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Long-term prognosis of asphyctic neonates from an intensive care unit: Intrauterine retarded infants at high risk of cerebral palsy

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The surviving asphyctic infants born during the three-year period 1977 to 1979 and admitted to the regional neonatal intensive care unit were prospectively followed up to 2 and 4 years of age. According to outcome the children were divided into three subgroups:

1 who did not show any consequence of asphyxia;
2 who showed syndromes classified as cerebral palsy;
3 whose psychomotor functions were found to be retarded.

The cerebral palsy group mainly consisted of children who were born with a weight deficit after 37 weeks gestation. Only 4 out of the 15 children were premature and among them only 1 was of very low birth weight. Thus, dysmaturity was the main somatic characteristic of the severely handicapped children. In addition to intrauterine growth retardation, the high rate of congenital anomalies was a further feature of the cerebral palsy group.

Gestational complications (toxaemia, haemorrhage, threatening abortion or premature delivery), as well as the distortions of the most important biochemical variables (pH, calcium, bilirubins and glucose level) either in themselves or in combination had a similar incidence in the three subgroups. Among postnatal conditions, only the incidence of convulsions seemed to be important prognostically.

On the basis of the great difference in outcome it is concluded that there is no simple relationship between asphyxia and eventual handicap. There are certainly some other noxious factors (e.g., dysmaturity, congenital anomalies, etc.) associated with, or related to asphyxia which can be of great aetiological significance.

The present study deals with the follow-up of asphyxiated newborn infants admitted to the regional neonatal intensive care unit of the Department of Paediatrics in Pécs. The main purpose was to analyse the different prenatal, natal and postnatal characteristics of newborns and their relationship to the neurological and developmental outcome. In fact, a comparison was made between three subgroups of children, namely normal, developmentally retarded and mentally and physically severely damaged children. The study is intended to serve as a basis for evaluation of further follow-up studies of critically ill newborns admitted to our neonatal intensive care unit in the future. Such a feedback is expected to be helpful in judging the adequacy of intensive care and treatment on the one hand and to identify the various preventable risk factors of asphyxia on the other hand.

Material and Methods

The surviving asphyctic newborns admitted to the regional neonatal intensive care unit were followed prospectively. Selection was based on symptomatic asphyxia with its major or minor manifestations. Apnoea at birth needing resuscitation, ventilation either by mask or intubation, meconium stained amniotic fluid, metabolic acidosis, the immediate response to asphyxia as measured by Apgar score < 6, oxygen and bicarbonate therapy in the delivery room, poor condition with cerebral symptoms, cardiomegaly, clinical and radiological signs of massive aspiration syndrome, cardiac decompensation, cyanosis, repeated apnoeic attacks, ventilation support on admission were regarded as major asphyctic and post-asphyctic signs. Apathy syndrome, absent sucking and swallowing response, gestational and perinatal history such as haemorrhage, abruption of placenta, toxaemia and umbilical cord anomalies were considered to be minor criteria. In all cases a combination of major and minor signs was observed showing that the patients had suffered significant asphyxia and acute sequelae constituting the so-called postasphyctic syndrome. The selected neonates did not only need immediate resuscitation as a preventive measure against acute emergencies such as anoxia and acidosis, but also transfer to the intensive care unit. The children born during the three-year period from 1977 to 1979 were followed-up to the end of 1980, that is to 1 to 4 years of age. During the first year the infants suspected of some damage were examined monthly and those who appeared normal, at intervals of three months. After the first year the handicapped children were seen every half year until the age of six, and those without clinically manifest sequelae at three, five and six years of age. The follow-up examinations included anthropometric measurements, standardized neurological and developmental evaluation based on status of motor functions, behaviour, ophthalmological and audiological screening. At the age of 3 and 5 years an intellectual test was performed. Those whose psychomotor function based on the developmental quotient was found to be within the range of 70 to 90 were regarded as developmentally retarded.

The children were divided into three subgroups. 1. Those who did not show any consequence of asphyxia throughout the follow-up period and appeared normal as far as physical and mental development were concerned. 2. Those with syndromes classified as cerebral palsy due to severe cerebral damage. 3 Children whose psychomotor function based on the developmental quotient was found to be in the range of 70 to 90 were regarded as developmentally retarded. These three subgroups of children were compared in order to explore the somatic, gestational, perinatal and postnatal characteristics at birth, and their relationship to the late sequelae of asphyxia.

The consequences of a major cerebral damage were classified as cerebral palsy which is not a single handicap but involves different syndromes. Among the 15 cases followed-up in the present survey, 7 spastic tetraplegia, 2 ataxic syndromes, 4 spastic diplegia, 1 hemiparesis and 1 monoparesis were seen. In addition, 13 children were slightly and 2 severely retarded mentally, 4 showed microcephaly, 3 had epilepsy, 1 sensorineural hearing loss, and 10 various minor ophthalmological defects.

The terms minor handicap or physical and mental retardation are very broad and encompass a great variety of conditions which are not all pathological in the classical sense. They can be defined in many ways, and therefore variations in their incidence may be expected. In the present study the so-called retarded group represents such a heterogeneous collection of minor long term consequences and mainly developmental retardation.

Within these three groups, the children were also classified according to birth weight gestational age and percentile position on

our local weight for gestational age chart. Gestational age less than < 37 weeks and a percentile position ≤ 10 were regarded as the criteria of prematurity and intrauterine growth retardation, respectively.

Results

Birth weight, gestational age and intrauterine growth rate of the total material

Table I shows the birth weight, gestational age and percentile distribution of the total population. In 13 infants weighing less than 2500 g, and 6 infants above 2500 g, the gestational age was unknown. According to the percentile position of weight for age, 77.4% of the newborns were below 50, and 27.4% below the 10 percentile. Thus the population showed a shift towards the lower percentiles.

Weight, gestational age and weight for age in the three subgroups

From Table II it is evident that 67% of the children with cerebral palsy were born with a birth weight less than 2500 g. The majority of these low birth weight children (7 out of 9) weighed between 2001—2500 g. This distribution already suggests that the cerebral palsy group consisted mainly of children who were born with a weight deficit after 37 weeks gestation. Gestational age and weight for age classification undoubtedly confirms this suggestion. Only 4 out of the 15 children were prematures according to gestational age and among them only one was of very low birth weight. No doubt, dysmaturity was the main characteristic of the severely handicapped children.

In contrast, the majority of mentally and developmentally retarded children were true preterm newborns (Table III): of the 37 low birth weight infants (<2500 g) 33 were born earlier than at 37 weeks (in 4 cases the gestational age was unknown) and 10 were of very low birth weight, 9 out of 45 classifiable children were below the 10th percentile at birth.

The majority of the children, 155 out of 218, had no handicap and represented the normal group. According to weight and gestational age distribution (Table IV), roughly 40% were of term weight (>2500 g) and gestational age (>37 weeks). The shift towards the lower intrauterine growth rates was also striking in this group of children, which, as already pointed out, turned out to be a general somatic characteristic of the population studied.

Incidence of congenital abnormalities in the three subgroups

It is known [11] that dysmaturity is often associated with minor or major congenital abnormalities which might be directly or indirectly related to permanent cerebral damage. Hydrocephaly, microcephaly, meningocele, Klippel—Feil-syndrome, cleft palate, oesophageal atresia and three minor abnormalities occurring in combination were classified as minor congenital anomalies. The incidence of

minor and major abnormalities found in the present material is shown in Table V. It is interesting that the occurrence rate (major and minor) in the total population as well as in the subgroups was found to be high. Particularly high (80%) was it in the group with severe cerebral sequelae.

TABLE I

Birth weight, gestational age and percentile distribution of the total children population followed

Birth weight, g	1500	1501—2000	2001—2500	2501—3000	3001—3500	3501—4000	4000
No. of children	32	62	45	36	27	14	2
Gestational age, weeks	30	31—33	34—36	37—41	42—43	Unknown	
No. of children	27	36	58	66	12	19	
Weight for gestational	10	10—50	50—90		90	Unknown	
No. of children	57	104	42		5	10	

TABLE II

Birth weight, gestational age and percentile distribution of the cerebral palsy groups children

Birth weight, g	1500	1501—2000	2001—2500	2501—3000	3001—3500	3501—4000	4000
No. of children	1	2	7	2	3	—	—
Gestational age, weeks	30	31—33	34—36	37—41	42—43	Unknown	
No. of children	1	1	2	8	1	2	
Weight for gestational age, percentiles	10	10—50	50—90	90			
No. of children	*9	4	2	—			

* Two neonates whose gestational age was unknown showed the typical somatic signs of dysmaturity and were therefore included in the group weighing $\leq$ 10 percentile

TABLE III

Birth weight, gestational age and percentile distribution of the mentally and developmentally retarded groups of children

Birth weight, g	1500	1501—2000	2001—2500	2501—3000	3001—3500	3501—4000
No. of children	9	19	8	6	3	3
Gestational age, weeks	30	31—33	34—36	37—41	42—43	Unknown
No. of children	13	10	10	8	1	6
Weight for gestational age, percentiles	10	10—50	50—90		90	Unknown
No. of children	9	26	8	2	3	

TABLE IV

Birth weight, gestational age and percentile distribution of children with normal outcome

Birth weight, g	1500	1501—2000	2001—2500	2501—3000	3001—3500	3501—4000	4000
No. of children	22	41	30	28	21	11	2
Gestational age, weeks	30	31—33	34—36	37—41	42—43	Unknown	
No. of children	14	24	46	50	10	11	
Weight for age, percentiles	10	10—50	50—90		90	Unknown	
No. of children	39	74	32		3	7	

TABLE V

Frequency of congenital anomalies in the three subgroups of children

	Major congenital anomalies		Minor congenital anomalies		Total anomalies	
	Number	Percentage	Number	Percentage	Number	Percentage
Normal children	8	3.8	49	22.4	57	26.2
Children with cerebral palsy	7	46.6*	5	33.3	12	80
Retarded children	5	10.4	16	33.3	21	43.7

* Significantly different from that of normal children ($p < 0.001$) and from that of the retarded children ($p < 0.02$)

Incidence of clinical signs of asphyxia

The frequency of meconium stained amniotic fluid, Apgar score less than 6 and the therapeutic measures pointing towards the poor postasphyctic condition necessitating admission immediately after birth are shown in Table VI. It can be seen that meconium stained amniotic fluid was more frequently encountered in the severely handicapped children. Still, the incidence of an Apgar score less than 6, and the number of newborns needing resuscitation or bicarbonate therapy did not differ between the three subgroups.

Prenatal and postnatal events and complications

Although the population followed up was selected by different criteria of asphyxia as the principal cause of serious mental and physical impairment, we also looked for other events and complications operating over a period of time during gestation,

TABLE IV

Frequency of clinical indications of perinatal asphyxia

	Meconium stained amniotic fluid		Apgar score < 6		Resuscitation		Bicarbonate therapy	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Children with normal outcome	23	14.8	93	58.7	65	41.9	148	99.3
Children with cerebral palsy	5	33	9	60	7	46.6	13	86.6
Retarded children	6	12.5	36	75	23	47.9	47	98
Total population	34	15.1	138	63.3	95	43.5	208	95.3

TABLE VII

Frequency of toxaemia and threatening abortion or premature delivery

	Toxaemia		Threatening abortion or premature delivery	
	Number	Percentage	Number	Percentage
Children with normal outcome	64	41.3	80	51.6
Children with cerebral palsy	4	26.6	7	46.6
Retarded children	23	47.9	30	62.5
Total population	91	41.7	117	53.6

TABLE VIII

Incidence o the relevant postnatal manifestations and therapeutic interventions

	IRDS		Recurrent apnoea		Convulsions	
	Number	Percentage	Number	Percentage	Number	Percentage
Children with normal outcome	10	6.9	44	28	15	9.6
Children with cerebral palsy	4	7.3	11	23	4	26.6
Retarded children	—	—	5	33	4	8.3
Total population	14	6.4	60	27.5	23	10.5

	Other cerebral symptoms		Ventilation		O_2-therapy	
	Number	Percentage	Number	Percentage	Number	Percentage
Children with normal outcome	90	58	24	15.5	144	99.3
Children with cerebral palsy	30	62.5	7	14.4	47	98
Retarded children	9	60	1	6.6	12	80
Total population	129	59	32	14.6	203	93.1

around or after birth. These pathological conditions might represent antecedents or consequences of asphyxia and more or less contribute to the handicap.

In Table VII the frequency of toxaemia and threatening abortion or premature delivery can be seen. Both complications were frequent in every subgroup with no significant difference. Thus, a large proportion of the pregnancies were of high risk.

The incidence of the most relevant postnatal events and manifestations as well as therapeutic interventions is shown in Table VIII. The occurrence rate of IRDS was lower than 10% in the normal and retarded group, and it was not observed at all in the CP group. The proportion of infants affected by recurrent apnoea exceeded, however, 20% in every group. Cerebral symptoms such as convulsions, increased tremor, abnormal reflex responses and motor behaviour were frequently seen quite independently of the outcome of the asphyctic insult. Prognostically it appears important that the incidence of convulsions in the CP group exceeded that observed in the retarded and normal children.

Neonatal biochemical distortions potentially relevant to the outcome of asphyxia

Neonatal biochemical factors which might add to the brain damage incurred during perinatal asphyxia have also been explored in the population studied. In Table IX, the mean blood glucose, calcium and pH values

TABLE IX

Mean (± SD) postnatal blood glucose, pH, serum calcium and bilirubin levels of the three subgroups of children

	Blood glucose mg/dl	Serum calcium mg/dl	pH	Maximum serum bilirubin, mg/dl
Children with normal outcome	50.4±19.5 n = 119	8.2±1.2 n = 102	7.3±0.10 n = 138	12.3±6.8 n = 133
Children with cerebral palsy	46±19 n = 10	7.6±1.4 n = 10	7.25±0.09 n = 15	12.6±6.6 n = 9
Retarded children	51±13 n = 35	7.8±1.3 n = 38	7.3±0.08 n = 41	13±5.9 n = 41

at admission, and the mean maximum postnatal serum bilirubin levels can be seen. Neither mean value distinguished between the children with different outcome. It is interesting that the frequency of hypoglycaemia was practically the same in the normal children and in those with cerebral palsy (27.7% vs. 30%). The incidence of calcium and pH values lower than 7 mg/dl and 7.20, respectively, was somewhat but not significantly higher in the CP group in comparison to the retarded and normal children. The mean maximum serum bilirubin level exceeding 15 mg/dl was not significantly different in the three groups.

DISCUSSION

The question that often arises in connexion with the outcome of an asphyctic insult is, what constitutes a clinically significant episode of asphyxia? The duration and degree of asphyxia are those criteria whose knowledge would be important to avoid the inconsistencies in the definition of asphyxia in follow-up studies. Since these criteria are either lacking or not precisely recorded we have used our own criteria given in the section of Materials and Methods. We believe that these minor and major asphyctic features constitute a reliable guide to the presence of asphyxia and its acute sequelae in the immediate postnatal period which, in fact, necessitated admission to the intensive care unit for further treatment and observation.

Somatic, gestational age and intrauterine growth characteristics

The distribution of intrauterine growth rates of the three groups of children showed a shift to the lower weight for gestational age zones. Growth retardation defined as birth weight $\leq 10\%$ is a striking feature of the children suffering from cerebral palsy. The majority of low birth weight CP children (weight <2500 g) were full term infants (gestational age ≥ 37 weeks). Only one severely handicapped child had a very low birth weight.

This suggests that it is the dismaturity associated with asphyxia which should be regarded as a major risk factor of cerebral palsy rather than prematurity with very low birth weight (<1500 g). Although several previous follow-up studies [2, 9, 10, 16, 22, 23, 24] undoubtedly show that growth retardation is an important determinant of severe handicap, the single cerebral palsy patient with very low birth weight found in this study does not diminish the aetiological role of immaturity associated with perinatal asphyxia in the pathogenesis of severe brain damage. The actual prevalence of major handicaps in very low birth weight infants depends on several factors such as the frequency of high risk pregnancy, length and severity of asphyxia, peri- and neonatal care, and what is very important, the ultimate prevalence at different ages will depend on the survival of asphyctic very low birth weight infants. It is reasonable to suggest that a high mortality in this group of neonates would lead to a low incidence of severe permanent handicap, since the majority of critically ill and seriously damaged asphyctic infants by peri- and intraventricular haemorrhage would not survive. Our regional neonatal intensive centre is a referral unit, and the mortality of seriously affected premature infants weighing less than 1500 is rather high. This can be one of the reasons that in the present survey only one spastic child of very low birth weight was encountered. The large proportion of premature infants weighing less than 1500 g who showed minor, mostly developmental consequences of asphyxia points, however, towards the possibility that the outcome of acutely asphyctic immature infants is seldom characterized by cerebral palsy syndromes; it mainly threatens more mature, but intrauterine retarded infants suffering from chronic or subacute asphyxia. This would support the conclusion of several surveys that the improved quality of perinatal management largely contributes to the improved outcome of very low birth weight infants. The different sensitivity to asphyxia of the immature and more differentiated brain could also explain the considerably higher frequency of cerebral palsy in small for gestational infants than in those of very low birth weight. Since severe handicap usually results from more than one gestational or perinatal factor, it is also possible that the combination of asphyxia and intrauterine malnutrition is associated with a more unfavourable outcome than the combination of immaturity and asphyxia.

The significance of intrauterine growth retardation

The high proportion of intrauterine growth retardation in the CP group of children observed in the present survey confirms previous observations. Hagberg et al [16] found that in a cohort of 357 CP children, weight for age beyond 35 weeks of gestation was much less than the normal average for respective age. The sizable

portion of twins in this group also points to the aetiological role of dysmaturity whose importance considerably increases during the second part of the third trimester. From this survey it also follows that the frequency of cerebral palsy increases with increasing weight deficit for gestational age. Sabel et al [22] and Scherzer and Miké [24] also stressed the importance of smallness for dates. According to Hagberg et al [16] it appears that fetal deprivation of supply in the aetiology of cerebral palsy has recently become a more important factor in Sweden.

In an epidemiological study of cerebral palsy in Western Australia Dale and Stanley [10] also found that intrauterine growth retarded infants were high risk of spastic cerebral palsy. In their survey only 2.9% of the control population was small for dates compared with 17.8% of the cases.

In contrast Ellenberg and Nelson [14] found that the birth weight for gestational age was within normal limits in full term infants suffering from CP. They regard low birth weight and short gestation as the most important risk factor of cerebral palsy. Drillien [11] examining infants weighing less than 2000 g observed no difference in the incidence of cerebral palsy among small and large for dates newborns in comparison to true premature infants. She stated that some cases of mental and neurological deficit were due to hypoglycaemia, but the most striking feature was the much higher incidence of congenital anomalies (both minor and major) in those who were markedly underweight for gestational age. Drillien is inclined to believe that in some children the handicap is due to some developmental malformation. The global incidence of major and minor abnormalities in the three subgroups of the present survey was also rather high, particularly in the children who had been small for dates. This might support the contention that congenital developmental anomalies could be a further factor contributing to the severity and possibly type of handicap.

The significance of intrauterine retardation as a risk factor should also be kept in mind when the outcome of low (2500 g) or very low ($<$1500 g) birth weight infants is to be explored. Commey and Fitzhardinge [9] examined the neurodevelopmental state of 149 newborns of very low birth weight at two years of age. Thirty per cent had a major handicap, and the second highest risk were infants with evidence at birth of severe intrauterine growth retardation. Twelve of 28 malnourished babies of less than 33 weeks gestation were handicapped compared with only three of 28 preterm babies of appropriate weight for gestation and with similar neonatal course. Thus the growth retarded preterm infants showed a significantly higher incidence (49%) than that seen in very low birth weight but appropriate for gestational age. Commey and Fitzhardinge's survey in fact confirmed the conclusion of Hagberg et al. [16] that cerebral palsy increases progres-

sively with increasing fetal malnutrition and decreasing gestational age. As a result, the very small for gestational age prematures have a fifteenfold greater risk of CP. In the present survey only 4 of the CP children were premature and among them one had a very low birth weight and two were small for gestation.

In contrast to these findings Ellenberg and Nelson [14] reported that the risk of CP was highest among very low birth weights appropriate for gestational age and it was also higher among infants weighing 1501 to 2500 g if they were true prematures than if they were small for dates. This discrepancy and uncertainties in the prevalence of a history of low birth weight in children with cerebral palsy either appropriate or retarded for age are probably due to the biases in the selection of patient population as it has been pointed out by Brown[4].

Despite some inconsistencies in the observations cited it appears justified to conclude that smallness for date both in preterm and term infants represents a high risk factor of cerebral palsy. On the basis of the present study we agree with Hagberg et al. [16] that "fetal growth retardation and other factors summarized in the term fetal deprivation supply, stand out as particularly important, probably both as predisposing and directly damaging factors". This brings into focus the prenatal factors operating during a certain period of time, causing cerebral palsy, or making the brain more vulnerable to asphyxia, or other perinatal complications.

The significance of asphyxia in premature and mature infants

During the last decade great efforts have been made to decrease the mortality of very low birth weight infants [6, 13, 17, 18, 20, 21, 27, 29]. As to the aetiology of late handicaps in this group of neonates, the potential factors are difficult to evaluate. The question which often arises is whether prematurity, immaturity or asphyxia are directly related to brain damage or developmental and intellectual retardation. Although asphyxia can be regarded as the single most important adverse condition causing long term sequelae the great difference in outcome (intact survival, impaired survival with different neurological, developmenta[1] and behavioural sequelae, death) makes it difficult to attribute the handicap only to asphyxia [1, 5, 25, 26]. It should always be kept in mind that the majority of asphyctic newborns show no sequelae and even a severe asphyctic insult must not always have grave consequences. Mulligan and Shennon [19] reported that gestational age was not related to the incidence of sequelae of asphyctic neonates and the severity of impairment was similar in mature and premature infants. Does this mean that the risk factors of cerebral damage following an asphyctic insult are independent of gestational age and birth weight? We have no evidence to settle this problem.

The present study has confirmed the previous observation [1, 5, 25, 26]

that the majority of neonates affected by an asphyctic insult show no long term abnormalities. Out of 218 asphyctic newborns 15 developed major handicaps and 48 were found to show some neurodevelopmental disability and intellectual performance. The remainder were found to be normal. This strikingly demonstrates that there is not a simple relationship between asphyxia and eventual handicap. Scott [25] found that even infants whose respiration could be restored within the first 20 minutes may be normal at follow up. Out of the acute consequences of acute asphyxia (metabolic acidosis, meconium stained amniotic fluid, the immediate neonatal status as judged by the Apgar score, and resuscitation either by mask or intubation), only intrauterine meconium passage occurred more frequently in the cerebral palsy group, but the difference was not significant.

There are certainly other noxious factors associated with or related to asphyxia which can be of a great aetiological significance. It is therefore difficult to ascribe a causal significance to prematurity or asphyxia as a single factor leading to various long term effects. The prevention of either one of the two important conditions by adequate care of the pregnant mother and modern management of the perinatal period can be expected to lead to a marked reduction in the incidence of major handicaps simply because it also prevents those secondary conditions which directly or indirectly lead to long term neurological abnormalities. A recent review [28] of the reported data appears to support the suggestion that increased survival of the very low birth weight in infant is not associated with an increased incidence of brain damage.

The prognostic value of pre- peri- and postnatal factors in asphyxiated neonates

In order to correlate pre- peri- and postnatal factors and complications with the outcome of high risk neonates one has to find reliable predictors of the late status which can be of help in establishing a better management and successful prevention.

In the present survey gestational complications such as toxaemia and haemorrhage indicating threatening abortion or premature delivery had the same incidence in the three subgroups of children. It would, of course, be important to know additional variables such as the duration and degree of asphyxia, severity of toxaemia and postnatal condition as well as the biochemical abnormalities potentially capable of causing cerebral damage. Among the postnatal conditions only the incidence of convulsions seemed to be important prognostically which according to Volpe has a high predictive value for an unfavourable outcome [8, 30].

Some authors [3, 7, 12] reported that transient neurological signs in high risk neonates can be predictive of less severe developmental abnormalities or schooling difficulties.

Therefore they regard transient poor conditions and transient neurological signs important which may pinpoint to later sequelae. In the present study cerebral symptoms other than convulsions were frequently seen in the three groups, showing that asphyxia was often associated with neonatal cerebral morbidity which, however, was not predictive of the outcome. The same applies to the distortions of the important biochemical variables (pH, calcium, bilirubin, glucose) which either by themselves or in combination do not seem to be helpful in identifying those asphyctic newborns who are at high risk of major sequelae. In connexion with hypoglycaemia, <30 mg /dl in full term, and <20 mg/dl in preterm neonates, it should be stressed that in neither case was it judged as symptomatic hypoglycaemia, which is known not to be followed by cerebral damage.

Although the neonatal conditions and isolated cerebral signs have no great predictive value, one should not disregard the potentiality of certain signs, for example of neonatal convulsions.

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