Nutrition and Health, 2001, Vol. 15, pp. 169–175
0260-1060/01 $10

THE EFFECT OF INTRAUTERINE GROWTH RESTRICTION ON THE DEVELOPMENT AND HEALTH OF CHILDREN

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ABSTRACT

The neurodevelopmental and cognitive outcome of long-term Intrauterine Growth Restriction (IUGR) has been followed up from pregnancy to school age at the Tel Aviv Child Development Centre.

INTRODUCTION

Intrauterine growth retardation (IUGR) is defined by a birth weight (BW) of 2 SD below the mean for gestational age, and affects 3–10% of all newborns. Traditionally, IUGR is classified into "symmetric" or "asymmetric" types. Intrauterine growth retardation induced by intrauterine infection, genetic causes, congenital malformations, environmental insults and severe malnutrition results in early "symmetric" restriction of fetal growth, uniformly affecting the brain and other body organs. Vascular-(placental) induced IUGR occurs later in gestation, leading most often to an "asymmetric" newborn with the brain and heart being relatively less affected than the skeleton, liver, thymus, spleen and adrenals. (Pryor, 1996; Leeson and Aziz, 1997).

The intrauterine process resulting in IUGR is a well-known risk for brain insult (as well as for hypertension, diabetes and coronary heart disease) (Hadders-Algra *et al.*, 1988; Harel *et al.*, 1991; Barker, 1997; Kok *et al.*, 1998).

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Results of intrauterine insults may not, however, be evident until later in life (Robertson *et al.*, 1990; Hawdon *et al.*, 1990, Low *et al.*, 1992; Sung 1993). It is, therefore, crucial to follow-up IUGR newborns 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 interpretation of available data on this subject (Goldeberg *et al.*, 1998): 1) The definitions and etiologies of IUGR 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 results of neonatal care practised some 20–30 years ago, and not the modern intensive care provided during the past 10 years; 3) In many follow-up studies of older IUGR 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.

Our prospective, long-term follow-up study of IUGR children, initiated 9 years ago, was specifically designed to overcome most of these difficulties. The study describes the neurodevelopmental and cognitive outcome of IUGR children followed-up from pregnancy to school age at the Tel Aviv Child Development Center. The study specifies the nature of the most prevalent neurodevelopmental difficulties found in IUGR children, changes observed in the clinical picture from early childhood through school age, identifies significant risk factors, and indicates clinical predictors associated with later outcome.

METHODS

Over 320 children with IUGR are currently involved in our long-term research program, 120 reached 3 years of age, 90 are 6–7 years of age, and 15 children are 9 years of age.

Included in the study were all newborns born at the Lis Maternity Hospital, Tel Aviv, from September 1992 with a birth weight under the 5th percentile for gestational age, according to the Israeli percentile curves (Leiberman *et al.*, 1993). Excluded were newborns suffering from genetic syndromes, congenital infections or malformations.

The children included in the study all had a late "asymmetric" type of IUGR. We assume, therefore, that the large majority of the children in this study had suffered a vascular- (placental) induced IUGR. This assumption was supported by pathological studies of the placentas, revealing vascular pathology in over 88% (e.g. obliterated vessels, placental infarcts, increased syncitial knots, and lack of inflammatory changes).

The children recruited for the study were followed-up yearly from birth to school age by neurodevelopmental and psychological evaluations. Risk parameters were assessed using three detailed questionnaires: 1) A

sociofamilial risk questionnaire covering parental health, education, socioeconomic status and maternal obstetric history; 2) Obstetric risk questionnaire covering the present gestational and delivery data; and 3) Neonatal risk questionnaire describing the perinatal course according to medical records. All questionnaires were designed and scored in accordance with Prechtl's (Prechtl, 1982) "optimality concept", each item given an "optimal" or "suboptimal" score, according to accepted standards in the literature. The final score was expressed as the percent of optimal items out of the total number of items in each questionnaire. Psychological evaluations were performed by standard IQ tests.

The data presented in this study demonstrate the changes observed in the IUGR group vs. appropriate for gestation age (AGA) controls matched for gestational age and socioeconomic status at two points of the follow-up: age 3 (n = 112) and age 6–7 years (n = 81).

RESULTS

A significant difference in growth parameters ($P < 0.001$) was found in both ages between IUGR children and AGA controls. At both ages 3 and 6–7 years, the neurodevelopmental score was poorer ($P < 0.005$; $P < 0.05$) in the IUGR group vs. controls. At age 6–7 the IUGR children had lower IQ (Wechsler Preschool and Primary Scale of Intelligence [WPPSI]) scores ($P < 0.05$). No differences were found in IQ (Stanford-Binet) at age 3 years (Tables 1 and 2).

A specific profile of difficulties in coordination, lateralization spatial and graphomotor skills, and abundance of associated movements was found to be typical of IUGR children at age 6–7 years, hinting at possible later learning disabilities.

The clinical parameters best predicting neurodevelopmental outcome at 3 years were the *cephalization index* (Harel *et al.*, 1985) (head circumference/birth weight), an index first described by us in 1985, based on the "brain-sparing" effect, and reflecting, therefore, the severity of the IUGR process ($P < 0.005$). Also significant was the neonatal risk score (the cumulative score achieved on the neonatal questionnaire; $P < 0.05$), birth weight ($P < 0.05$), and height at 3 years ($P < 0.05$) (Table 3), (Fattal-Valevski *et al.*, 1999).

The best predictor of neurodevelopment at 6–7 years was the neonatal risk score, and the weight and height at age 6–7 ($P < 0.05$) (Table 4). Maternal education had the most significant impact on IQ at this age ($P < 0.001$). Head circumference at age 6–7 years was the only somatic parameter that correlated with IQ (Table 5). At both age groups neurodevelopmental outcome was worse in IUGR children with neonatal complications than those without ($P < 0.05$).

Children with IUGR diagnosed prenatally had the same IQ and neurodevelopmental outcome as those diagnosed at birth, probably due to early delivery and good obstetric and perinatal care provided for the first group

TABLE 1

Comparison between children with intrauterine growth retardation and controls—3 years of age

	IUGR (n=85)	Controls (n=42)	P
Birth parameters			
Gestational age, wks	37.5 ± 2.1	37.6 ± 3.0	N.S.
Birthweight, gr	1860 ± 407	2765 ± 682	<.0001
Head circumference, cm	30.5 ± 2.0	32.8 ± 2.5	<.0001
Cl, cm × 10^2/gr	1.7 ± 0.4	1.25 ± 0.3	<.0001
Risk questionnaire scores			
Sociofamilial, %*	90.7 ± 7.3	90.8 ± 8.1	N.S.
Obstetric, %*	82.3 ± 8.6	94.1 ± 6.2	<.0001
Neonatal, %*	80.9 ± 11.7	89.8 ± 12.2	<.0005
Three-year parameters			
Weight, kg	12.7 ± 1.7	13.8 ± 1.7	<.001
Height, cm	92.5 ± 3.5	95.0 ± 4.0	<.005
Head circumference, cm	48.2 ± 1.8	49.1 ± 1.5	<.05
Developmental parameters			
Neurodevelopmental, %*	89.0 ± 9.0	93.2 ± 7.0	<.001
Psychologic**	94.9 ± 16.4	94.9 ± 9.1	N.S.

*Percent of optimal items; **Stanford-Binet Intelligence Scale
IUGR = intrauterine growth retardation; NS = not significant
Cl = cephalization index (head circumference:birthweight ratio)

TABLE 2

Comparison between children with intrauterine growth retardation and controls—6–7 years of age

Birth parameters	IUGR (n=81)	Controls (n=41)	P
Birth parameters			
Gestational age, wks	37.6 ± 2.2	37.2 ± 3.9	N.S.
Birthweight, gr	1864 ± 401	2760 ± 763	<.0001
Head circumference, cm	30.6 ± 1.8	33.1 ± 3.1	<.0001
Cl, cm × 10^2/gr*	1.72 ± 0.48	1.31 ± 0.37	<.0001
Risk questionnaire scores			
Sociofamilial, %**	89.4 ± 7.0	88.2 ± 7.4	N.S.
Obstetrical, %**	79.6 ± 7.9	87.8 ± 12.2	<.0001
Neonatal, %**	79.3 ± 11.5	87.7 ± 17.5	<.005
Six-year 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
Developmental parameters			
Neurodevelopmental, %**	85.6 ± 11.5	89.2 ± 6.1	<.05
IQ***	101.38 ± 14.1	107.0 ± 13.9	<.05

*Cl = head circumference: birth weight; **Percent of optimal items; ***Wechsler Preschool and Primary Scale of Intelligence [WPPSI]

TABLE 3

Parameters significantly correlated with 3-year neurodevelopmental score in children with intrauterine growth retardation (n=85)

	R	P*
Perinatal parameters:		
CI**	-0.3594	<.005
Neonatal risk score	0.2936	<.05
Birthweight	0.2867	<.05
3-year parameters		
Height	0.3191	<.05

*Pearson correlation; **On multivariate regression analysis, the best predictor was CI (P < .01)
CI = cephalization index (head circumference:birthweight ratio)

TABLE 4

Clinical parameters most significantly correlated with 6–7 year neurodevelopmental score in the intrauterine growth retardation (IUGR) group (n=81).

	R*	P
Perinatal parameters:		
Neonatal risk score	0.3266	<0.05
6–7 year parameters		
Weight	0.3247	<0.05
Height	0.2866	<0.05

*Pearson correlation

TABLE 5

Risk parameters most significantly correlated with IQ score in the group with intrauterine growth retardation (IUGR) (n = 81)

	R*	P
Maternal education	0.4248	<0.001
6–7 year parameters		
head circumference	0.4918	<0.001

suffering from earlier-onset, more severe type of IUGR, than the newborns diagnosed at birth.

CONCLUSION

Most IUGR children lag behind in their somatic and neurocognitive development from birth through school age. At a younger age the biologic risk parameters seem to have a greater influence on neurodevelopment, while later environmental influences, such as maternal education, gain importance with cognitive performance.

Children with IUGR demonstrate a specific profile of neurocognitive disabilities at pre-school age, possibly hinting at later learning disabilities. Early diagnosis and intervention may reduce these difficulties to a minimum.

REFERENCES

Barker, D.J.P. (1997). Intrauterine programming of coronary heart disease and stroke. *Acta. Paediatr.*, **423**, 178–182.

Fattal-Valevski, A., Leitner, Y., Kutai, M., Tal-Posener, E., Tomer, A., Lieberman, D., *et al.* (1999). Neurodevelopmental outcome in children with intrauterine growth retardation: a 3-year follow-up. *J. Child. Neurol.*, **14**, 724–727.

Goldenberg, R., Hack, M., Grantham-McGregor and Schurch, B. (1998). Report of the IDECG/ IUNS working group on IUGR effects on neurological, sensory, cognitive and behavioral function. *Eur. J. Clin. Nutr.*, **52**, S1.

Hadders-Algra, M., Huisjes, H.J. and Touwen B.C.L. (1988). Preterm or small-for-gestational-age infants: neurological and behavioural development at the age of 6 years. *Eur. J. Pediatr.*, **147**, 460–467.

Harel, S., Tal-Posener, E., Kutai, M. and et al. (1991). Intrauterine growth retardation and brain development: Parts I and II. Neurodevelopmental outcome. *Int. Pediatr.*, **6**, 114–120.

Harel, S., Tomer, A., Barak, Y. and et al. (1985). The cephalization index: a screening device for brain maturity and vulnerability in normal and intrauterine growth retarded newborns. *Brain. Dev.*, **7**, 580–584.

Hawdon, J.M., Hey, E., Kolvin, I. and Fundudis, T. (1990). Born too small—is outcome still affected? *Dev. Med. Child. Neurol.*, **32**, 943–953.

Kok, J.H., Den-Ouden, A.L., Verloove-Vanhorick, S.P. and Brand, R. (1998). Outcome of very preterm small for gestational age infants: the first nine years of life. *Br. J. Obstet. Gynaecol.*, **105**, 162–168.

Leeson, S. and Aziz, N. (1997). Customized fetal growth assessment. *Br. J. Obstet Gynaecol.*, **104**, 648–651.

Leiberman, J. R., Fraser, D., Weitzman, S. and Glezerman, M. (1993). Birthweight curves in southern Israel populations. *Isr. J. Med. Sci.*, **29**, 198–203.

Low, J.A., Handley-Derry, M.H., Burke, S.O. and et al. (1992). Association of intrauterine fetal growth retardation and learning deficits at age 9 to 11 years. *Am. J. Obstet. Gynecol.*, **167**, 1499–1505.

Prechti, H.F.R. (1982). Assessment methods for newborn infant: a critical evaluation. In Stratton, P. (ed), *Psychology of the Human Newborn*. John Wiley & Sons, New York, p. 21.

Pryor, J.E. (1996). The identification and long-term effects of fetal growth restriction. *Br. J. Obstet. Gynaecol.*, **103**, 1116–1122.

Robertson, C.M.T., Etches, P.C. and Kyle, J.M. (1990). Eight-year school performance and growth of preterm small-for-gestational-age infants: a comparative study with subjects matched for birth weight or for gestational age. *J. Pediatr.*, **116**, 19–26.

Sung, I.K., Vohr, B. and Oh, W. (1993). Growth and neurodevelopmental outcome of very low birth weight infants with intrauterine growth retardation: comparison with control subjects matched by birth weight and gestational age. *J. Pediatr.*, **123**, 618–624.