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Neuropsychological Outcome of Children With Intrauterine Growth Restriction: A 9-Year Prospective Study

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ABSTRACT

OBJECTIVE. The aim was to evaluate the effect of late-onset intrauterine growth restriction on the neuropsychological profile and on academic achievements at 9 years of age using a large-scale prospective paradigm.

STUDY DESIGN. We followed up 123 infants diagnosed with late-onset intrauterine growth restriction yearly for 9 years. They were matched with 63 children for gestation age and multiple socioeconomic factors and evaluated by an extensive neuropsychological battery to assess intelligence quotient, academic achievements, learning and memory, visuomotor skills, visuospatial integration, attention, language, executive functions, and creativity.

RESULTS. Children with intrauterine growth restriction had lower intelligence quotient and more frequent neuropsychological difficulties. Difficulties in executive functioning, inflexibility-creativity, and language, indicative of frontal lobe dysfunction, were typically affected by intrauterine growth restriction and were rarely identified in the control group. Learning difficulties accompanied by lower academic achievements were more prevalent in the intrauterine growth restriction group, particularly when anthropometric catch-up was incomplete.

CONCLUSIONS. The longitudinal findings reaffirm that functional coherence depends on preestablished structural growth and reorganization of the central nervous system. The neuropsychological profile at 9 years of age indicates that late-onset intrauterine growth restriction compromises frontal network functioning.

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Key Words
outcomes of high-risk infants, neurocognitive, long-term follow up, executive function/dysfunction, intrauterine growth retardation

Abbreviations
BSP—brain-sparing process
CI—cephalization index
IUGR—intrauterine growth restriction
BW—birth weight
CNS—central nervous system
IQ—intelligence quotient
EGA—estimated gestational age
WISC-R95—Wechsler tests of intelligence-revised
ROCF—Rey-Osterrieth Complex Figure
NEPSY—Neuropsycholological Evaluation for Children
HC—head circumference
ANOVA—analysis of variance
NS—not significant
CUG—catch-up growth
AGA—appropriate-for-gestation age

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STUDIES HAVE SHOWN that fetuses whose growth in utero is restricted develop in an adverse preterm environment, deficient in essential nutrients. Compensatory processes trigger circulatory changes[1] and neural adaptive modifications[2] aimed at conserving the developing brain.[3] Undernutrition and/or hypoxia in late pregnancy results in an asymmetrically growth-retarded infant whose head circumference is relatively preserved as a result of a physiologic adaptation, often termed the brain-sparing process (BSP), by which a major selective blood flow is redistributed and directed to the brain. This asymmetric IUGR growth is characterized by birth weight that is at <10th percentile for estimated gestation age with normal head circumference and lengths. The BSP is triggered by third-trimester insult interfering with delivery of oxygen and nutrition during the cellular hypertrophy phase of fetal growth.[4] It is frequently encountered in cases of placental insufficiency or maternal diseases or multiple pregnancies. Asymmetrical IUGR is often characterized by a disproportionately large head compared with body size, a body that looks thin, a facial appearance of "old man," an umbilical cord that is thin with little Wharton's jelly, a scaphoid abdomen, and little subcutaneous fat. A variable that captures well the discrepancy between head growth relatively to body growth is the cephalization index (CI).[5,6] It has been reported as a highly powerful index in accounting for outcome at the first 3 years after birth.[6]

BSP is considered to be favorable for neonatal survival after preterm birth without major developmental handicaps.[7–9] However, these sparing processes may not suffice to fully compensate for the aberrant cellular successions and the altered neurodevelopmental route associated with it. Recent studies have reported that children born with intrauterine growth restriction (IUGR) have subtle long-term cognitive impairments, soft neurologic symptoms,[10–16] and learning difficulties in school.[8,17–19] The neuropsychological basis for these difficulties is not clear.[2] Elucidating specific neuropsychological deficits may contribute to both understanding the long-term pathogenic sequelae of IUGR and aiding in devising a tailored intervention of this developmentally at-risk population.[20]

It has been shown that head growth is an important predictor of cognitive abilities,[21] particularly as it relates to birth weight (BW).[5,6] Also, persistence of microcephaly was associated with adverse neurodevelopmental outcome at 3 years.[22] Recent findings[23] demonstrated early structural brain alterations in premature infants born with IUGR when measured early in prenatal and term ages. These changes consist of a significant reduction in intracranial volume and in cerebral cortical gray matter that are maintained throughout the neonatal period. Although regional brain changes have not yet been studied in this risk population, in view of the limitations of the BSP affecting the asymmetric IUGR fetus, selective cortical vulnerability should be expected.

Data allude to susceptibility of hippocampal structures[24,25] and limbic and frontal lobe susceptibility.[26] These data may suggest a unique neuropsychological profile that develops as the central nervous system (CNS) matures through childhood.

It is not clear whether prematurity and IUGR pose discrete challenges to the developing nervous system.[27,28] Prematurity has been extensively studied. Differential regional vulnerabilities in the developing brains of preterm children[29,30] have also been studied recently. Cortical volumes in preterm neonates tested near term were reduced, particularly in the sensorimotor and parieto-occipital regions and inferior occipital cortices, whereas other regions were relatively normal in size.[31] Furthermore, it has been suggested that the neonatal effects spread as the nervous system continues to develop. By 8 years of age, changes are more widespread. These changes appear as smaller volumes than in term controls in the sensorimotor cortex and also in the adjacent premotor, parieto-occipital, subgenual, and midtemporal regions and the cerebellum.[29,31]

It is highly plausible that the systemic uterine insults progress into childhood and throughout adult life.[24,27] The long-term neuropsychological sequels of these processes are not yet fully understood. Limited but significant behavioral correlates were reported at the neonatal phase with attention and with intelligence quotient (IQ) at school age. However, in view of the specificity of the cortical regions involved, improved neurodevelopmental measures and specific neuropsychological profiles as related to IUGR may be expected.[31]

In this long-term, large-scale prospective study, an extensive neuropsychological evaluation was used, including standardized procedures and clinical referral judgments to advance our understanding of the long-term evolving brain-behavior relationships resulting from IUGR and prematurity processes. Timing and rate of brain catch-up growth (CUG) have been suggested as mediating factors of long-term outcome.[21,32] The relationship between rate of catch-up and neuropsychological outcome will be examined.

METHODS

Subjects

All children with IUGR (BW <10th percentile) who were diagnosed at birth were eligible to participate except for those with genetic disorders and unrelated comorbidities. All of the neonates in this study, IUGR and controls alike, were born at Lis Hospital (Tel Aviv, Israel) between January 1, 1992, and December 31, 1995 and were admitted to the neonatal unit of the Dana Children's Hospital, Tel Aviv Medical Center, which covers the residential area of Tel Aviv, Israel. This study was approved by the Helsinki Committee of the Tel Aviv Sourasky Medical Center. Informed parental consent was obtained in all of the cases. Inclusion criteria were midsecond trimester- to third trimester-onset IUGR (verified clinically and/or by ultrasound); absence of fetal infections; and congenital malformations, such as congenital heart disease and metabolic and chromosomal disorders at birth. Estimated gestational age (EGA) was calculated by the date of the last menstrual period. Pathologic studies of the placentas revealing vascular placental insufficiency were confirmed (detailed in interim report).[13]

On receipt of parental consent at the neonatal nursery, risk questionnaires were completed regarding prenatal, parental, obstetric, and neonatal sources.[6,13] Subjects were followed-up periodically for 9 to 10 years by developmental psychologists and pediatric neurologists. Previous interim summaries of cognitive and neurodevelopmental outcome were reported at 3 and at 6 years of age.[6,13] At 9 years of age, informed consent was also obtained from the participating child. No major CNS-related pathogenic processes, such as meningitis, or traumatic brain injury or severe anomalies were noted in any of the nonexcluded subjects in the current report.

The reported data represent a preliminary subsample of the first 123 neonatally diagnosed children who reached their 9-year evaluation point. The experimental group was matched at 9 years of age with a group of 63 children selected from the same community in the Tel Aviv municipal area. The groups were randomly sampled according to birth registries kept at the municipal well-infant clinic and the registry of the public school neighboring the clinic. They were carefully matched for testing age, parental ages, maternal education, parental occupation, and EGA, as suggested specifically for the study of IUGR (Table 1).[33] In light of good prenatal care, affordable recommended nutrition intake, and good social and familial support in both groups, this cohort offered a solid opportunity to observe the direct effects of prematurity and IUGR, irrespective of major confounds, such as teen motherhood, poor socioeconomic factors, poor nutrition, and poor health care. An additional sub-

TABLE 1 **Characteristics of the Study Participants and Demographic Description of the Participating Groups**

Variable	IUGR (*N* = 123)	Control (*N* = 63)	*P*
Obstetric/neonatal			
BW, g	1853.6 ± 416.8	2829.7 ± 761.7	< .001
Percentile	<5th	WNL	
Neonatal HC, cm	30.5 ± 1.9	33.5 ± 4.2	< .001
Percentile	>10th	WNL	
Complicated hospital stay (>3 complications)[a]	66.4	27.4	< .001
Estimated gestational age	37.0 ± 2.6	36.7 ± 6.9	NS
Prenatal complications score[a]	9.4 ± 7.1	11.2 ± 7.9	NS
Neonatal complications score[a]	11.7 ± 12.8	8.9 ± 13.9	NS
Prematurity (% <37)	29.1	33.8	NS
Extremely low BW (% <750)	0.1	0	NS
Maternal smoking, %	12.8	21.4	NS
Demographic			
Gender, % male	49.1	44.2	NS
Age at test, mo	112	111	NS
Weight at 9 y, g	2793 ± 716 (WNL)	3106 ± 610 (WNL)	< .004
HC at 9 y, g	51.2 ± 1.8 (WNL)	52.1 ± 2.6 (WNL)	< .006
Height at 9 y, cm	131.28 ± 6.1 (WNL)	135.0 ± 6.7 (WNL)	< .001
Parental			
Maternal age at delivery	30.5 ± 5.8	30.5 ± 4.6	NS
Paternal age at delivery	33.6 ± 6.3	32.5 ± 4.5	NS
Maternal education, y	13.0 ± 2.3	13.5 ± 3.6	NS
Maternal health	19.6 ± 1.9	20.0 ± 0.0	NS
Paternal health	19.5 ± 2.7	18.6 ± 5.3	NS
Parental occupation[b]	4.4 ± 3.1	5.0 ± 2.6	NS
Parental education, y	12.8 ± 2.6	12.9 ± 2.9	NS
Familial community			
Parity, %	0.20 ± 0.6	0.38 ± 0.7	NS
Socioeconomic status[c]	1.5 ± 1.2	1.6 ± 1.2	NS
No. of children in family	2.4 ± 1.1	3.0 ± 1.2	NS
Child's place in family	2.0 ± 1.1	2.0 ± 0.9	NS

WNL indicates within normal limits

[a] Adapted from Fattal- Valevski et al.[6]

[b] Coded on a 9-level scale (1 = nonproficient, 2 = proficient, 3 = farmer, 4 = hand artisan, 5 = salesman, 6 = clerkship, 7 = managerial, 8 = free profession, 9 = academic research).

[c] Composite score based on maternal education parental occupation and welfare aid.

sample of 50 children was lost to follow-up (25 did not join the follow-up program, and 25 were followed-up to 5 years old but refused further evaluations). Analysis of socioeconomic status (maternal education and parental occupation) revealed that the nonfollowed-up group did not differ from the followed-up group in these variables. Furthermore, *t* test for equality of means of the prenatal, parental, obstetric, and neonatal questionnaires of the attrition group versus the participating IUGR group showed no differences in these measures. The *t* test comparisons of Bayley Mental Development Scales IQ scores at ages 1 and 2 years of the partially followed-up group versus the experimental group of the current report (followed-up fully) demonstrated that global competence of these groups was also similar.

Procedure

The cognitive performance of the experimental group was evaluated yearly using the Bayley Mental Development Scales up to 2 years of age, Stanford-Binet at 3 years of age, and the Wechsler Preschool and Primary Scale of Intelligence at 4, 5, and 6 years of age. At 9 years of age, the participants were evaluated with an extensive neuropsychological testing battery. The testing battery included estimation of cognitive abilities using 2 methods: (1) a 2-test short form of the Wechsler tests of intelligence-revised (WISC-R95)[34,35] and (2) the Goodenough-Harris Draw-A-Person test.[36] Academic achievements were evaluated by the achievement scale tests of the Kaufmann Assessment Battery for Children[37]; learning and memory skills by the Rey-Osterrieth Complex Figure (ROCF),[38] Rey Auditory Verbal Learning Test,[39] and the Visual Auditory Digit Span Evaluation[40]; attention and executive functions using selected subtests of the Neuropsycholological Evaluation for Children (NEPSY)[41]; language skills using selected tests from the WISC-R95 and the Kaufmann Assessment Battery for Children; visuomotor skills using copy designs tasks of the NEPSY and the ROCF; visuospatial integration using the arrows task of the NEPSY; and creativity using selected tests from the NEPSY. A social worker kept in touch with the participating families throughout the follow-up program. The full battery was administered individually at the Institute for Child Development, Tel Aviv Sourasky Medical Center. The tests were administered by an experienced and certified psychologist, who was blinded to the subjects' group affiliation. No compensation or travel fees were given for participation. The patients' parents received a report on their child's performance, and recommendations for intervention were made when relevant. All of the participants completed the full battery that took ~4 hours to administer. Performance was coded bimodally, once using standardized scores according to the norms and once coded by the clinician for referral purposes using additional qualitative considerations. Clinical referral indications for intervention were scored by psychological specialists who were blinded to the subject's group assignment. Ratings (optimal, questionable, and suboptimal) were based on composite scores of performance and on qualitative parameters. Scores were rechecked by a trained experimenter blinded to patients' appearance and group. Interrater agreement was >95%. Biometric measures (ie, head circumference [HC], height, and length) were collected periodically on the day of examinations by a certified nurse.

Statistical Analysis

Unpaired *t* test was used to determine differences in outcome measures at 9 years of age evaluating cognitive abilities, academic achievements, learning and memory skills, visuomotor skills, visuospatial integration, attention skills, language skills, executive functions, and creativity. Both standardized scoring and clinical judgment scores were analyzed.

Standardized data are presented as mean ± SE. Analysis of variance (ANOVA) of these outcome measures with the following covariates was conducted: (1) prematurity, (2) maternal education, (3) gender, and (4) neonatal complications score, detailed in previous reports.[6,13] A cutoff criterion of a composite score that is >3 was used to control for the effects of these factors on outcome in addition to the effect of IUGR.

χ^2 of frequency of normal versus suspected or abnormal performance clinical scores was calculated in the following domains: achievements, learning and memory skills, visuoperceptual and spatial organizational skills, language, and executive and creativity domains. These analyses were also complemented by frequency count of referred intervention, targeting these specific domains, to capture qualitative performance deficiencies, such as domain-specific symptomatic behavior, which is not always captured well in quantitative standard scores.

Regression analysis of variables best predicting 9-year-old neuropsychological outcome was conducted with prematurity, maternal education, and CI as covariates. CI was calculated as follows: CI = neonatal $HC \times 10^2/BW$ (g).[5,6,13] Correlations of all outcome measures, such as cognitive abilities, academic achievements, learning and memory skills, visuomotor skills, visuospatial integration, attention skills, language skills, executive functions and creativity were analyzed.

RESULTS

Measures of BW, EGA, maternal and paternal ages, maternal and paternal education, paternal occupation, and socioeconomical variables regarding level of proficient work, family size, and child's place in the family are presented in the demographic table (Table 1). From the table it can be seen that the groups differed significantly in BW as expected. They also differed, as expected, on the propensity for neonatal complications.[42] Both groups were well matched apropos parental, familial, and socioeconomical measures of gestational age, maternal and paternal ages, maternal and paternal education, paternal occupation, and socioeconomical variables regarding level of proficient work. Anthropometric growth by 9 years was more restricted in the IUGR group relative to the control group. This difference is comparable to other cohorts, which followed significantly less subjects.[43]

Mean cognitive competence during childhood in the experimental group was lower than that of matched controls irrespective of means of IQ evaluation (WISC-R95 short form estimation, $P < .001$; Goodenough-Harris Goodenough-Harris Draw-A-Person test, $P < .019$). ANOVA of standardized scores on neuropsychological tests with prematurity, neonatal complications, and maternal education as covariates showed that the children in the experimental group scored lower than the controls in domains that probe associative and higher-order cortical association areas, including specific language tasks (vocabulary: $P < .019$; verbal problem solving: $P < .006$), visuomotor functioning (design copying: $P < .001$; block design: $P < .009$), executive functioning (visual attention: $P < .003$; form fluency: $P < .001$; Tower of London: $P < .014$), and learning and memory (visual auditory digit span evaluation: $P < .001$; ROCF measures: design copy: $P < .001$, immediate recall: $P < .024$, delayed recall: $P < .002$). ANOVA of standardized scores on neuropsychological tests with prematurity, neonatal complications, and maternal education as covariates showed no differences between the groups on perceptual tasks (eg, auditory attention: not significant [NS]; perception of visual orientation: NS), simple design copying (design copy of the NEPSY: NS), verbal fluency tasks (Rey Auditory Verbal Learning Test: NS; semantic and phonetic verbal fluency: NS), and coding (digit symbol coding: NS). Performance on most tasks was also partly accounted by maternal education (*P*s range between .001 and .038). Neonatal complications accounted for differences in verbal fluency alone. Specific domains were uniquely affected by IUGR and not by additional factors. These were selected executive tasks, including form fluency ($P < .043$), and selected verbal tasks, including persons and places ($P < .042$) and riddles ($P < .013$). Gender affected performance only on the log-term reconstruction of the ROFC. Male subjects had greater difficulty compared with female subjects ($P < .05$). There was also a significant gender-by-group-interaction effect on this measure, that is, females in the control group performed at the expected level for their age (mean percentile score: 49.89), but their performance was lower than expected in the IUGR group (mean percentile score: 30.02; $P < .05$).

The propensities for specific neuropsychological abnormal or suspected abnormal profile scores, as determined by standardized scores and clinical judgments, are presented in Fig 1. The figure shows 3 striking findings: (1) overall, children with IUGR tended to score more frequently in the abnormal range relative to matched controls irrespective of the domain studied; their risk to score in the abnormal range typically doubled/was twofold greater relative to controls; (2) some domains were almost exclusively affected by IUGR and not by prematurity alone; these domains are creativity, visuomotor integration, language, and executive functions; and (3) most children with IUGR had some difficulty in learning and memory, irrespective of the content learned.

Figure 2 depicts the statistically significant correlations ($P < .05$) between CI and HC measurements with IQ scores obtained from the same children. It shows the usefulness of CI and HC measures throughout the first decade of life. CI was significantly better correlated with IQ than neonatal HC in the IUGR population but not in

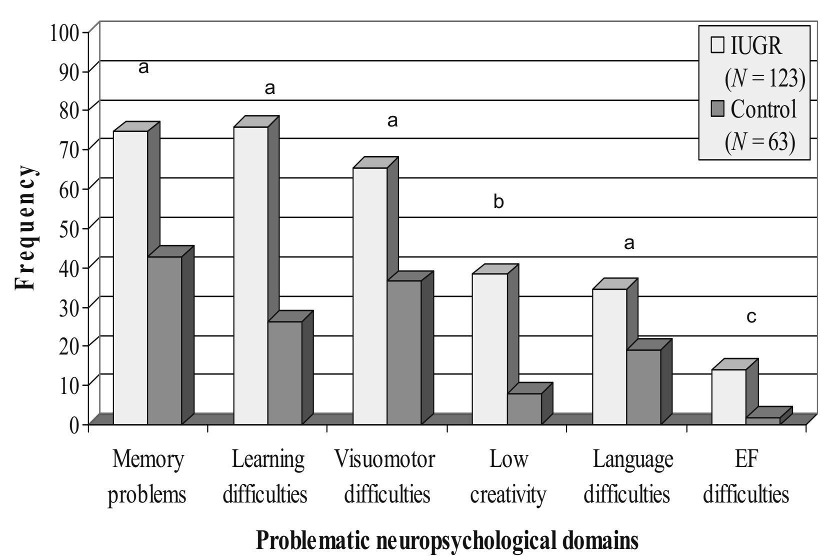

FIGURE 1
Comparison between IUGR and control children: neuropsychological borderline/suboptimal performance at 9 to 10 years. [a] $P < .001$; [b] $P < .05$; [c] $P < .01$.

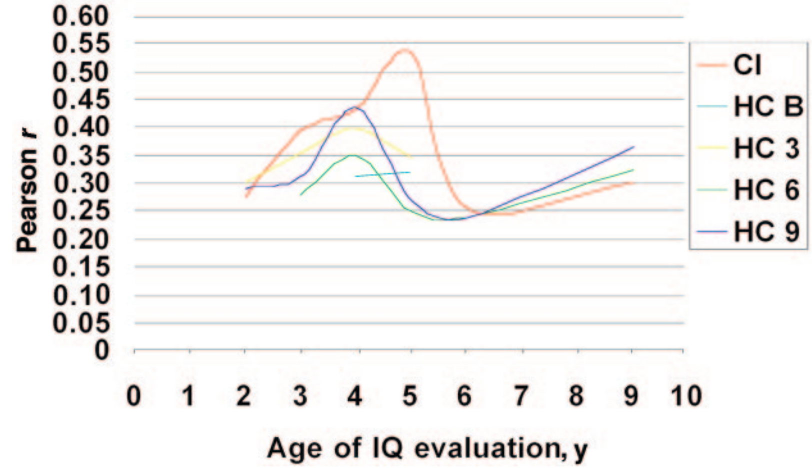

FIGURE 2
Correlations between HC and cognitive competence in both groups through the first decade of life. CI = neonatal HC× 10^2/BW (g); HCB = HC at birth (cm); HC3 = HC at 3 years old corrected age; HC 6 = HC at 6 years of age; HC 9 = HC at 9 years of age.

the matched control group. The relationship of CI to IQ scores is particularly strong during the first 5 years of life, where it surpasses more concurrent HC measurements. The CI maintains significant moderate correlations with IQ score through the 9-year point. However, from 6 years of age it loses its relative power, so that from year 6 on, a marked change occurs; the year-6 HC measure and the year-9 measures are better correlated with the year-9 IQ than previously attained HC measurements.

Two alternative classification criteria were used to evaluate the effect of catch-up on the neuropsychological outcome: (1) failed catch-up by 3 years of age on all 3 growth measures: height, weight, and HC <5th percentile at 3 years (ie, complete CUG); and (2) failed catch-up on weight, height, or HC by 3 years of age (ie, selected CUG). A χ^2 analysis showed that 17.1% of the IUGR group was complete CUG, whereas an additional 11.3% of the IUGR sample was diagnosed with selected CUG. Multivariate ANOVA for the neuropsychological outcome measures as a function of catch-up grouping showed that of the domains exclusively affected by IUGR, visuomotor functioning, namely, perception of direction, was affected by rate of catch-up (arrows test of the NEPSY: $P < .001$ for the complete CUG grouping and $P < .024$ for the selected CUG grouping), such that the complete CUG group performed better than the selected CUG group. However, frontal functions, such as language skills, executive functioning, and creativity, which were affected by IUGR, were typically not affected by postnatal rate of catch-up.

Finally, academic achievement scores were analyzed (Fig 3). ANOVA of standardized scores of IUGR and control groups with prematurity, neonatal complications, and maternal education as covariates showed differences between scores as a function of group assignment on general knowledge (F = 11.705; $P < .002$; $R^2 = 0.25$), reading decoding (F = 8.204; $P < .032$; $R^2 = 0.19$), reading comprehension (F = 8.831; $P < .019$; $R^2 = 0.20$), and arithmetic (F = 8.38; $P < .009$; $R^2 = 0.23$). Maternal education contributed further to all of the achievements scores (Ps $< .001$). Neonatal complications contributed to the variance found in arithmetic ($P < .027$) but were not significant in explaining differences in the academic domains. Gender and prematurity did not contribute further to the variance of the academic achievements at this age. Multivariate ANOVA

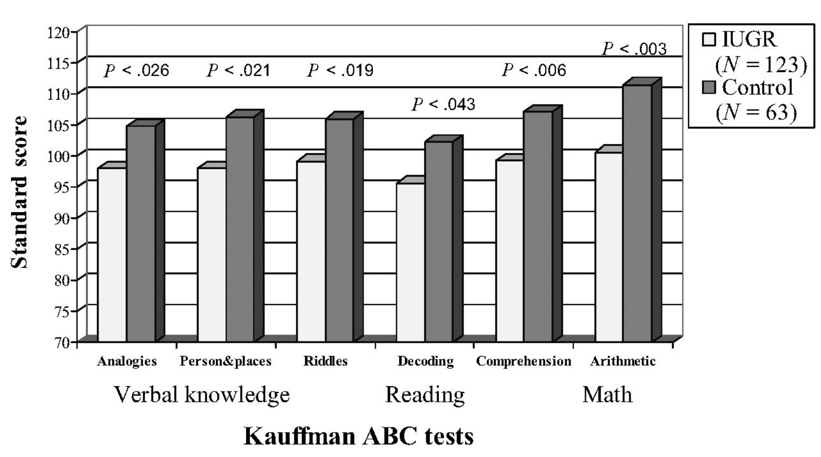

FIGURE 3
Comparison between IUGR and control children: school achievements at 9 to 10 years.

comparing the achievement scores of the complete CUG grouping and selected CUG grouping showed that catch-up was affecting all of the academic achievements but reading decoding; complete CUG classification yielded more significant group differences in academic achievements than the selected CUG classification (ANOVA using complete CUG grouping differences: verbal analogies, $P < .016$; general information, $P < .006$; verbal problem solving, $P < .003$; arithmetic, $P < .001$). Selected CUG grouping differences were less useful in differentiating between the IUGR CUG rate groups (ANOVA using selected CUG grouping showed differences in general information, $P < .032$, and arithmetic, $P < .018$ alone).

DISCUSSION

Volumetric brain size studies motivated our current work to identify the possibly affected cognitive, sensory, or motor abilities.[44] Furthermore, the present study was designed to examine whether the structural neonatal differences reported for IUGR are expressed in the discrete neuropsychological profile that is discriminated from the profile characterizing controls, matched for prematurity and socioeconomical factors.

This study demonstrated that IUGR has a long-term neuropsychological effect on general cognitive competence, as well as on discrete neuropsychological skills. The effects were different and independent of those caused by prematurity or by neonatal complications that accompany IUGR. The major finding of this study was the unique contribution of IUGR to the neuropsychological profile of 10-year-old children. The profile was characterized by a small but significant reduction in IQ and specific neuropsychological difficulties. The unique data of the present study allude to specific neuropsychological relative difficulties in creative problem solving, attention, and executive functions; visuomotor organization; and higher-order verbal skills. This pattern was consistent with increased susceptibility in brain growth, particularly with the development of frontal lobe structures.[23]

The specificity of the IUGR process to frontal processes may be validated in view of recent reports.[26] They showed that frontal lobe measures increased significantly between 24 and 43 weeks of gestation, weeks at which IUGR peaks. The frontal lobe measures, Sylvian-callosal distance, fontanellar-callosal distances, and frontal triangular area, were strongly correlated with HC in a sample composed of full-range premature neonates born appropriate-for-gestation age (AGA) and small-for-gestation age. These measures in the AGA group differed significantly from those of the small-for-gestation age group. The authors speculated that a sonographically small fetal HC implies growth restriction of the fetal frontal lobe. Indeed, neonatal HC and, significantly more so, the neonatal CI[20] were related to the evolving IQ measures throughout the first decade. Interestingly, we found that HC measurements at most ages were correlated with IQ scores. Stronger correlations appear between HC measure at a certain age and the IQ of the subsequent year. This reaffirms that functional coherence depends on preestablished structural growth and reorganization of the CNS.

Does this frontal growth restriction translate to frontal-related symptoms as the infant grows? Initial reports with limited samples or short-term follow-up supported this hypothesis.[45–47] The current findings may also contribute to the understanding of long-term findings on extremely low BW cohorts. These samples often have subjects who were diagnosed with severe IUGR. The current study strongly supports the persistence of frontal lobe-related functions during the first decade of life. The specific neuropsychological profile has been reported in extreme cases of prematurity and low BW. These samples have been known to be more susceptible to IUGR. Neuropsychological studies of extremely premature and very low BW children did not study IUGR directly, yet have reported deficits in global intelligence, learning, attention, visuoperceptual memory, and some executive functions.[44,48] Our findings demonstrated that lower-risk premature children, not necessarily very premature, although all IUGR, exhibited a similar trend of neuropsychological deficits. Results of the current study allowed for extrapolating from the special cases of extreme prematurity who may have had IUGR to the full spectrum of the IUGR pathogenesis process.

What deficits may be directly accounted by the prenatal restriction of growth as opposed to postnatal lack of sufficient growth catch-up? The analyses conducted on this large prospective sample showed that the prenatal growth restriction resulted in specific behavioral symptoms that correspond with malfunctioning of frontal structures. The specific neuropsychological profiles found at 9 years of age indicate that late-onset IUGR compromises frontal network functioning. Findings reaffirm that functional coherence depends on preestablished structural growth and reorganization of the CNS. The rate of postnatal growth catch-up was not related to executive functions but was related to specific visuospatial deficits, such as perception of object orientation and graphomotor deficits. Academic achievements were also lower than in IUGR children whose anthropometric growth through the third year of postnatal life was not indicative of catch-up. Children in the IUGR group whose height or weight or HC caught up but whose catch-up was not evident on the other dimensions did not perform as well at 9 years of age as IUGR children who completed catch-up by 3 years of age in all 3 of the domains (height, weight, and HC).

Memory and learning difficulties were not specific to the IUGR factor but appeared, although in different severities, in both groups. Because the groups were matched for prematurity and an array of socioeconomic status factors, this finding alluded to possible heterogeneous mechanisms accompanying both prematurity and IUGR. They may be consistent with hippocampal gray matter reductions[49] because of enhanced neuronal cell death in the immature brain, N-methyl-d-aspartate-mediated excitotoxicity, and enhanced neuronal apoptosis as a result of multiple metabolic stresses related to high-risk pregnancies not specific to IUGR.[48]

In addition to the specific frontal symptoms detected in the IUGR group, the current findings replicated previous findings reported on smaller sample sizes with regard to a minor yet significant reduction in cognitive competence.[46,50,51] The small reduction in IQ replicates findings by others, who have smaller follow-up cohorts of children diagnosed with IUGR through the first years of life.[52] The compatibility of global competence of this cohort with other samples supports the representativity of the sample and underscores the validity of the neuropsychological findings.

Comorbidity related to IUGR during the neonatal period also increases the risk of long-term neuropsychological outcome.[42] Neonatal complications are more frequent and more morbid when occurring in neonates born with IUGR. More neonatal complications (>3) were related to more/increased pervasive effects on cognitive competence and on academic performance. Simultaneously, no such effects on cognitive competence, academic skills, and executive performances were expressed in the control group. These findings may imply that the resiliency of AGA neonates is apt for withstanding neonatal complications. The IUGR system may have less compensatory resources to efficiently withstand neonatal complications, and, thus, the long-term effects of these complications are extensive and become more and more pronounced as the child matures.[6,53]

The importance of the current findings is in highlighting the specificity of the IUGR process in affecting particularly frontal functions. It also underscores the long-term component of this process in affecting neuropsychological capacities and academic achievements throughout the first decade of life. These may impact performance at school and compromise social performance.

From a methods perspective, it is important to note the unique contribution of studying this cohort with the experimental paradigm selected. The cohort used is characterized by relatively low socioeconomical risk relative to other cohorts and nonmaternal malnutrition. This permitted a more direct observation on the long-term pathogenesis of IUGR irrespective of these confounds. The prospective paradigm, although painstaking, alleviated some of the concerns regarding selective attrition. Finally, the procedure used, a comprehensive neuropsychological assessment, was successful in evaluating the comprehensive neuropsychological profile of these developmentally at-risk children. All of the premature infants and the children diagnosed with IUGR were able to complete the full battery. Therefore, we believe that this method can serve as a useful tool to comprehensively evaluate the neuropsychological outcome of developmentally challenged cohorts.

CONCLUSIONS

Using a large-scale prospective paradigm and a comprehensive neuropsychological evaluation at 9 years of age, we have successfully shown the unique contribution of IUGR to a reduction in IQ and relative difficulties in creative problem solving, attention and executive functions, visuomotor organization, and higher-order verbal skills. This pattern was consistent with increased susceptibility in brain growth, particularly with the development of frontal lobe structures. Our data are consistent with previous reports on more extreme cases and smaller sample sizes. They suggest that IUGR processes, expressed by restricted HC, are mostly susceptible to frontal lobe-related suboptimal development.

These findings have implications for 2 future study directions. First, it is important to study this long-term process as the child progresses to the second decade of his life, because, to date, similar studies focused on retrospective studies and/or reported solely on extreme cases. Second, early intervention that targets long-term morbidities related to IUGR, specifically, attention mechanisms, early on in development and more efficient executive control strategies may improve long-term performance of children with IUGR as they mature and ease their adjustment to demanding social and educational requirements.

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SCIENCE TEST SCORES STILL LAG

"Despite efforts in many states to bolster science education, a key national test shows no improvement among middle and high school students in their grasp of the subject. The results of the National Assessment of Educational Progress, or NAEP, are likely to heighten concern about the future competitiveness of American workers in science and technology, and to fuel corporate pressure on states and the federal government to do more for science education. Over the years, American secondary school students have consistently fared poorly on international science tests compared with their counterparts in other developed countries. Some US science teachers and education advocacy groups contend that the 2001 'No Child Left Behind' federal law worsened this problem by emphasizing reading and math at the expense of science. Researchers say the latest test results also point to the continuing struggle by school districts to find educators who are trained in the field. Although the law requires all teachers to be 'highly qualified' in their subject areas by the end of this school year, the US Education Department has said it may grant an extension to states that make a good-faith effort but fail to meet the deadline. . . . 'It's hard for any CEO to look at this report and not feel pessimistic about the future of the American work force,' said Michael Petrelli, vice president for national programs and policy at the Thomas B. Fordham Foundation, a conservative think tank active in education issues. 'How many more wake-up calls do we need?' added John Castellani, president of the Business Roundtable, a corporate advocacy group."

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