Original Article

Journal of Child Neurology
Volume 22 Number 5
May 2007 580-587
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10.1177/0883073807302605
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Neurodevelopmental Outcome of Children With Intrauterine Growth Retardation: A Longitudinal, 10-Year Prospective Study

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One hundred twenty-three children with intrauterine growth retardation were prospectively followed from birth to 9 to 10 years of age in order to characterize their specific neurodevelopmental and cognitive difficulties and to identify clinical predictors of such difficulties. Perinatal biometric data and risk factors were collected. Outcome was evaluated at age 9 to 10 by neurodevelopmental, cognitive, and school achievement assessments. Sixty-three children served as controls who were appropriate for gestational age. Significant differences in growth ($P < .001$), neurodevelopmental scores ($P < .001$), intelligence quotient (IQ) ($P < .0001$), and school achievements measured by the Kaufmann Assessment Battery for Children ($P < .001$) were found between the children with intrauterine growth retardation and controls. Children with intrauterine growth retardation demonstrated a specific profile of neurocognitive difficulties at school age, accounting for lower school achievements. The best perinatal parameter predictive of neurodevelopment and IQ was the Cephalization Index ($P < .001$). Somatic catch-up growth at age 2 and at age 9 to 10 correlated with favorable outcome at 9 to 10 years of age.

Keywords: intrauterine growth retardation; neurodevelopmental outcome; Cephalization Index; Kaufmann Assessment Battery for Children

The term *intrauterine growth restriction* is the most common generic term used to describe a fetus with a birth weight at or below 2 standard deviations for gestational age. This condition affects 3% to 10% of all newborns.[1] Intrauterine growth retardation describes a fetus that does not reach full growth potential: that is, a fetus with normal growth potential at the 50th percentile. Because of maternal, fetal, or placental disorders occurring alone or in combination, the fetus becomes growth restricted (<2 standard deviations for gestational age) and is at risk of adverse perinatal outcome and long-term sequelae.

The intrauterine process resulting in intrauterine growth restriction is a well-known risk for brain insult as well as for hypertension, diabetes, and coronary heart disease.[1-5] Recently, Tolsa et al[6] described a significant reduction in intracranial volume and cerebral cortical gray matter in preterm newborns with intrauterine growth restriction, compared with preterm newborns who were appropriate for gestational age. Measurements were evaluated by volumetric magnetic resonance imaging (MRI) within the first 2 weeks of life. The results of these intrauterine insults may not, however, become evident until later in life.[7-12] Therefore, it is crucial to follow newborns with intrauterine growth restriction who are at risk of developing neurodevelopmental and cognitive deficits, in order to make an early diagnosis and provide these neonates with necessary special intervention.

Although the need to follow this high-risk group is well accepted, it is not clear what percentage of these children will in fact show significant cognitive deficits, what risk factors conjointly occurring with intrauterine growth restriction are associated with or related to these later outcomes, and whether any early markers exist that could predict those newborns with intrauterine growth restriction who will experience higher morbidity later in life.

Several factors hamper the interpretation of some of the data published on this subject.[13] First, the definitions and

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This study was made possible by a grant from the Gulton Foundation, New York

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Leitner Y, Fattal-Valevski A, Geva R, et al. Neurodevelopmental outcome of children with intrauterine growth retardation: a longitudinal, 10-year prospective study. *J Child Neurol*. 2007;22:580-587.

etiologies of intrauterine growth restriction differed greatly between studies. Second, most studies were retrospective and did not consider other conditions that adversely affect neurodevelopment, such as prematurity or perinatal complications. Furthermore, many studies reflected the results of neonatal care practiced some 20 to 30 years ago and not the modern intensive care provided over the past decade. Third, in many follow-up studies of older children with intrauterine growth restriction, controlling for postnatal influences, such as socioeconomic and environmental factors, and a high attrition rate became major problems in analyzing outcome. The present prospective study, initiated in September 1992, was specifically designed to overcome most of these limitations. We have previously reported the results of follow-up at ages 3 and 6 to 7 years.[14,15]

This study describes the specific neurodevelopmental and cognitive outcomes of children with intrauterine growth restriction followed from birth to school age. The study specifies the nature of the most prevalent difficulties found in children with intrauterine growth restriction and identifies significant risk factors and clinical predictors associated with these outcomes.

Table 1. Biometric Parameters and Risk Scores in Children With Intrauterine Growth Restriction and Controls

Parameter	Intrauterine Growth Restriction (n = 123)	Control (n = 63)	*P*
At birth			
Gestational age, wk	36.9 ± 2.6	37.6 ± 3.4	NS
Birth weight, g	1842 ± 411	2826 ± 755	<.0001
Head circumference, cm	30.5 ± 1.9	33.5 ± 4.2	<.0001
Cephalization Index[a]	1.72 ± 0.41	1.37 ± 0.42	<.0001
At 9-10 y			
Somatic			
Weight, kg	27.9 ± 7.1	31.1 ± 6.1	<.005
Height, cm	131.3 ± 6.1	135.0 ± 6.8	<.0001
Head circumference, cm	51.2 ± 1.8	52.1 ± 2.6	<.01
Risk questionnaire scores[b]			
Sociofamilial	90.8 ± 6.9	88.7 ± 7.9	NS
Obstetric	81.4 ± 9.0	88.0 ± 8.3	<.01
Neonatal	80.2 ± 12.4	89.7 ± 15.4	<.001

NOTE: NS = not significant.
a. Cephalization Index = head circumference/birth weight × 10^2.
b. Percentage of optimal items.

Methods

Study Population

Inclusion Criteria. We included all consecutive infants born at Lis Maternity Hospital (previously Serlin Maternity Hospital), Tel Aviv Sourasky Medical Center, from September 1992 with a birth weight less than the 10th percentile for gestational age, according to the Israeli percentile curves published by Liebermann et al.[16] All such infants identified by the participating obstetricians and neonatologists were referred to the study. Gestational age was calculated according to the date of the last menstrual period.

Exclusion Criteria. We excluded newborns diagnosed with genetic syndromes or major malformations or showing evidence of congenital infection.[17] Overall, we excluded 8 children: 4 with congenital heart disease, 2 with genetic syndromes, 1 with neurofibromatosis type 1, and one with congenital cytomegalovirus infection.

The children included in the study group all had a late (mid-second-third trimester) onset intrauterine growth restriction, verified clinically and/or by ultrasound, and all demonstrated the asymmetric type of intrauterine growth restriction, reflecting the "brain-sparing" effect and resulting in a high brain/body ratio.[18-20] Therefore, we assumed that the majority of children in this study had suffered a vascular (placental)-induced intrauterine growth restriction. This assumption was also supported by pathologic studies of the placentae that revealed vascular pathology in more than 85% (eg, obliterated vessels, placental infarcts, increased syncytial knots, and lack of inflammatory changes).

Three hundred twenty-two children identified as having intrauterine growth restriction were recruited for the study over the past 10 years. Of this group, 123 children who reached 9 to 10 years of age participated in the analysis (Table 1).

Attrition (20% over 10 years) was attributable to inability to trace families who had moved location, failure in positive communications, parental minimization of the importance of follow-up, and technical difficulties such as transportation, parking, and others. No significant differences were found between the patients who were lost to follow-up and the study group in biometric, perinatal, or socioeconomic status.

Control Group

This group comprised sixty-three 9- to 10-year-old children who were age-matched for gestational age and socioeconomic status. These children were randomly selected according to birth registries kept at the municipal well-baby care clinics in the Tel Aviv area (Table 1).

Procedure

All newborns identified as having intrauterine growth restriction by the obstetricians or neonatologists who participated in this study were examined in the maternity ward by a pediatric neurologist. A neurobehavioral examination of the newborn was performed, and biometric data were collected (birth weight, length, head circumference). The Cephalization Index (ie, the ratio between head circumference and birth weight × 10^2), first described by Harel et al,[21] was calculated as reflecting the severity of

intrauterine growth restriction and the magnitude of the brain-sparing process.

Risk parameters were then assessed using 3 detailed questionnaires: (1) a sociofamilial risk questionnaire that covered parental health, education, socioeconomic status, and maternal obstetric history; (2) an obstetric risk questionnaire that encompassed the present gestational and delivery data; and (3) a neonatal risk questionnaire that described the perinatal course according to the medical records.[15]

All questionnaires were designed in accordance with Prechtl's[22] optimality concept; each item was given an "optimal" versus "suboptimal" score, according to accepted standards in the literature. The final score was expressed as the percentage of optimal items out of the total number of items in each questionnaire. The content validity of the questionnaires was verified by a team of clinicians (obstetricians, neonatologists, pediatric neurologists, and developmental psychologists) who participated in this study.

From birth, the children were followed up annually at the Institute for Child Development by a team of pediatric neurologists and psychologists. At each follow-up visit, children underwent a detailed neurodevelopmental examination; head circumference, height, and weight measurements; and formal neuropsychological testing.

At age 9 to 10 years, the neurodevelopmental examination included not only the standard physical and neurological evaluation but also special tests to determine brain maturation: dynamic and passive coordination skills; timed coordination tests (as described by Denckla[23]); presence of "soft" neurological signs, such as motor impersistence; presence of associated movements and/or mirror movements; parietal functions, such as finger agnosia and localizations; lateralization; the quality and clarity of speech; short-term memory; several basic visuomotor and graphomotor organizational skills; and a clinical impression of attention abilities and motor hyperactivity.

The complete examination included 72 items and took 45 to 60 minutes to complete. Several neurologists in our team were enrolled in the study to minimize past familiarity with the children and their clinical status. The test protocol was initially validated, and no significant inter-examiner or intra-examiner variability was found. The full protocol of the neurodevelopmental evaluation at age 9 to 10 years is available on request.

The subjects' estimated IQ was constructed based on performance on the general information subtests and the block design subtest of the Wechsler Intelligence Scale for Children (WISC) R95 2-test short form.[24] Academic achievements at school were evaluated using the Kauffman Assessment Battery for Children (K-ABC).[25] The control group underwent the same battery of tests.

The study was approved by the Ethics Review Committee of the Tel Aviv Sourasky Medical Center.

Statistical Analysis

The unpaired *t* test was used for between-group comparison of biometric parameters, risk factors, and neurodevelopmental scores (study vs controls). The same analysis was conducted to compare children with intrauterine growth restriction with and without neonatal complications.

Because of the importance of time, the children with intrauterine growth restriction were followed up as close as possible to their birthday anniversary, using exams adequate to their age. Examinations were performed at constant time intervals in order to collect data on all subjects at equal stages. Thus, time dependency was taken into consideration in the analysis of the data.

We defined *suboptimal neurological outcome* of children with intrauterine growth restriction as those with neurodevelopmental scores less than the control group (ie, mean ± 1.5 standard deviations).

We defined *suboptimal cognitive outcome* of children with intrauterine growth restriction as IQ score of less than or equal to 85 (by the estimated IQ).

We defined *neonatal complications* as those study children who scored more than 2 of 11 suboptimal items in the neonatal questionnaire dealing with potential brain damage.

We defined *suboptimal catch-up* in biometric parameters (weight, head circumference, and height) of children with intrauterine growth restriction as those who did not reach the 10th percentile for age.[16]

When variables were found to have an abnormal distribution, the nonparametric Mann-Whitney test was performed. Correlations between biometric data, risk factors, and 9- to 10-year neurodevelopmental and cognitive outcomes were performed by Pearson correlations. Significantly correlated parameters were further analyzed by multiple regression analysis to identify the best predictors of outcome at 9 to 10 years.

Results

Biometric Parameters

Of the 123 children with intrauterine growth restriction in the study group, 30% were preterm and 46% were males. Significant differences were found for all biometric birth parameters between the study and control groups, except for gestational age, as expected. A strong significant difference was also detected in the Cephalization Index, which described the ratio between head circumference and birth weight $\times 10^2$, as previously mentioned.[21]

At age 9 to 10 years, somatic growth measures (head circumference, height, and weight) remained significantly lower in the intrauterine growth restriction group. Overall, approximately 18% to 20% of the study children were found to be below the 10th growth percentile for their age in at least one of the biometric parameters at age 9 to 10 (Table 1).

Table 2. Developmental Outcome in Children With Intrauterine Growth Restriction and Controls

Developmental Parameter	Intrauterine Growth Restriction (n = 123)	Control (n = 63)	*P*
Neurodevelopment[a]	85.9 ± 9.6	91.2 ± 5.1	<.001
IQ[b]	98.39 ± 12.9	107.5 ± 10.4	<.001
School achievement[c]	588.6 ± 80.2	636.63 ± 55.7	<.001

a. Percentage of optimal items.
b. Estimated IQ.
c. Kauffman Assessment Battery for Children school achievement.

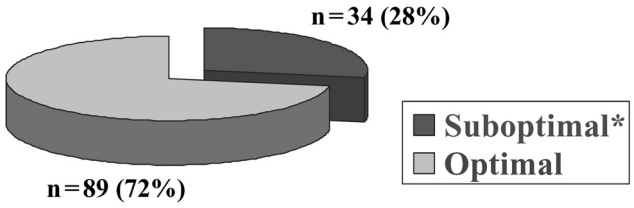

Figure 1. Neurological outcome of intrauterine growth restriction group (n = 123).

Risk Parameters

The children with intrauterine growth restriction and the control children were initially matched for sociofamilial risk. Nevertheless, such matching was not "artificial," because our study group comprised the vascular type of intrauterine growth restriction, dispersed analogously among different socioeconomic groups. In contrast, significantly lower scores were observed in the neonatal and obstetric questionnaires of the intrauterine growth restriction group, reflecting their initial higher risks and biologic vulnerability (Table 1). Sociofamilial risk was assessed only once, at birth, and not when children reached 9 to 10 years of age.

Neurodevelopmental and Cognitive Outcome

Neurodevelopmental scores of children with intrauterine growth restriction at age 9 to 10 were significantly lower compared with controls ($P < .001$) (Table 2). The children with intrauterine growth restriction most frequently received suboptimal scores for those specific items related to motor coordination (passive and active equilibrium and timed coordination performance) ($P < .05$).

Muscle tone (both axial and limb) was clinically judged to be lower in the intrauterine growth restriction group ($P < .05$). Significant differences were also found in clinical rating of activity and attention span: Children with intrauterine growth restriction demonstrated significant motor hyperactivity and a shorter attention span ($P < .001$) and inferior graphomotor skills compared with controls ($P < .05$). They also received significantly lower scores regarding the clinical impression of their speech and language abilities ($P < .001$).

It is noteworthy that the neurodevelopmental problems identified were relatively minor and related most frequently to the quality of neurodevelopmental performance. No children with cerebral palsy or severe neurological deficits were included in the study.

Cognitive competence as measured by the estimated IQ (WISC-R95 2-test short form) was significantly lower than that of the control group ($P < .001$), even though it was well within the normal range for age, grade, and academic semester (Table 2). Significantly more difficulties than in the control group were found in memory performance ($P < .001$), visuomotor functions ($P < .001$), and learning abilities ($P < .001$). Less commonly encountered difficulties were found in creativity, language abilities, and executive functioning

Academic achievements measured by the K-ABC were lower than those of controls ($P < .001$). Performance of controls was fully expected from their competence scores, whereas learning difficulties and particularly language-based difficulties were found in the children with intrauterine growth restriction, explaining the discrepancy between their competence level and academic achievements. Accordingly, the most frequent interventions reported by the parents of children with intrauterine growth restriction at age 9 to 10 years were remedial education (43% vs 15% in controls), neurological follow-up (19.8% vs 1.5%), speech therapy (12.2% vs 3.2%), and psychological intervention (11.4% vs 3.2%).

Suboptimal neurodevelopmental outcome (1.5 standard deviation below the mean achievement of the study group) was found in 28.6% of the children with intrauterine growth restriction (n = 34) (Figure 1). Suboptimal cognitive performance (IQ below 85) was found in 15% (n = 19) of the children (Figure 2).

Risk Factors Correlated With Outcome in Intrauterine Growth Restriction

Multiple regression analysis of all risk parameters revealed that the Cephalization Index at birth was the strongest and best predictor of both neurodevelopmental performance and IQ at school age ($P < .001$). Neonatal risk score was also a strong predictor of neurodevelopmental outcome at 9 to 10 years of age (Table 3). Environmental parameters, such as the prenatal risk score, paternal occupation, and maternal education, significantly correlated with IQ ($P < .01$) (Table 4).

Mental developmental index and neurodevelopmental score at age 2 years strongly correlated with

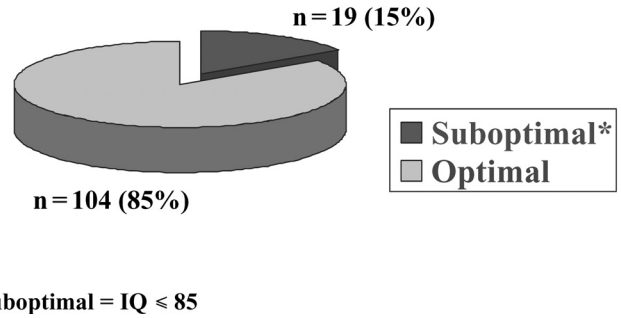

Figure 2. Cognitive outcome of intrauterine growth restriction group (n = 123).

Table 3. Clinical Parameters Most Significantly Correlated With 9- to 10-Year Neurodevelopmental Score in Children With Intrauterine Growth Restriction (n = 123)

Parameter	r^a	*P*
Perinatal		
Cephalization Index[b]	0.331	<.001
Neonatal risk score	0.308	<.001
Birth weight	0.280	<.005
Obstetric risk score	0.200	<.05
Parental risk score	0.181	<.05
2 y		
Neurological score	0.556	<.001
Mental developmental index	0.529	<.001
9-10 y		
Head circumference	0.243	<.01
Weight	0.259	<.005

a. Pearson correlation.
b. Cephalization Index = head circumference/birth weight × 10^2.

neurodevelopment at 9 to 10 years ($P < .001$), whereas mental developmental index and head circumference most strongly correlated with 9- to 10-year IQ.

Of all the parameters measured at age 9 to 10, weight and head circumference were most significantly correlated with the neurodevelopmental outcome at the same age ($P < .005$ and $P < .01$, respectively) (Table 3). Head circumference at age 9 to 10 was the strongest parameter correlated with IQ at that age (Table 4).

Intrauterine Growth Restriction Subgroup Analysis

To analyze factors that correlated with both optimal and suboptimal outcomes in intrauterine growth restriction and to identify early predictors of outcome, we divided the study group into different subcategories according to the following criteria: (1) somatic catch-up, (2) neonatal high risk, and (3) timing of intrauterine growth restriction diagnosis (eg, diagnosis in utero vs at time of delivery).

Table 4. Risk Parameters Most Significantly Correlated With IQ Score in Children With Intrauterine Growth Restriction (n = 123)

Parameter	r^a	*P*
Perinatal		
Cephalization Index[b]	0.325	<.001
Parental risk score	0.280	<.01
Paternal occupation	0.296	<.01
Birth weight	0.284	<.01
Maternal education	0.321	<.01
2 y		
Mental developmental index	0.536	<.001
Head circumference	0.430	<.001
9-10 y		
Head circumference	0.374	<.001

a. Pearson correlation.
b. Cephalization Index = head circumference/birth weight × 10^2.

Somatic Catch-up. Within the intrauterine growth restriction group we identified the children who were above the 10th growth percentile in height, weight, and head circumference at age 9 to 10 as having "optimal" somatic growth. Those who were below the 10th growth percentile in at least 1 growth parameter were thus identified as "suboptimal." The subgroups were then analyzed to establish whether they differed in neurocognitive outcome at age 9 to 10. We also examined whether the same criteria of optimal somatic catch-up at age 2 were predictive of outcome at age 9 to 10. As illustrated in Table 5, the performance of children with suboptimal somatic catch-up at age 9 to 10 was significantly worse in the neurodevelopmental and cognitive assessments ($P < .005$) than in children with intrauterine growth restriction with optimal catch-up in somatic growth. Somatic catch-up at 2 years of age is predictive only of IQ at age 9 to 10 ($P < .05$) but not of neurodevelopment at the same age.

Neonatal High Risk. Within the study group, 25 children were identified as having multiple neonatal complications (defined as >2 suboptimal scores out of 11 items in the neonatal risk questionnaire dealing with potential brain insult). The data (Table 6) showed a significant difference in all birth parameters between the 2 subgroups. After statistical correction for gestational age, a significant difference in both neurodevelopment and IQ scores was identified ($P < .05$).

Timing of Diagnosis of Intrauterine Growth Restriction. A comparison was made between 2 other subgroups of intrauterine growth restriction regarding the timing of obstetric diagnosis: newborns diagnosed as intrauterine growth restricted in utero by ultrasound and those diagnosed as intrauterine growth restricted only in the delivery room. Because most women in our study were receiving regular obstetric follow-up, the first subgroup could be considered an earlier onset, more severe type of

Table 5. Correlation of Somatic Growth Status in Children With Intrauterine Growth Restriction With Developmental Parameters at 9 to 10 Years of Age

Somatic Growth Status	Neurodevelopment[a]	*P*	IQ[b]	*P*
Optimal catch-up[c] at 2 y (n = 36, 44%)	88.54 ± 5.8		103.54 ± 10.3	
Suboptimal catch-up[d] at 2 y (n = 46, 56%)	85.8 ± 14.9	NS	97.5 ± 14.9	<.05
Optimal catch-up at 9-10 y (n = 86, 72%	88.37 ± 5.9		101.1 ± 10.9	
Suboptimal catch-up at 9-10 y (n = 35, 28%)	80.06 ± 13.8	<.005	91.5 ± 15.2	<.005

a. Percentage of optimal items.
b. Estimated IQ.
c. Optimal catch-up (>10th percentile in weight, head circumference, and height).
d. Suboptimal catch-up (<10th percentile in one or more biometric parameters).

Table 6. Comparison Between Children With Intrauterine Growth Restriction With and Without Neonatal Complications in Relation to Their Developmental Outcome at 9 to 10 Years of age

Parameter	Intrauterine Growth Restriction With Neonatal Complications (n = 25)	Intrauterine Growth Restriction Without Neonatal Complications (n = 98)	*P*
Perinatal			
Gestational age, wk	34.7 ± 2.8	37.6 ± 2.1	<.0001
Birthweight, g	1488 ± 458	1945 ± 339	<.0001
Head circumference, cm	29.2 ± 2.1	30.8 ± 1.6	<.0001
Cephalization Index[a]	2.09 ± 0.61	1.62 ± 0.28	<.0001
Developmental			
Neurodevelopment[b]	82.87 ± 12.2	86.9 ± 8.8	<.05
IQ[c]	94.1 ± 15.8	99.8 ± 12.1	<.05

a. Cephalization Index = head circumference/birth weight × 10^2.
b. Percentage of optimal items.
c. Estimated IQ.

Table 7. Comparison Between Children With Intrauterine Growth Restriction Diagnosed Before and at Birth

Parameter	Intrauterine Growth Restriction Diagnosed Before Birth Induction (n = 25)	Conservative (n = 44)	Intrauterine Growth Restriction Diagnosed at Birth (n = 35)	P
Perinatal				
Gestational age, wk	33.6	38.1	37.8	<.001
Birth weight, g	1330	2007	2000	<.001
Head circumference, cm	28.3	31.1	31.2	<.001
Cephalization Index[a]	2.28	1.58	1.6	<.001
Developmental				
Neurodevelopment[b]	82.8	87.1	87.7	NS
IQ[c]	95.4	99.7	99.7	NS

NOTE: NS = not significant.
a. Cephalization Index = head circumference: birth weight × 10^2.
b. Percentage of optimal items.
c. Estimated IQ.

intrauterine growth restriction than the subgroup diagnosed only in the delivery room, which probably signified a milder form of very late onset intrauterine growth restriction. Data regarding timing of diagnosis and nature of obstetric management (induction of labor or conservative management) were fully available for 69 mothers. This data indicated a significant difference between these subgroups in the biometric birth parameters (especially the Cephalization Index, the index reflecting the severity of intrauterine growth restriction) but not in outcome measured by IQ or neurodevelopment (Table 7).

Discussion

Asymmetric, vascular-placental-induced intrauterine growth restriction is the most prevalent type observed in more affluent societies. This present, prospective cohort study was

specifically designed to characterize the nature and frequency of the difficulties encountered by these children at school age and to identify risk factors and clinical parameters that could guide the clinician in understanding the prognosis.

Our results clearly showed that at school age, children with intrauterine growth restriction lag behind in somatic growth, neurodevelopmental performance, cognition, and school achievements, compared with matched control children who are appropriate for gestational age.[7-13]

We found that children with intrauterine growth restriction demonstrated a specific profile of minor neurodevelopmental and cognitive difficulties. The most frequent cognitive difficulties were in memory performance, learning abilities, visuomotor functions, and attention span. The inferior achievements of the study children could not be attributed to their abilities (IQ) alone but rather to specific learning disabilities. The observation of relatively preserved cognitive abilities together with learning and attention difficulties was previously described by Low et al[9] when correlating motor proficiency and neurological index with learning deficits at age 9 to 11 years. Similar findings were also described by O'Keefe et al,[26] who found that adolescents who at term had been small for gestational age experienced more learning and attention difficulties than groups who had not been small for gestational age. These authors did not find a significant difference in IQ between the groups.

Of more than 100 risk parameters analyzed in the present study, the Cephalization Index at birth (more than the head circumference or birth weight alone) had the most marked correlation with both neurodevelopmental status and cognitive performance at age 9 to 10, again emphasizing the importance of brain sparing in the process of intrauterine growth restriction. Hutton et al,[27] using the ratio of actual birth weight to expected birth weight in intrauterine growth restriction as an index of the severity of intrauterine growth restriction, found a correlation of this ratio with IQ. This is in contrast to O'Keefe et al,[26] who did not find body asymmetry to be related to IQ or learning abilities at age 14. One possible explanation for this important difference could be the fact that O'Keefe et al examined only children who had been small for gestational age at term and probably not those children with more severe growth restriction diagnosed in utero and born preterm.

Although a biometric parameter such as the Cephalization Index proved to be the best predictor of outcome, factors such as the parental risk questionnaire, maternal education, and paternal occupation were significantly related to IQ at age 9 to 10, indicating the importance of environmental contribution to later performance.

Examination of subgroups within the intrauterine growth restriction study group showed somatic catch-up to be clearly associated with neurocognitive outcome; thus, at both ages 2 and 9 to 10 it may be possible to predict that children with intrauterine growth restriction with complete catch-up will have better cognitive performance at school age. The fact that no correlation was found between the catch-up status at age 2 years and the neurodevelopmental performance at age 9 to 10 may stem from the fact that catch-up growth is not yet completed by some of the children with intrauterine growth restriction at that age, so the analysis of catch-up at age 2 cannot serve as a reliable prognostic judgment of later neurodevelopmental performance.

The relationship between somatic growth and cognitive performance could probably be attributed to a common denominator of the effect of the intrauterine growth restriction process on brain development: a more severe insult that would eventually affect cognition could possibly also reprogram the hypothalamic-pituitary-adrenal axis, which, as described by Cianfarani et al,[28] may result in a permanent modification of the neuroendocrine (cortisol) response to stress and a higher risk of growth failure. We previously found a significantly lower level of insulin-like growth factor-1 in a group of 14 children with intrauterine growth restriction who were below the 10th percentile for height, whereas the group as a whole had lower cortisol levels than the controls ($P < .001$).[29] It is merely logical to expect that once hormonal reprogramming has occurred, it will further affect not only somatic growth but, later in life, also brain development.

Our comparison of 2 different subgroups of children with intrauterine growth restriction—those with and without perinatal complications—indicated their specific impact on neurodevelopmental outcome. It is obvious that the subgroup with such complications was of younger gestational age, but because gestational age alone was not found to have a significant influence on outcome in our group, we can assume that we are observing a "clean" additive effect of the combination of perinatal complications and intrauterine growth restriction on neurocognitive outcome. Taking into consideration the fact that these children have an increased biological vulnerability to perinatal complications, as shown by us and other authors,[17] the prevention of such complications by good obstetric and perinatal care is of utmost importance. When comparing children with intrauterine growth restriction diagnosed before birth with those diagnosed at birth, we are actually observing 2 different types of intrauterine growth restriction: a higher risk, earlier onset (mid-second–third trimester) type and the mildest form initiated late in pregnancy (end of third trimester). Nonetheless, the almost identical outcome probably reflects the results of good obstetric management, timely delivery, and careful neonatal care.

To the best of our knowledge, the present study is the only one to specify the exact nature of the cognitive difficulties faced by children with intrauterine growth restriction and to point at simple measures, such as the Cephalization Index and somatic growth indices, as clearly correlated with outcome at school age.

Early prenatal diagnosis of intrauterine growth restriction and proper obstetric care could significantly reduce the neonatal risk and improve outcome. Finally, the

understanding of the nature of the specific difficulties faced by these children at school age should make it possible for us to identity them and design proper interventions (eg, occupational therapy, physiotherapy, remedial education) before academic failure ensues.

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