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Noradrenaline content of cerebrospinal fluid in preterm and term infants recovering from perinatal asphyxia

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Noradrenaline content was measured in the cerebrospinal fluid of 17 full-term and 16 premature newborns with or without perinatal asphyxia. Upon the effect of asphyxia the noradrenaline content of cerebrospinal fluid exhibited a more than three-fold increase (from 2.61 ± 1.45 μg/l to 10.86 ± 4.02 μg/l) in mature newborns, but it decreased to about half of the control value in premature babies (from 2.39 ± 0.72 μg/l to 1.25 ± 0.70 μg/l). The observations emphasize the role of central noradrenergic structures in the organization of asphyxia-induced stress-response and in the regulation of adaptation to extrauterine life.

Labour and delivery, particularly when complicated with perinatal asphyxia, result in a highly elevated activity of the sympathicoadrenal system in the neonate. The functional role of this increased activity in neonatal adaptation is not clearly established. However, increased plasma catecholamine levels during the immediate neonatal period have been implicated in regulating cardiopulmonary and metabolic adaptation to extrauterine life [4, 8]. Since catecholamines do not pass across the blood-brain barrier, measurement of their plasma level reflects only the function of the peripheral sympathicoadrenergic system but fails to give information on the activity of the central nervous catecholaminergic system.

With respect to the intimate involvement of central nervous noradrenergic structures in the organization of stress reactions [9], the present study was undertaken to compare CSF noradrenaline (NA) content of healthy newborn infants with that of newborn infants challenged by severe stress, i.e. perinatal asphyxia.

Material and Methods

CSF samples were obtained by lumbar puncture from 17 full-term and 16 preterm infants at 2—3 days of age. In asphyctic newborns the indication of lumbar puncture was the asphyxia itself, in the other cases perinatal infection was suspected but later excluded by further laboratory and clinical examinations.

The newborns were divided into two groups on basis of the one-minute Apgar score: the non-asphyxic group included 8 full-term and 8 preterm infants with Apgar score of 7—10, while the asphyctic group consisted of 9 full-term and 8 preterm mature infants with Apgar score less than 6. The clinical and laboratory data of the infants are shown in Table I.

The asphyctic newborns required intermittent positive pressure ventilation at the delivery room which was followed by oxygen therapy with Fi O_2 more than 0.5 lasting for several hours. 13 newborns were

TABLE I

Clinical and laboratory data of the healthy and asphyctic newborn infants

	Term		Preterm	
Number of patients	8	9	8	8
Apgar score	7 – 10	<6	7 – 10	<6
Gestational age, weeks	38.0 ± 1.6	38.6 ± 1.4	33.6 ± 2.5	32.9 ± 2.1
Birth weight, g	2958 ± 258	2908 ± 290	2005 ± 272	1890 ± 267
Postnatal age, hours	34.2 ± 2.6	36.5 ± 3.1	35.0 ± 3.2	30.0 ± 4.3
pH	7.23 ± 0.06**	7.07 ± 0.06**	7.33 ± 0.08**	7.08 ± 0.04**
BE, mmol/l	−10.28 ± 5.49*	−14.18 ± 5.50*	−5.80 ± 4.0**	−12.66 ± 2.74**
pCO_2, mmHg	38.42 ± 10.26*	57.87 ± 17.28*	41.80 ± 7.85*	65.83 ± 14.38*
CSF noradrenaline, μg/l	2.61 ± 1.45**	10.86 ± 4.02**	2.39 ± 0.72*	1.25 ± 0.70*

* = $p < 0.01$
** = $p < 0.001$

given sodium bicarbonate in order to correct base deficit exceeding 15 mmol/l after oxygen administration.

Acid-base parameters were measured according to the method of Astrup [1]. CSF-NA was determined by the spectrofluorimetric aluminium oxide adsorption procedure as modified by Hahn [5]. Student's *t* test was used for statistical analysis.

RESULTS

As shown in Table I, mean birth weight, gestational age and postnatal age were nearly identical in the two groups. Arterial blood pH and pCO_2, and base deficit, however, indicated a significantly more severe acidosis in infants recovering from perinatal asphyxia than in those without asphyxia. CSF-NA was essentially the same in the healthy full-term and preterm infants (2.61 ± 1.45 μg/l and 2.39 ± 0.7 μg/l, respectively).

In response to perinatal asphyxia however, a striking difference between preterm and term infants could be observed in CSF-NA. While in full-term infants perinatal asphyxia resulted in a significant increase of CS-NA to 10.89 ± 4.92 μg/l ($p < 0.001$), in asphyctic preterm infants it was markedly depressed to 1.25 ± 0.70 μg/l ($p < 0.01$), about half of that found in healthy preterm controls.

DISCUSSION

Progressive increase in plasma catecholamine levels has been reported to be associated with advancing labour and with stressful stimuli such as fetal distress, instrumental delivery, and emergency Caesarean section when compared with those

found in infants born after uncomplicated vaginal delivery or elective Caesarean section [8]. No data are, however, available, on CSF catecholamines either in healthy newborn infants, or in infants presenting with perinatal asphyxia.

In the present study we could provide reference values for CSF-NA in healthy preterm and full-term newborn infants and could demonstrate a significant increase in CSF-NA when full-term infants were challenged by asphyxia. In contrast, asphyxiated preterm infants displayed a considerable lower CSF-NA level than preterm infants without perinatal asphyxia.

The reason for the difference in response to asphyxia is not quite clear. One may assume that preterm infants have less developed brain NA reserves than full-term ones and it is more rapidly depleted when subjected to hypoxaemia. In this respect it is of interest that lower plasma adrenaline and NA levels were found in preterm than in full-term infants and the response to asphyxia was also more limited in prematures [7, 8].

A further possibility to be considered is that enzyme systems involved in NA synthesis are more sensitive to hypoxia and acidosis when not fully mature and thus the activity of these enzymes will decrease due to the inhibitory effect of asphyxia.

The observed alterations of CSF-NA may have some clinical implications. Brain damage occurring subsequent to perinatal asphyxia often results in death or in neurological abnormalities in those who survive. Studies on CSF monoamines from children presenting with minimal brain dysfunction, in particular with hyperactivity and attention deficit, revealed a reduced activity of cerebral catecholaminergic system [6].

It is reasonable to assume that perinatal asphyxia and the subsequent alterations in cerebral monoamine metabolism result in permanent neurochemical changes responsible for the observed late neurological sequelae.

In a preliminary study on CSF-NA in newborn infants born to mothers on long-term methyldopa therapy we could demonstrate a striking depression of the CSF-NA level [2]. On the basis of this observation we suggested that the clinical symptoms consistent with "iatrogenic neonatal parkinsonism" and reduced brain growth [3] found in such infants might be ascribed to the reduction of dopaminergic tone in favour of the cholinergic tone in the developing central nervous system.

These findings indicate the prime importance of cerebral monoamines in neonatal adaptation and stress the need for further studies to explore the processes leading to alterations in central nervous monoaminergic systems during the neonatal period and later in life.

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