Original Article

Six-Year Follow-Up of Children With Intrauterine Growth Retardation: Long-Term, Prospective Study

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ABSTRACT

This prospective study was designed to characterize the neurodevelopmental and cognitive difficulties specific to children with intrauterine growth retardation and to detect early clinical predictors of these difficulties. Eighty-one children with intrauterine growth retardation were monitored up to 6 to 7 years of age using biometric parameters, perinatal risk questionnaires, and detailed neurodevelopmental and cognitive assessments. Forty-one children served as age-matched, appropriate for gestational age controls. A significant difference in growth parameters ($P < .001$), neurodevelopmental score ($P < .05$), and IQ ($P < .05$) was found between the children with intrauterine growth retardation and controls. A specific profile of difficulties in coordination, lateralization, spatial and graphomotor skills, and abundance of associated movements is typical of the children with intrauterine growth retardation and hints at possible later learning disabilities. The clinical parameters best predicting neurodevelopmental outcome were the neonatal risk score ($P < .05$) and the weight and height at 6 years of age ($P < .05$). The children with intrauterine growth retardation with neonatal complications had lower neurodevelopmental scores than the controls but no difference in IQ. Intrauterine growth retardation children diagnosed prenatally had the same neurodevelopmental and IQ scores as those diagnosed at birth, probably due to the careful perinatal and obstetric care provided. Children with intrauterine growth retardation demonstrate a specific profile of neurodevelopmental disabilities at preschool age. Early diagnosis and intervention could probably reduce these difficulties to a minimum. (*J Child Neurol* 2000;15:781–786).

Intrauterine growth retardation is defined by a birthweight of 2 SD below the mean for gestational age and affects 3% to 10% of all newborns.[1,2]

The intrauterine process resulting in intrauterine growth retardation is a well-known risk for brain insult (as well as for hypertension, diabetes, and coronary heart disease).[3–6] The results of the intrauterine insults may not, however, be evident until later in life.[7–12] Therefore, it is crucial to follow-up newborns with intrauterine growth retardation who are at risk for neurodevelopmental and cognitive deficits in order to make an early diagnosis and provide them with the necessary special intervention.

Several factors hamper the interpretation of the data published to date on this subject matter[13]: (1) The definitions and etiologies of intrauterine growth retardation differ greatly between studies; (2) Many studies (specifically retrospective) do not take into consideration other conditions that have adverse effects on neurodevelopment, such as prematurity or perinatal complications. Furthermore, many studies reflect the results of the neonatal care practiced some 20 to 30 years ago and not the modern, intensive care provided during the past 10 years; (3) In many follow-up studies of older intrauterine growth retardation children, the control for postnatal influences, such as socioeconomic and environmental factors, together with a high attrition rate, became a major problem in analyzing outcome. The present prospective study, initiated 9 years ago, was specifically designed to overcome most of these limitations.

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The study describes the neurodevelopmental and cognitive outcome of intrauterine growth retardation children followed up from birth to preschool age. It specifies the nature of the most prevalent neurodevelopmental difficulties found in children with intrauterine growth retardation and identifies significant risk factors and clinical predictors associated with later outcome.

METHODS

Study Population

All consecutive infants born at the Lis Maternity Hospital (previously Serlin), Tel Aviv Sourasky Medical Center, from September 1992, with a birthweight under the 5th percentile for gestational age, according to the Israeli percentile curves published by Liebermann et al,[14] who were identified by the participating obstetricians and neonatologists and referred for the study, were included. Gestational age was calculated by the date of the last menstrual period.

Newborns diagnosed as suffering from genetic syndromes, major malformations, or showing evidence of congenital infection were excluded.[15] On the whole, we excluded eight children: four suffering from congenital heart disease, two with genetic syndromes, one with neurofibromatosis, and one with congenital cytomegalovirus infection.

The children included in the study group all had a late (mid-second to third trimester) onset intrauterine growth retardation, verified clinically and/or by ultrasound, and all showed the asymmetric type of intrauterine growth retardation, reflecting the "brain-sparing" effect, resulting in a high brain to body ratio.[16–18] We assumed, therefore, that the large majority of the children in this study had suffered a vascular-(placental) induced intrauterine growth retardation. This assumption was also supported by pathologic studies of the placentas, revealing vascular pathology in over 85% (eg, obliterated vessels, placental infarcts, increased syncytial knots, and lack of inflammatory changes).

Eighty-one of 99 children (81%), who reached 6 to 7 years of age, participated in the present analysis.

Attrition was due to inability to locate families who 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 lost-to-follow-up and study groups in biometric, perinatal, or socioeconomic status. Thirty percent of the children were preterm; 46% were boys.

Control Group

This group consisted of 41 appropriate for gestational age children, 6 to 7 years of age, matched for gestational age and socioeconomic status with the study group. The children were randomly sampled according to birth registries kept at the municipal well-baby care clinics in the Tel Aviv area.

Procedure

All newborns identified with intrauterine growth retardation by the obstetricians and/or neonatologists participating 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 (birthweight, length, head circumference). The cephalization index—the ratio between body weight and head circumference at birth, first described by Harel et al[19]—was calculated, reflecting the severity of the intrauterine growth retardation and the magnitude of the "head-sparing" process.

Risk parameters were then assessed using three detailed questionnaires: (1) a sociofamilial risk questionnaire covering parental health, education, socioeconomic status, and maternal obstetric history (Table 1); (2) an obstetric risk questionnaire covering the present gestational and delivery data (Table 2); and (3) a neonatal risk questionnaire describing the perinatal course according to the medical records (Table 3). All questionnaires were designed in accordance with Prechtl's[20] "optimality concept"; each

Table 1. Parental Risk Questionnaire

	Rating	
Item	*Optimal*	*Suboptimal*
Maternal age	16 – 35	<16 – >35
Marital status	Married	Other (single, separated, widowed, divorced)
Age at first marriage	18 – 35	<18 – >35
Education (mother)	>9 yr	<8 yr
Receiving welfare services	No	Yes
Number of siblings	<5	>5
Number of children in mother's family	<5	>5
Number of children in father's family	<5	>5
Maternal weight	Within 2 SD from mean for height	> or <2 SD for weight
Parental chronic disease	Absent	Present
Drug/substance abuse (past or present)	No	Yes
Poor social history*	No	Yes
Poor social history in parent's original family*	No	Yes
Abortions and miscarriages†	0 – 2	>2
Poor obstetric history‡	No	Yes
Premature births (<37 weeks)	No	Yes
Stillbirths and neonatal death	No	Yes
Small for gestational age (<2 SD for gestational age)	No	Yes
Large for gestational age (> 2 SD for gestational age)	No	Yes
Children with congenital anomalies	No	Yes
Parity	1 – 4	> 4
Blood group incompatibility and severe jaundice	No	Yes
Prolonged (unwanted) sterility (2 yr)	Absent	Present
Time period since last gestation	> 12 mo	< 12 mo
Use of contraceptives or intrauterine device (before present gestation)	No	Yes

*Family history of child abuse, parental replacement, severe marital conflict, death, crimes, and drug abuse.
†Any pregnancy terminated prior to 20 weeks where the infant was less than 500 g.
‡Poor obstetric history: one cesarean section, myomas, cervical incompetence, toxemia, uterine abnormalities, bleeding second half of gestation, cephalopelvic disproportion, eclampsia, polyhydramnion, and oligohydramnion.

Table 2. Obstetric Risk Questionnaire

Item	*Optimal Score*	*Suboptimal Score*
Maternal infection or other medical problem during pregnancy*	Absent	Present
Vaginal bleeding during pregnancy	Absent	Present
Rh or blood group incompatibility	Absent	Present
Drugs given to mother during pregnancy (exclude vitamins and iron)	No	Yes
Cephalopelvic disproportion	No	Yes
Blood pressure	Not exceeding 140/90	Over 140/90
Albuminuria	No (<2+)	Yes (>2+)
Edema	No	Yes
Hyperemesis (requiring hospitalization)	Absent	Present
Hemoglobin at end of pregnancy	≥10 (hematocrit ≥30%)	Hemoglobin <10 (hematocrit <30%)
Twins or multiple births (≥2)	No	Yes
Premature rupture of membranes	Spontaneous <24 hr prior to delivery	Other
Procedures during pregnancy†	None	Other
Steady prenatal care during 1st trimester	Present	Absent
Exposure to radiation or poisons	No	Yes
Weight gain	5–12 kg (at delivery)	<5 kg >12 kg
Unwanted pregnancy	No	Yes
Psychiatric disorders in pregnancy	No	Yes
Biophysical profile	9–10/10	<8/10
Smoking (>1 pack per day)	No	Yes
Mode of delivery	Spontaneous	Induced
Arrest disorders (descent or dilation)	Absent	Present
Prolonged 2nd stage (>20 min)	No	Yes
Drugs during delivery (excluding light sedation)	No	Yes
Amniotic fluid	Clear	Other
Fetal ultrasound	Normal	Abnormal
Fetal heart rate patterns‡	Normal	Abnormal
Fetal scalp pH	Normal (>7.25)	Abnormal (<7.25)
Cord prolapse	No	Yes
Cord around neck or knot in cord	No	Yes
Placenta previa or abruptio	No	Yes
Delivery	Spontaneous	Other: forceps, vacuum, cesarean section
Fetal presentation	Vertex, occipito-posterior vertex	Any other (breech, occipito-anterior, face, breech)
Number of cord vessels (arteries)	Two	One

*Maternal infection: rubella, toxoplasmosis, syphilis, cytomegalovirus; Other: herpes, influenza, colds, hepatitis, varicella, gestational diabetes, convulsions, urinary tract infection.
†Amniocentesis, laparoscopy, any surgery, general anesthesia.
‡Normal: no deceleration, normal beat-to-beat variability.

Table 3. Newborn Risk Questionnaire

Risk Item	*Optimal*	*Suboptimal*
Gestational age	37–42 wk (specify)	<37 – >42
Birth weight	>2,500 – <4,500 g	<2,500 – >4,500 g
Apgar score, 1 min	7–10	0–6
Apgar score, 5 min	7–10	0–6
Resuscitation in delivery room	None	Yes
Respiratory distress	No	Yes
Positive or suspected infection	No	Yes
Ventilatory assistance	No	Yes
Congenital anomaly (major anomaly or >3 minor anomalies)	No	Yes
Metabolic and blood disturbance*	No	Yes
Convulsions	No	Yes
Recurrent apneic episodes	No	Yes
Hyperbilirubinemia†	No	Yes
Temperature disturbance	No	Yes
Feeding within 24 hr	Yes	No
Surgery	No	Yes
Catherization of umbilical arteries	No	Yes
Length percentile	3rd – 97th percentile	<3rd – >97th percentile
Head circumference	3rd – 97th percentile	<3rd – >97th percentile
Parental emotional status after delivery	Good	Other

*Metabolic and blood disturbances: hypoglycemia (<40 mg%); hypocalcemia (<7 mg/L); hypomagnesemia (<1.25 mg/L); hypermagnesemia (>1.75 mg/L); acid base disturbance, 7.25 >pH >7.45; sodium (<130 mg/L, >150 mg/L); potassium (<3 mg/L, >5.5 mg/L); hyperviscosity: hematocrit > 65%; anemia: hematocrit <45%.
†Hyperbilirubinemia: bilirubin >15 mg% in full-term babies; >12 mg% in low birthweight babies; >10 mg% in very low birthweight babies (preterms).

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 of the total number of items in each questionnaire. The content validity of the questionnaires was verified by a team of clinicians participating in this study: obstetricians, neonatologists, pediatric neurologists, and developmental psychologists.

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, they underwent a detailed neurodevelopmental examination; head circumference, height, and weight measurements; and formal psychological testing.

At age 6 to 7 years, all children underwent a detailed neurodevelopmental examination designed to identify early signs of learning disabilities before school entry. This examination included the usual physical and neurologic evaluation, but special tests of brain maturation were also included: dynamic and passive coordination skill, presence of "soft" neurologic signs, parietal functions such as finger agnosia and localizations, lateralization, speech, short-term memory, attention, and several basic visuomotor organizational skills (72 items).

Cognitive abilities were assessed using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI).[21] The control group

underwent the same battery of tests. All of the examiners were blinded to the original diagnosis. 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 versus controls). The same analysis was carried out to compare children with intrauterine growth retardation and without "neonatal complications." We defined "neonatal complications" as those children with intrauterine growth retardation having more than three suboptimal items of 13 items in the neonatal questionnaire dealing with potential brain insult. When variables were found to have an abnormal distribution, the nonparametric Mann-Whitney *U*-test was performed. Correlations between biometric data, risk factors, and 6- to 7-year neurodevelopmental and cognitive outcomes were made by Pearson correlations. Significantly correlated parameters were further analyzed by multiple regression analysis to identify the best predictors of outcome at 6 to 7 years.

RESULTS

Biometric Parameters

Significant differences were found for all biometric birth parameters between the group with intrauterine growth retardation and the control group, except for gestational age, as expected. A significant difference was noted on the cephalization index describing the ratio between head circumference and birthweight, as mentioned previously (Table 4).

At age 6 to 7 years, growth measures remain significantly lower in the group with intrauterine growth retardation, as demonstrated. A slight catch-up in weight is seen when looking back at the results at 3 years of age.[22]

Risk Parameters

The children with intrauterine growth retardation and control children were initially matched for sociofamilial risk, as seen in Table 5. Nevertheless, it is important to emphasize that such matching was not "artificial," as our study group consists of the vascular type of intrauterine growth retardation, dispersed similarly among different socioeconomic groups. In contrast, significantly lower scores were found in the neonatal and obstetric questionnaires of the group with intrauterine growth retardation, reflecting their higher initial risks and biologic vulnerability.

Table 4. Biometric Parameters in Children with Intrauterine Growth Retardation and Controls

	Intrauterine Growth Retardation (n = 81)	*Control (n = 41)*	*P*
Birth parameters			
Gestational age (wk)	37.6 ± 2.2	37.2 ± 3.9	NS
Birthweight (g)	1864 ± 401	2760 ± 763	<.0001
Head circumference (cm)	30.6 ± 1.8	33.1 ± 3.1	<.0001
CI (cm × 10^2/g)*	1.72 ± 0.48	1.31 ± 0.37	<.0001
Somatic parameters			
Weight (kg)	19.3 ± 4.3	22.2 ± 5.0	<.005
Height (cm)	114.3 ± 5.5	118.6 ± 6.7	<.0001
Head circumference (cm)	50.0 ± 1.6	51.3 ± 1.7	<.0001

*CI = cephalization index (ratio of head circumference to birthweight).

Table 5. Risk Scores in the Group With Intrauterine Growth Retardation versus Controls

Score	*Intrauterine Growth Retardation (n = 81)*	*Control (n = 41)*	*P*
Sociofamilial (%)*	89.4 ± 7.0	88.2 ± 7.4	NS
Obstetric (%)*	79.6 ± 7.9	87.8 ± 12.2	<.0001
Neonatal (%)*	79.3 ± 11.5	87.7 ± 17.5	<.005

*Percentage of optimal items.

Neurodevelopmental and Cognitive Outcome

Neurodevelopmental score of children with intrauterine growth retardation at age 6 to 7 years was significantly lower compared with controls (Table 6). The specific items for which the children with intrauterine growth retardation were most often scored suboptimally were related to coordination (passive and active equilibrium), lateralization, presence of associated movements, and spatial and graphomotor skills. Accordingly, the most frequent early intervention in children with intrauterine growth retardation was their referral for occupational therapy: 27% of the children with intrauterine growth retardation were referred for occupational therapy, whereas only 17.8% of controls were recommended for similar intervention.

Children with intrauterine growth retardation were also more frequently advised to remain an extra year in kindergarten (8.6% versus 0% in controls), reflecting a general immaturity and the fine motor difficulties described above. It is important to emphasize that the neurodevelopmental problems identified were minor and related most frequently to the quality of neurodevelopmental performance. There were no children with cerebral palsy or severe neurologic deficits.

The IQ score of children with intrauterine growth retardation is normal for age yet significantly lower than matched controls ($P < .05$). The greatest differences were found in the performance IQ domains, specifically in items requiring spatial and graphomotor skills.

Table 6. Developmental Outcome in Group With Intrauterine Growth Retardation and Controls

Developmental Parameter	*Intrauterine Growth Retardation (n = 81)*	*Control (n = 41)*	*P*
Neurodevelopmental (%)*	85.6 ± 11.5	89.2 ± 6.1	<.05
IQ†	101.38 ± 14.1	107.0 ± 13.9	<.05

*Percentage of optimal items; †Wechsler Preschool and Primary Scale of Intelligence.

Table 7. Clinical Parameters Most Significantly Correlated With 6- to 7-Year Neurodevelopmental Score in Group With Intrauterine Growth Retardation (n = 81)

	*R**	*P*
Perinatal parameters		
Neonatal risk score	.3266	<.05
6- to 7-year parameters		
Weight	.3247	<.05
Height	.2866	<.05

*Pearson correlation.

Analysis of the clinical risk data collected demonstrates that neonatal risk score (the total score achieved on the neonatal questionnaire) (Table 7) is the only perinatal parameter significantly correlated with neurodevelopmental outcome at ages 6 to 7 ($P < .05$). The biometric parameters most significantly correlated with neurodevelopment were the weight and height achieved at ages 6 to 7 (see Table 7). The single significant risk parameter predictive of cognitive outcome at ages 6 to 7 (Table 8) was maternal education ($P < .001$).

The head circumference at ages 6 to 7 was strongly correlated with cognition at the same age ($P < .001$), whereas weight and height were not.

Intrauterine Growth Retardation Subgroups

Within the study group with intrauterine growth retardation, 14 children were identified as suffering from multiple neonatal complications (defined as >3 suboptimal scores of 13 items in the neonatal risk questionnaire dealing with potential brain insult). The data (Table 9) show a significant difference in all birth parameters between the two subgroups. After statistical correction for gestational age, a significant difference in neurodevelopmental score was found between the two subgroups, but there was no difference in IQ.

Two other subgroups of intrauterine growth retardation were also compared: the newborns diagnosed with intrauterine growth retardation in utero by ultrasound and those diagnosed in the delivery room. The first subgroup was diagnosed because of alarming clinical signs and could therefore be considered an earlier-onset, more severe type of intrauterine growth retardation than the subgroup diagnosed in the delivery room. The data (Table 10) show a significant difference between these subgroups in the biometric birth parameters, but not in IQ or neurodevelopment. We observed the same results also at age 3 years.

Table 8. Risk Parameters Most Significantly Correlated With IQ Score in the Group With Intrauterine Growth Retardation (n = 81)

	*R**	*P*
Maternal education	.4248	<.001
6- to 7-year parameters		
Head circumference	.4918	<.001

Table 9. Comparison Between Children With Intrauterine Growth Retardation With and Without Neonatal Complications (6–7 Years)

	Intrauterine Growth Retardation With Neonatal Complications (n = 14)	*Intrauterine Growth Retardation Without Neonatal Complications (n = 67)*	*P*
Perinatal parameters			
Gestational age (wk)	35.6 ± 2.1	37.9 ± 2.0	<.0001
Birthweight (g)	1562 ± 453	1950 ± 349	<.005
Head circumference (cm)	29.5 ± 2.5	30.9 ± 1.6	<.05
CI (cm × 10^2/g)*	2.05 ± 0.6	1.6 ± 0.3	<.0001
Developmental parameters			
Neurodevelopmental (%)†	78.7 ± 18.0	86.1 ± 9.0	<.05
IQ‡	98.0 ± 14.9	102.4 ± 13.5	NS

*CI = head circumference to birthweight; †percent of optimal items; ‡Wechsler Preschool and Primary Scale of Intelligence.

DISCUSSION

Our results clearly show that at preschool age, children with intrauterine growth retardation lag behind in somatic growth, neurodevelopmental performance, and cognition when compared with appropriate for gestational age matched control children, as already mentioned in the literature.[7–13] A small tendency to catch up in weight is observed when looking at the results we published at age 3.[21]

Children with intrauterine growth retardation demonstrate a specific profile of minor neurodevelopmental and cognitive difficulties. The nature of these difficulties may predict later learning disabilities and attention and emotional disorders, as described by Low et al,[9] when correlating "motor proficiency" and "neurologic index" with learning deficits at ages 9 to 11 years.

The prevalence of such disorders in the future and their correlation with the present neurodevelopmental difficulties remain to be verified by further follow-up of the same study group.

Table 10. Comparison Between Children With Intrauterine Growth Retardation Diagnosed Before and At Birth (6–7 Years)

	Intrauterine Growth Retardation Diagnosed Before Birth (n = 39)	*Intrauterine Growth Retardation Diagnosed At Birth (n = 25)*	*P*
Perinatal parameters			
Gestational age (wk)	37.1 ± 2.3	38.2 ± 1.8	.07
Birthweight (g)	1770 ± 421	2004 ± 321	<.05
Head circumference (cm)	30.1 ± 1.9	31.1 ± 1.4	<.05
CI (cm × 10^2/g)*	1.8 ± 0.4	1.6 ± 0.2	<.05
Developmental parameters			
Neurodevelopmental (%)†	84.5 ± 11.9	86.2 ± 12.7	NS
IQ‡	102.5 ± 15.5	102.5 ± 12.5	NS

*CI = ratio of head circumference to birth weight; †percent of optimal items; ‡Wechsler Preschool and Primary Scale of Intelligence.

Of over 100 risk parameters analyzed in the present study, the cumulative neonatal risk score was the most powerful in predicting neurodevelopment at ages 6 to 7 years. Taking into consideration the fact that children with intrauterine growth retardation have an increased biologic vulnerability for perinatal complications, as we and other authors[17] have shown, the prevention of such complications by good obstetric and perinatal care is of the utmost importance.

Although biologic risk seems to affect earlier neurodevelopmental profile, maternal education, having a major effect on verbal IQ, emerges as the most significant parameter predictive of cognition at ages 6 to 7 years, whereas it is not significant at an earlier age. This hints, perhaps, at the fact that environmental influences are gaining a greater impact on cognition at preschool age. Such an effect was also noted by other authors.[7,13]

By looking at two subgroups of children with intrauterine growth retardation — those with perinatal complications versus those without — we have shown their specific impact on neurodevelopmental outcome. It is obvious that the group with intrauterine growth retardation with such complications is of a younger gestational age, but since gestational age alone was not found to have a significant influence on outcome in our group, we can assume a "clean" effect of the perinatal complications and the intrauterine growth retardation on the observed outcome.

When comparing children with intrauterine growth retardation diagnosed before birth with those diagnosed at birth, we are actually looking at two different "grades" of intrauterine growth retardation: a higher-risk, earlier-onset (mid-second to third trimester) type and the mildest form of intrauterine growth retardation initiated late in pregnancy (end of third trimester). Nonetheless, the identical outcome reflects the results of good obstetric management, early delivery, and careful neonatal care.

In conclusion, the prospective nature of the study and the uniform vascular-induced population with intrauterine growth retardation matched socioeconomically with the appropriate for gestational age control group made it possible to analyze the true biologic effect of intrauterine growth retardation on growth and neurodevelopment. We have shown that the impact of these effects may be reduced to a minimum by early diagnosis, good obstetric and neonatal care, and early clinical intervention. Further follow-up of the same group to school age is needed in order to assess later academic and social achievements.

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