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NEUROLOGICAL FOLLOW-UP OF SMALL-FOR-GESTATIONAL AGE NEWBORN INFANTS

A STUDY OF RISK FACTORS RELATED TO PROGNOSIS AT ONE YEAR OF AGE

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SUMMARY — To examine the relative importance of some risk factors and neurological prognosis in the first year of life, 37 small-for-gestational age newborns were followed prospectively to 1 year of conceptional age. An abnormal neurological examination was found in 51.3% of the newborns and, at 12 months, 32.5% were still considered abnormal. Only 8.1% of the group had severe neurological sequelae at 1 year of corrected age. The developmental tests showed little changes during the first year, with abnormality rates varying from 16.1 to 25%. The following risk factors were analyzed concerning their relation to neurological and developmental abnormalities: high-risk pregnancy, maternal hypertension, social class, pre-term birth, neonatal asphyxia and weight and height less than 2.5 percentile at the age of 1 year. The statistical analysis showed a high correlation between subnormal weight gain and neurological ($p=0.0001$) and developmental ($p=0.001$) abnormalities at 1 year. None of the other risk factors were statistically related to neurological prognosis at 1 year.

KEY WORDS: small-for-gestational newborn infants, neurological follow-up, prognosis, risk factors.

Evolução neurológica do recém-nascido pequeno para a idade gestacional: estudo de fatores de risco relacionados ao prognóstico com 1 ano de vida

RESUMO — Para estudarmos a importância relativa de alguns fatores de risco sobre o prognóstico neurológico, no primeiro ano de vida, 37 recém-nascidos (RN) pequenos para a idade gestacional (PIG) foram seguidos, prospectivamente, até 1 ano de idade concepcional. O exame neurológico neonatal foi anormal em 51,3% das crianças e, aos 12 meses, 32,3% ainda apresentavam anormalidades neurológicas. Entretanto, somente 8,1% das crianças apresentavam anormalidades neurológicas severas, com 1 ano de idade. Os testes de desenvolvimento apresentaram taxas de anormalidades que variaram de 16 a 25%, nas várias faixas etárias. Os seguintes fatores de risco foram analisados em relação à sua interferência com o prognóstico neurológico: gestação de alto risco, hipertensão arterial materna, nível sócio-econômico materno, prematuridade, asfixia neonatal e peso e estatura abaixo do percentil 2,5, na idade de 1 ano. A análise estatística demonstrou correlação altamente significativa entre presença de anormalidades neurológicas ($p=0,0001$) e no teste de desenvolvimento ($p=0,001$) e peso abaixo do percentil 2,5, na idade de 1 ano. Nenhum dos outros fatores de risco apresentou correlação significativa com o prognóstico neurológico, na idade de 1 ano.

PALAVRAS-CHAVE: recém-nascido pequeno para a idade gestacional, evolução neurológica, prognóstico, fatores de risco.

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The small-for-gestational age (SGA) infants are an interesting group for developmental studies. Their abnormal intra-uterine growth points to potential abnormalities or insults that could affect fetal normal development during gestation. The small weight of these infants is just a «risk marker» and does not necessarily imply that all SGA infants are abnormal or suffered intra-uterine insults [54]. Some animal experiments and studies in humans suggest the existence of a critical period in central nervous system (CNS) development in which undernutrition may cause irreversible damage [6,43,56]. Two hypotheses were raised to explain the vulnerability of the CNS. Winick [55] stated that, if undernutrition occurs during the cellular division phase of development, it would lead to a permanent reduction of cell number; later on during development, in the hypertrophic phase, undernutrition would determine a decrease in cell size that would be reversible with adequate nutrition. The second hypothesis, according to Dobbing [5], states that the CNS is more vulnerable to an irreversible lesion if undernutrition occurs during the two «growth spurt» phases; the first one, between the 15th and 20th weeks of gestation, is related to neuronal division and the second, between the 30th week gestation and the first 2 years of life, is related to glial cell division, myelination, axonal and dendritic growth and the establishment of synaptic connections. Both theories have a lot in common but differ in that the period of neuronal division is limited to the first phase of the «growth-spurt», while the second one opens the possibility of undernutrition interfering with mechanisms not directly related with cellular hyperplasia, as is the case of myelination [7,8]. Experimentally, myelination can be irreversibly delayed when animals are submitted to undernutrition at early ages [1,25,43]. Studies in humans showed that both intra-uterine and extra-uterine undernutrition, up to the first year of life, lead to a higher rate of cognitive problems [4,34], although these children's outcome is strongly influenced by socioeconomic factors that may contribute to their poor performance [17].

The present study is a prospective follow-up of a group of SGA infants, up to the age of one year, designed to evaluate the influence of some risk factors on the outcome. There was no control group and the correlations were drawn within the study group.

PATIENTS AND METHOD

Between January 1984 and November 1986, 85 SGA newborn inborn infants were selected for the study and evaluated in the neonatal period. Infants with neonatal seizures, meningitis, hypoxic-ischemic encephalopathy, symptomatic hypoglycemia, congenital infections, mechanical ventilation for more than 24 hours, congenital malformations, pneumothorax, intracranial hemorrhage or hyperbilirrubinaemia with exchange transfusions were excluded from the study group. Forty-eight infants were excluded at the follow-up: 29 infants were lost to follow-up, 18 returned only once or did not attend the 1 year visit and one infant had a congenital cardiac malformation diagnosed at follow-up. No difference in sex, race, social class, pre-term birth, Apgar scores, birthweight or pregnancy risk factors was detected between these infants and the study group. Thirty-seven SGA infants were prospectively followed up to the age of 1 year conceptional age.

General neonatal data of the study group are given in Table 1. Gestational age ranged from 32 to 40 weeks (mean 37.35 w), estimated through examination of somatic and neurologic items by the Capurro method 2. There were 21 female and 16 male infants, 19 colored and 18 white. The mean birth-weight was 2002 g (1030 to 2580 g). Nine newborns (24 3%) had neonatal asphyxia, defined as a 1' Apgar score <7. Birth-weight and gestational age were plotted on a standard chart based on the population that attends the Maternity-Hospital. The newborns classified as SGA were those whose birth-weight fell below the 10th percentile for their gestational age.

All newborns received a full neurological examination in the neonatal period, performed by one of the authors (J.L.D.G.), according to the technique of Prechtl [42]. The term infants were examined at the hospital, between the 3rd day and 10th day of life. The pre-term infants were examined at term concepctional age (38-42 w) either at the neonatal unit or at the outpatient clinic. The infants were free of catheters (IV or naso-gastric tube) or phototherapy.

The follow-up visits were scheduled at 3,6,9 and 12 months conceptional age, with an error of more or less 15 days. The correction for gestational age was made during the whole study period. A neurological examination was performed by the same person (J.L.D.G.) at each visit together with the Denver Developmental Screening Test (DDST), following a

general pediatric examination, performed by one of the authors (H.F.), with measurement of weight and height. If the infant was febrile or had an illness that could interfere with the results, the examination was re-scheduled. This is why there are different number of cases for each age group, as can be seen in Table 2.

The neonatal neurological examination was classified as normal or abnormal. The abnormal group was further sub-divided in one of the following neonatal neurological syndromes: hyperexcitability, apathetic, hypotonic, hypertonic and hemisyndrome.

Weight and height were plotted against a normal chart for the São Paulo population [29]. The infants weight and height were classified as being above or below the 2.5 percentile, at 1 year. During the follow-up period, no case of overt clinical undernutrition was detected.

Social class was defined according to the mothers level of instruction. Lower class, when the mother had incomplete primary or no education; medium class, complete primary or incomplete secondary; and higher class, those with complete secondary or universitary education.

X^2 and Fischer test were used for statistical analysis and the level of significance established at $p=0.05$.

Table 1. General neonatal data of the study group.

Case	Sex	Race	G. A. (w)	Weight (g)	Height (cm)	OFC (cm)	APGAR (1' and 5')
1	F	B	39	2440	47	33	8 - 10
2	M	W	34	1260	38	31.5	4 - 6
3	F	B	39	2100	47	33	9 - 10
4	F	B	33	1030	33.5	32.5	3 - 6
5	F	B	39	2400	47	34	7 - 10
6	M	B	40	2520	47	34	9 - 10
7	F	B	39	2350	47	33	9 - 10
8	F	W	36	1470	40	32.5	8 - 10
9	M	B	38	2360	45	33	9 - 10
10	F	B	39	2500	48	32	9 - 10
11	M	W	32	1270	40	33.5	8 - 9
12	F	W	33	1970	41	33	6 - 9
13	F	W	40	2380	45	32	9 - 10
14	F	W	37	1800	44	33.5	9 - 10
15	F	W	36	2100	45.5	32	8 - 10
16	M	W	40	2440	46	32.5	5 - 8
17	F	B	38	2400	46	31	7 - 10
18	M	W	38	2300	46	33	2 - 8
19	M	B	38	1980	43	32	8 - 10
20	M	B	33	1050	36.5	35	8 - 9
21	M	B	40	2450	48	31.5	8 - 10
22	M	B	37	1650	41	30	8 - 10
23	F	W	38	1800	43	31	7 - 9
24	F	B	40	2580	47	32.5	9 - 10
25	F	W	37	1850	42	32.5	7 - 10
26	F	B	35	1750	45	30.5	8 - 9
27	F	W	40	2180	47	32	8 - 10
28	F	W	37	1780	41	32	8 - 9
29	M	B	39	2450	45.5	32.5	7 - 9
30	M	W	35	1400	40	34	6 - 9
31	M	B	37	1820	43	31.5	6 - 9
32	F	B	38	2220	43	32	9 - 10
33	M	W	37	1920	43	31.5	4 - 8
34	M	B	40	1940	42	30.5	1 - 6
35	F	W	38	2220	45	31	9 - 10
36	M	W	33	1490	40.5	33.5	9 - 10
37	F	W	40	2460	47.5	32	8 - 10

OFC, occipito-frontal circumference; G.A., gestational age; W, white; B, black; F, female; M, male.

RESULTS

Results of neurological examinations according to age are shown in Table 2. In the newborn period, 19 infants (51.3%) had an abnormal neurological examination. The hypotonic syndrome was found in 10 cases (52.6%), followed by hyperexcitability in 6 (31.5%). Three infants had association of syndromes, 2 with hypotonia and hyperexcitability and 1 with hyperexcitability and hypertonia.

The newborn neurological examination showed a high rate of false positives, as shown in Table 3. Of 19 newborns with abnormal evaluation in the neonatal period, 11 (58%) were normal at 1 year. The rate of false negatives was lower. Only 4 infants (22%) of the 18 with a normal neonatal examination were abnormal at 1 year.

During the follow-up period, a decline in the number of neurologically deviant infants was observed, from 59.4% at the 3rd month to 32.5% at the end of the first year. There was an abrupt drop in the percentage of abnormal infants at 6 months (Fig. 1) but, after pairing, statistical anlysis showed no significant differences between age groups.

The DDST results during the follow-up period showed abnormality rates between 16 to 25% (Fig. 1) and no significant differences between age groups. All infants considered abnormal by DDST at 1 year had also an abnormal neurological examination.

Although a high rate of neurologically deviant infants was observed, only 3 of 12 neurologically abnormal infants (cases 16, 20 and 25) were severely compromised at 1 year, as can be seen in Table 4. The others had mild to moderate degrees of developmental delay, without important focal neurological signs, together with mild/moderate tone and posture abnormalities. Thus the incidence of severe neurologic sequelae in the study was 8.1%.

At 1 year, 11 infants (30%) had weight below the 2.5 percentile and 17 cases (46%) had height below the 2.5 percentile. The percentage of infants that were below the 2.5 percentile for weight ranged from 19 to 30% and for height, from 42 to 57%. During follow-up, 5 infants developed infectious diseases and were hospitalized for less than 2 weeks, all of them in the first 6 months of life.

Table 2. Neurological and developmental examinations for each age group.

Age	Neurological examination			DDST		
group	NL	ANL	Tot	NL	ANL	Tot
Newborn	18 (48.7%)	19 (51.3%)	37			
3 m	13 (40.6%)	19 (59.4%)	32	24 (77.5%)	7 (22.5%)	31
6 m	22 (66.6%)	11 (33.3%)	33	26 (83.9%)	5 (16.1%)	31
9 m	19 (63.3%)	11 (34.4%)	30	24 (80.0%)	6 (20.0%)	30
12 m	25 (67.5%)	12 (32.5%)	37	27 (75.0%)	9 (25.0%)	36

DDTS, Denver Developmental Scale Test; NL, normal; ANL, abnormal; m, months; Tot, Total.

Table 3. Comparative data of neurological evaluation at the newborn period and 1 year.

		Neonatal	
		Normal	Abnormal
1 year	Normal	14 (78%)	11 (58%)
	Abnormal	4 (22%)	8 (42%)
Total		18 (100%)	19 (100%)

Table 4. Clinical status of the infants with abnormal neurological examination at 1 year of age.

Case	Clinical status
8	Moderate hypotonia + developmental delay
11	Mild hypertonia + hiperactive reflexes of lower extremities + developmental delay
12	Moderate hypotonia + developmental delay
14	Moderate hypotonia + developmental delay
16	Severe hypotonia + developmental delay
18	Moderate hypotonia + developmental delay
20	Right hemiparesis + seizure
25	Global spasticity + bilateral pyramidal signs + poor visual and auditory contact
28	Mild hypertonia in lower extremities + developmental delay
30	Moderate hypotonia + developmental delay
32	Mild hypertonia of right lower extremity + mild developmental delay
34	Moderate hypotonia + microcephaly + developmental delay

Table 5. High-risk pregnancies.

Maternal arterial hypertension	16
Urinary tract infection	5
Epilepsy	3
Toxemia	2
Smokers (>20 cigarettes/day)	4
Maternal age >35 years	3
Maternal age <18 years	5
Multiparity	2

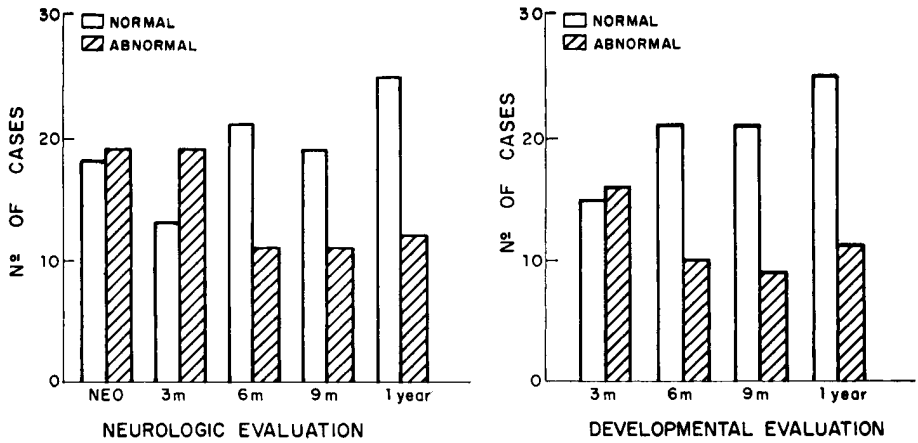

Fig. 1. Neurological and development evaluation during the study period.

At 1 year of age, one infant (case 34) was microcephalic. The majority had occipito-frontal circumference (OFC) between the 10th and 50th percentile. One infant (case 20) had a hemigeneralized seizure at 11 months of age.

Most of our cases came from low class families, that constitute the main population attended in our institution. Data on mothers educational level was obtained in 29 cases; 22 were classified as coming from the lower class and 7 from the medium class, with no case from the higher class.

The etiologies of high-risk pregnancies are shown in Table 5. Thirteen cases had more than one etiology and arterial hypertension was the most common, present in 16 cases.

Comparison between data from the neurologic and developmental findings was undertaken with the following risk-factors: high-risk pregnancy, neonatal asphyxia, pre-term birth, maternal arterial hypertension, weight, height and social class. There was a strong correlation between neurologic ($p=0.0001$) and developmental ($p=0.0011$) abnormalities, and weight below the 2.5 percentile at one year of age. There was also a significant relation between neonatal asphyxia and developmental abnormalities at the age of 3 months ($p=0.015$) but, at 1 year, it just failed to reach the significance level ($p=0.052$).

COMMENTS

Half of our infants had neurological abnormalities in the newborn period. This rate is similar to that found by Michaelis et al.[33], and higher than Schulte et al.[46] that disclosed 36% of neurologically abnormal SGA infants in the newborn period. The hypotonic and hyperexcitability syndromes were the most frequent neurologic abnormalities found in the newborn period in these studies. Jungens-van der Zee et al.[22] observed that 35% of the neurologically abnormal SGA newborns had the hypotonic syndrome. Others [11,24] found hypertonia to be the most common neurologic abnormality in SGA newborns.

Although not significant, we found a tendency towards normalization of neurological abnormalities during the first year of life, a fact pointed out by other studies [28,33,47]. The abrupt drop in abnormality rates, observed around the 6th month, is in agreement with Drillien's data on low-birth-weight infants; 60% of the infants with tone abnoramalities at an early age showed a normalization of the neurological examination around the end of the first year [9].

At 1 year, 32.5% of the infants of our study were neurologically abnormal, only 8.1% with severe abnormalities. Holmqvist et al.[21] found neurological abnormality rates in the range of 6.25 to 24.5% in a study of SGA infants followed up to 2 years of age, with 3.9% of the cases being severely handicapped. Dunn et al.[12] found 8% of neurologically deviant SGA infants, in the Vancouver study, but no reference is made about their degree. Authors who studied only pre-term SGA infants in the first 2 years of life observed incidence of severe neurological sequelae ranging from 2.8 to 21% [3,27,49,50].

The DDST showed a rather constant abnormality rate in the various age groups of our study. This result is in agreement with studies that used developmental tests to evaluate SGA infants in the first year of life [14,28,32,40,50-52]. It was difficult to compare our results with those of the literature because most studies expressed their results in absolute numbers. Holmqvist et al.[21] found an abnormality rate of 14% using the DDST in a study of SGA infants followed up to 2 years.

All infants diagnosed as having a developmental delay by the DDST, at the age of 1 year, had an abnormal neurologic examination. The infants with abnormal neurologic examination and normal DDST, at 1 year, had neurologic abnormalities characterized by changes in muscle tone and reflexes that would not necessarily interfere with the results of developmental scales. This observation emphasizes the need of a full neurological evaluation besides developmental tests.

The ultimate prognosis of our infants can not be estimated. Some authors noted that infants with neurologic abnormalities at the age of 1 year have a higher risk of being abnormal at school age [9,10,13,15,30,49]. Others found that, if

the neurologic abnormalities are not severe, they tend to disappear in the long-term follow-up or that there is no relationship between early evaluations and long-term outcome [14,19].

One infant had an isolated, right-sided, afebrile seizure at the age of 11 months. The incidence of epilepsy in follow-up studies of SGA infants ranged from 3.7 to 6.25% [9,12,16,23].

We found a significant relation between neurologic and developmental abnormalities, and weight below the 2.5 percentile at 1 year. Although no laboratory tests were performed to further classify these children as having undernutrition, clinically there were no signs that suggested the diagnosis. Holmqvist et al.[21] followed up 250 SGA infants, 80% born at term, observing a significant relation between neurological abnormalities and weight and height below 3 SD, at 1 year of age. Ounsted et al.[38] reported 30% of developmental abnormalities, at 4 years, in SGA children whose weight fell below the 10th percentile. In those above this level the abnormality rate dropped to 10%.

We found no significant relationship between neurodevelopmental outcome and social class, while most of the follow-up studies of high-risk newborns correlate socio economic status and outcome [12,31,35,36,39,45,49]. The uneven distribution of our cases and the short follow-up period may have contributed to the results, as the relationship starts to be significant only after 2 years of age [10,14,18,32,44,51].

Our results differ from reports associating maternal arterial hypertension and high-risk pregnancy, to developmental outcome. It is important to point out that most of the studies used a control group when comparing results [10,20,26,37,41,48].

Most of the follow-up studies of SGA infants relate neonatal asphyxia to long-term outcome [3,16,28,39,53]. In our study neonatal asphyxia was significantly related to developmental abnormalities at 3 months of age and, at 1 year, it just failed to reach the significance level ($p = 0.052$). We excluded infants with clinical signs of hypoxic-ischemic encephalopathy and no case had a 5' Apgar score <6.

We conclude that adequate weight gain is an important factor in the neurological outcome of SGA infants during the first year of life.

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