example is provided by the work of Aguayo and his colleagues (1). The principle of these experiments was to make use of the fact that peripheral axons grow extensively along Schwann cells but do not do so along glial cells. A length of sciatic nerve was removed from a mouse and transplanted at one end into a region of the CNS. The other end of the graft was inserted into a distant part of the CNS. Neurons of the CNS were thus given the opportunity to grow along Schwann cells. Retrograde staining of axons with horseradish peroxidase in well-established grafts have shown that intrinsic neurons of different regions of the CNS, such as cortex, thalamus, retina, spinal cord can project over long distances to enter other regions of the nervous system. What is not yet clear is the extent to which synaptic connections can be established by the growing axons at their destination. In other experiments Björklund and his colleagues (2) have shown that embryonic nerve cells known to contain