Chapter 3

Brain development, intelligence and cognitive outcome in children born small for gestational age

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Horm Res Paediatr 2010;73:6–14

ABSTRACT

Intrauterine growth restriction (IUGR) can lead to children born small for gestational age (SGA). SGA is associated with increased neonatal morbidity and mortality as well as adult short stature, cardiovascular disease, insulin resistance, diabetes mellitus type 2, dyslipidaemia and end stage renal disease. In addition, SGA children have decreased levels of intelligence and cognition although the effects are mostly subtle. The overall outcome of each child is the result of a complex interaction between intrauterine and extra uterine factors. Animal and human studies show structural alterations in the brains of individuals with IUGR/ SGA. The presence of growth hormone receptors in the brain implicates that the brain is also a target for growth hormone (GH). Exogenous GH theoretically has the ability to act on the brain. This is exemplified by the effects of GH on cognition in GH deficient adults. In SGA children, data on the effect of exogenous GH on intelligence and cognition are scant and contradictory.

INTRODUCTION

Intrauterine growth restriction (IUGR) can lead to children born small for gestational age (SGA) (Saenger *et al.*, 2007). SGA is associated with increased neonatal morbidity and mortality. Also at advanced age, these children are often smaller than children born appropriate for gestational age (AGA) (Saenger *et al.*, 2007). Furthermore, SGA children are at risk for cardiovascular disease, insulin resistance, diabetes mellitus type 2, dyslipidaemia and end stage renal disease in adulthood (Saenger *et al.*, 2007). In addition to a negative influence on these physical and metabolic parameters, decreased levels of intelligence and cognition has been described in SGA children. However, the nature and the severity of these intellectual and cognitive vulnerabilities differ widely between study populations (Noeker 2005).

Intelligence comprises a set of abilities to understand, learn and apply knowledge and can be expressed in terms of intelligence quotient (IQ). Cognition is the knowledge-handling aspect of behaviour and can be discerned in the following cognitive domains: speech & language, visuospatial and visuoconstructive skills, motor skills, learning and memory, attention and executive functions such as planning, problem-solving and self-monitoring (Noeker 2005).

Both intelligence and cognition are determined by genetic diversity and variations in pre- and postnatal environment. Intelligence and cognition can be regarded as functions of the brain (Noeker 2005). Given the observed decreased intellectual and cognitive abilities of SGA children, it can be expected that brain architecture and brain functioning differ between SGA and AGA children.

Interest on this topic has increased since the approval of GH therapy for treatment of SGA children (Lee *et al.*, 2003). The effect of GH therapy on height has been documented carefully (Maiorana and Cianfarani, 2009; Clayton *et al.*, 2007). Interestingly one group described an effect of GH on intelligence and cognition in SGA children (Van Pareren *et al.*, 2004) whereas another group did not find any significant effect of GH intelligence (Lagrou *et al.*, 2007).

In this review we summarize literature on brain development after IUGR in animals and in humans. Furthermore we have reviewed and analyzed studies on intelligence and cognition in SGA children. Finally we discuss the effects of exogenous GH on the brain, intelligence and cognition.

DEFINITIONS

Intrauterine growth restriction (IUGR) is defined as a process of reduced fetal growth velocity resulting in a failure for the fetus to attain its growth potential. It is a prenatal

diagnosis, based on serial ultrasound measurements during pregnancy (Bertino *et al.*, 2007). Unfortunately for most pregnancies multiple ultrasound measurements are not available. Small for gestational age (SGA) is defined as a birth weight and/ or length below a pre defined cut-off limit (Bertino *et al.*, 2007). A group of SGA children therefore will not only comprise children born small due to IUGR, but also constitutionally small children. When, for example, the 5th percentile is taken as cut-off limit, approximately 20% of the children termed SGA will not be growth restricted but constitutionally small (Mamelle *et al.*, 2001). To study the effects of IUGR, in most studies a predefined cut-off limit is used, although from a methodological point the use of serial ultrasounds is preferable (Bertino *et al.*, 2007).

BRAIN DEVELOPMENT AFTER INTRAUTERINE GROWTH RESTRICTION

Studies in animals

Since there is much difficulty in obtaining specimens for histopathological study of human IUGR brains, most of the knowledge of central nervous system in IUGR has been derived from animal studies. Different methods to induce chronic IUGR have been used in various animal species (mostly rat, sheep and guinea pig) to study the effects of IUGR in mid or late gestation on the brain. Frequently used methods are uterine artery ligation, embolization or malnutrition (Vuguin 2007). The cerebral cortex, the hippocampus and cerebellum were the areas most extensively studied. In IUGR animals, total body weight and brain weight are reduced. However brain weight is reduced to a lesser extent, indicating that the brain is relatively spared (Morrison 2008). When investigated, both hippocampus and cerebellum have reduced volume compared to controls (Lister *et al.*, 2005; Mallard *et al.*, 2000; Mallard *et al.*, 2000). Histopathological studies demonstrate a reduced cortical thickness and a reduced number of neurons in IUGR animals (Hayakawa *et al.*, 1999; Lister *et al.*, 2005; Mallard *et al.*, 2000; Tashima *et al.*, 2001). Neuronal migration to the cortex can be delayed (Sasaki *et al.*, 2000) and dendritic and axonal outgrowth is retarded (Mallard *et al.*, 1998; Dieni and Rees 2003; Mallard *et al.*, 2000). In addition delayed and reduced myelination was evident (Mallard *et al.*, 1998; Nitsos and Rees 1990; Mallard *et al.*, 2000; Sizonenko *et al.*, 2006). There are many factors that contribute to distribution and severity of the brain damage found in IUGR animals. The timing, duration and severity of the growth restriction in relation to the schedule of brain development of several areas within the brain determine the extent of brain damage in each species (Sizonenko *et al.*, 2006). In summary, IUGR animal experiments demonstrate that IUGR results in a various outcome of abnormal fetal brain development.

Studies in humans

There are very few post-mortem studies of human brains of SGA children (Chase *et al.*, 1972). In a small group of term SGA infants, without documented IUGR, reduced brain weight and cell number of the brain was found compared to normal birth weight controls of similar age (Chase *et al.*, 1972). In addition, the total amount and concentration of myelin lipids was reduced in SGA infants. With magnetic resonance imaging (MRI) it is possible to study brain anatomy in humans in vivo. Imaging studies in combination with ultrasound measurements of fetuses during pregnancy reveal that, despite brain sparing, IUGR leads to a reduction of brain volume (Duncan *et al.*, 2005). Several studies in premature infants with documented IUGR and children born SGA, show a reduction of total brain volume, most pronounced in cerebral cortical gray matter (Dubois *et al.*, 2008; Toft *et al.*, 1995; Borradori-Tolsa *et al.*, 2004). The degree of volume reduction was well correlated with both head circumference and functional outcome at term, especially attention (Borradori-Tolsa *et al.*, 2004). In contrast to brain volume, cortical gyrus and sulcus formation is less affected (Dubois *et al.*, 2008).

Unfortunately there are no longitudinal MRI studies of brain development in SGA children from birth onwards. In adolescents born SGA at term age with postnatal catch up growth, a trend towards smaller cerebral cortical volume is found compared to control adolescents but this difference was not significant (Martinussen *et al.*, 2005; Skranes *et al.*, 2005). Studies in SGA children without catch up growth are not available.

In summary, both animal and human studies demonstrate a consistent underdevelopment of the brain in animals and children born SGA.

INTELLIGENCE AND COGNITION IN CHILDREN BORN SGA

We reviewed studies investigating intelligence and cognition in children born SGA. We included studies reporting results derived from intelligence and cognitive tests performed by the children themselves. Studies based on questionnaires filled in by parents or schoolteachers were excluded. Another inclusion criterium was a control group consisting of children born AGA with similar gestational age. Studies as early as possible were included, dating from 1972 until February 2009. Because prematurity is an independent risk factor of inferior outcome on intelligence and cognition (Van Baar *et al.*, 2009; Yanney and Marlow 2004; Lundgren *et al.*, 2001; Gutbrod *et al.*, 2000), studies were grouped according to gestational age into term children or preterm children (see Table 3.1) (Gutbrod *et al.*, 2000; Westwood *et al.*, 1983; Viggedal *et al.*, 2004; Fitzhardinge and Steven 1972; Paz *et al.*, 1995; Paz *et al.*, 2001; Strauss and Dietz 1998; Strauss 2000; O'Keeffe *et al.*, 2003; Theodore *et al.*, 2009; Kulseng *et al.*, 2006; Harvey *et al.*, 1982; Sommerfelt *et al.*, 2000; Sommerfelt *et al.*, 2002; McCarton *et al.*, 1996; Feldman and Eidelman

Table 3.1 Intelligence and cognition in children born small for gestational age, compared to children born appropriate for gestational age (matched for gestational age)

	Author	Definition for SGA	Sample size SGA	Age at assessment (yrs)	IQ	Cognitive domains				
						Speech & Language	Visuospatial & Visuoconstructive skills	Manual dexterity & Motor skills	Learning & Memory	Executive function & Attention
Born at term	Westwood et al. 1983	P2.3	33	19	↓*					
	Viggedal et al. 2004	P2.3	17	1.5, 24	↓*		↓		↓	
	Fitzhardinge& Steven 1972	P3	96	4, 6, 8	↓*	↓				
	Paz et al. 1995	P3	64	17	↓*					
	Paz et al. 2001	P3/ P10	944	17	↓*					
	Strauss & Dietz 1998	P5	2719	7	↓*	↓				
	Strauss 2000	P5	1064	5, 16		↓	↓*			
	O' Keeffe et al. 2003	P10	596	14	=	↓				↓
	Theodore et al. 2009	P10	385	7	=					
	Kulseng et al. 2006	P10	60	14	=					=
	Harvey et al. 1982	P10	51	5	↓*, ↓**		↓**	↓**		
	Sommerfelt et al. 2000, 2002	P15	311	5	↓*, ↓∞	=	=	↓	=	
Born preterm	McCarton et al. 1996	P3	129	6	↓					
	Gutbrod et al. 2000‡	P10	115	4.7	↓*	=				
	Feldman et al. 2006	P10	40	2	↓					
	Sung et al. 1993	P10	27	1, 2, 3	↓	-				
Born term and born preterm (mixed groups)	Lundgren et al. 2007	P2.3	5890	18	↓					
	Frisk et al. 2000	P2.3	71	8	↓	↓†	↓†			↓†
	Tideman et al. 2007	P2.3	19	18	↓					↓
	Hollo et al. 2002	P2.5	118	10	↓					
	Fattal-Valevski et al. 1999	P5	85	3	=					
	Leitner et al. 2007	P10	123	9 to 10	↓*, ↓∞					
	Geva et al. 2006‡, 2006‡, 2008‡	P10	123-138	9 to 10	↓*	↓	=	↓	↓	↓
	Silva et al. 1984	P10	96	3, 5, 7, 9	↓*					

Legend to Table 3.1

↓ Lower than control group
= Equal to control group
* Significant difference but within the normal range
** In children born SGA with onset of slow headgrowth before 26 weeks of gestation
∞ Performance IQ only
‡ With prematurity as a covariate
† Only in children with prenatal head growth compromise

Abbreviations

P2.3 Below 2.3rd percentile
P2.5 Below 2.5th percentile
P3 Below 3rd percentile
P5 Below 5th percentile
P10 Below 10th percentile
P15 Below 15th percentile
SGA Small for gestational age

2006; Sung *et al.*, 1993; Frisk *et al.*, 2002; Tideman *et al.*, 2007; Hollo *et al.*, 2002; Fattal-Valevski *et al.*, 1999; Leitner *et al.*, 2007; Geva *et al.*, 2006a; Geva *et al.*, 2006b; Geva *et al.*, 2008; Silva *et al.*, 1984) .

Children born at term

For the studies included in Table 3.1, the birth weight cut-off for defining SGA varied widely, ranging from P2.3 to P15. The group size differed also considerably. In most studies IQ was assessed only once but in some studies children were tested repeatedly with several years in between.

From Table 3.1, it is clear that in most studies the IQ in SGA children is significantly lower than in AGA controls. However, this difference never exceeded one standard deviation (15 IQ points). Within studies, the more severely affected SGA children had the lowest IQ. The difference in IQ score between SGA and AGA children was positively related to the birth weight cut-off. In general, studies with more stringent criteria for defining SGA reported larger differences in IQ scores between SGA children and AGA controls but this association must be interpreted with caution because many different test batteries with different psychometric properties were used.

For the different cognitive domains, much less data are available. When tested, SGA children performed worse on various cognitive domains, compared to their normal counterparts. Given the widespread cognitive vulnerabilities in the different studies, it can be expected that when tested systematically, SGA children will perform worse across cognitive domains. This is exemplified by the fact that being born SGA is associated with poorer school performance and SGA children experience more learning difficulties (Lundgren *et al.*, 2001; Hollo *et al.*, 2002; Geva *et al.*, 2006b).

Children born preterm

As can be expected, for children born preterm, the IQ in both AGA and SGA groups was lower than that of children born at term. Still, most studies found a significant lower IQ in preterm children born SGA compared tot preterm children born AGA.

CONCEPTUAL MODEL OF INTELLIGENCE AND COGNITION IN CHILDREN BORN SGA

Being born SGA imposes a child at risk for impairments in intelligence and cognition, but, as stated earlier, the overall outcome of each individual is the result of a complex interaction between several factors as visualised in Figure 3.1 Some of these factors op-

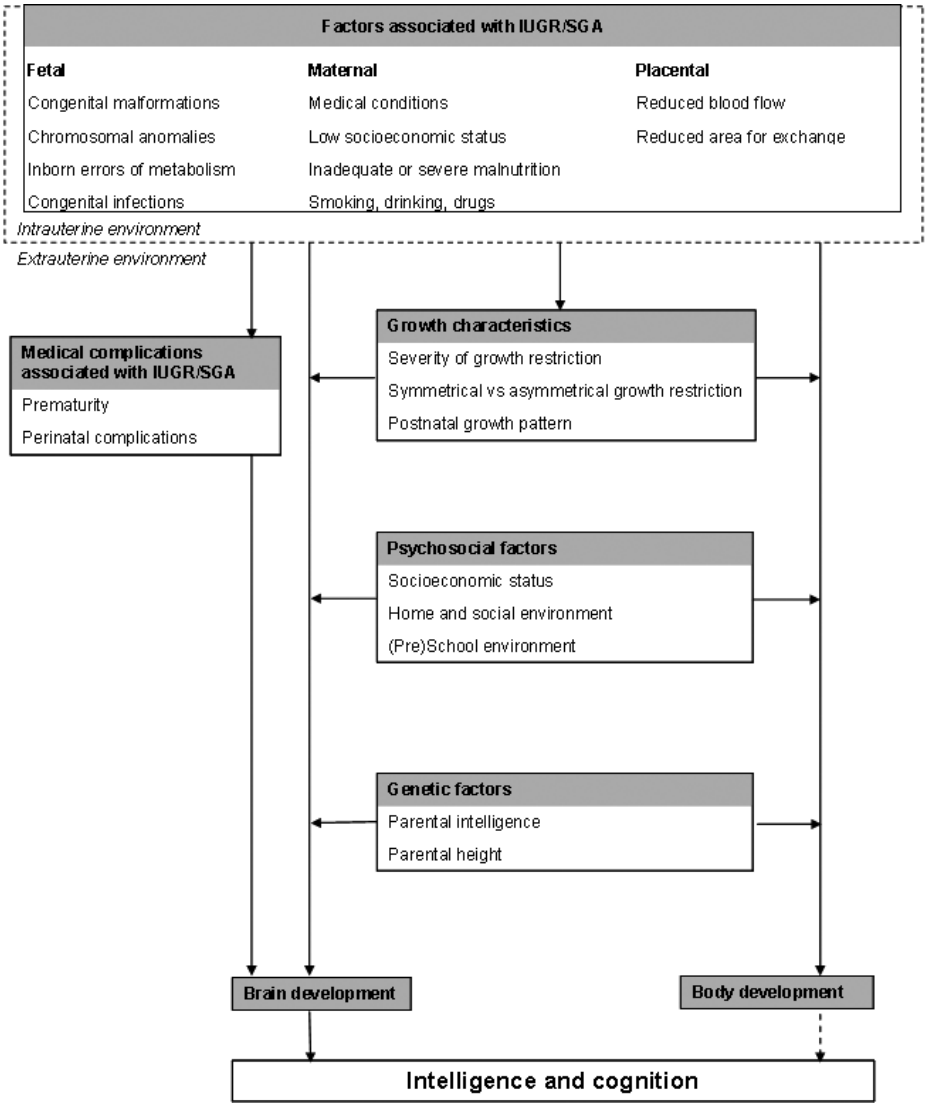

Figure 3.1 Conceptual model of intelligence and cognition in children born small for gestational age. Abbreviations: IUGR, intrauterine growth restriction; SGA, small for gestational age. Adapted from Ref Noeker et al.

erate independently, others are associated with being born SGA, i.e. perinatal morbidity and lower socioeconomic status (Fattal-Valevski *et al.*, 1999; Gutbrod *et al.*, 2000; Hollo *et al.*, 2002; Lundgren *et al.*, 2001; McCarton *et al.*, 1996; Theodore *et al.*, 2009). Intrauterine factors that determine growth and growth restriction can be divided in fetal, maternal and placental factors (Bryan and Hindmarsh 2006). The severity of growth restriction (O'Keeffe *et al.*, 2003), prenatal head growth pattern (Lundgren *et al.*, 2001; Frisk *et al.*, 2002; Harvey *et al.*, 1982), perinatal complications including prematurity (Fattal-Valevski *et al.*, 1999; Westwood *et al.*, 1983; Lundgren *et al.*, 2001), are key players in defining the situation of the SGA child at birth.

After birth, postnatal catch up growth of both body and head can follow various patterns. Good catch up growth is associated with better outcome at later age with respect to IQ and cognition (Lundgren *et al.*, 2001; Frisk *et al.*, 2002; Geva *et al.*, 2006b). Remaining factors determining the final outcome in SGA children are nutrition, psychosocial factors and genetic factors. The most important factors are home and school environment, socioeconomic status and parental intelligence (Sommerfelt *et al.*, 2000; Theodore *et al.*, 2009; Westwood *et al.*, 1983; Morley et al., 2004; Rao et al., 2002).

GROWTH HORMONE AND THE BRAIN

Distribution of GH receptors (GHR)

From animal studies it is known that GHR as well as insulin-like growth factor (IGF)-I receptors are found on all cell types of the brain. They are most abundant in the fetal and juvenile brain and decline thereafter with age (Lobie *et al.*, 2000). GHR distribution in the human neonatal brain is largely unknown. Only one study using human fetal brain has been published and demonstrates the existence of GHR on neurons of the cerebral cortex (Hill *et al.*, 1992). Studies in human adults demonstrate the presence of GHR and IGF-I receptors in different areas of the human brain but mainly concentrated in the choroid plexus, pituitary, hippocampus, putamen and hypothalamus (Harvey and Hull 2003).

Origin of production of GH

While local production of GH in the brain (neural GH) of animals is clearly demonstrated, local production of GH in the human brain is less clear (Harvey *et al.*, 2002). Although the blood-brain-barrier (BBB) was generally considered to be impermeable to peripheral (or pituitary) GH, both animal and human studies demonstrate that peripheral GH can pass the BBB (Johansson *et al.*, 1995; Harvey and Hull 2003; Pan *et al.*, 2005). During pregnancy, human placental GH, also named GH2 or GH-V, is secreted by the placenta and gradually replaces maternal pituitary GH (Mirlesse *et al.*, 1993).

GH action in the brain

The presence of GHR in the developing brain suggests a role for GH in neural development and neural function. Using cell culture systems, it was found that GH induces neuronal and glial proliferation and differentiation (Ajo *et al.*, 2003; Harvey and Hull 2003). GH Deficient mice have a microcephalic brain that is hypomyelinated, with retarded neuronal growth and poor synaptogenesis. GH administered during critical stages of brain development increases brain size in GH deficient mice (Harvey and Hull 2003; Noguchi 1996). Animal studies further demonstrate that GH has a neuroprotective effect following hypoxic-ischemic injury (Scheepens *et al.*, 2001; Shin *et al.*, 2004).

Some but not all the effects of GH are thought to be mediated via IGF-I (Ajo *et al.*, 2003; Lobie *et al.*, 2000; Russo *et al.*, 2005). Animal studies show an important role of IGF-I in brain growth and development with demonstrated effects on proliferation and differentiation of neurons and glial cells and synaptogenesis (Arsenijevic and Weiss 1998; D'Ercole *et al.*, 2002; Russo *et al.*, 2005; Ye *et al.*, 2002). IGF-I knock out mice have reduced brain size whereas mice with transgenic overexpression of IGF-I have increased brain size (Beck *et al.*, 1995; Carson *et al.*, 1993). In addition IGF-I promotes cell survival through anti-apoptotic actions (Hodge *et al.*, 2007). Clinical studies in patients with IGF-I deficiency due to a genetic defect of the IGF-I gene reveal microcephaly and psychomotor retardation and an association has been described between IGF-I levels and intelligence in childhood (Gunnell *et al.*, 2005; Walenkamp and Wit 2008).

In conclusion, GH and IGF-1 both possess multiple common effects in the brain. The specific effects of GH and the effects of GH mediated by IGF-1 in the brain remain to be determined.

GH THERAPY AND BRAIN DEVELOPMENT, INTELLIGENCE AND COGNITION IN HUMANS

The presence of GHR in areas of the brain that are thought to be involved in neurocognitive functioning, indicates that substitution of GH in various patient groups may positively influence brain development and subsequently intelligence and cognition. The effect of GH therapy on intelligence and cognition has been investigated in both children and adults. The effect of GH therapy on intelligence and cognition was studied in children with growth hormone deficiency, idiopathic short stature, Prader Willi and Turner syndrome. No clear beneficial effects of GH therapy on IQ and cognition have been described in these patient groups although the number of studies is very limited (Ross 2005; Myers *et al.*, 2007). Adults with growth hormone deficiency (GHD) have IQ's within the normal range. Several studies indicate that GHD can lead to small, but clinically relevant cognitive impairment. Most extensively studied are memory, processing

speed and attention (Falleti *et al.*, 2006). In contrast with the lack of effect of exogenous GH in children, GH therapy has been shown to be have beneficial effect on cognition in adults (Falleti *et al.*, 2006).

GH therapy in children born SGA

There are two cohorts of SGA children in which the effect of GH therapy on intelligence and cognition has been evaluated (Van der Reijden-Lakeman 1996; Van der Reijden-Lakeman *et al.*, 1997; Van Pareren *et al.*, 2004; Lagrou *et al.*, 2007). In The Netherlands, children born SGA without catch up growth were evaluated after two and eight years of GH treatment (Van der Reijden-Lakeman 1996; Van der Reijden-Lakeman *et al.*, 1997; Van Pareren *et al.*, 2004). In 53 treated children, a positive effect of GH treatment on performance and total IQ scores as well as attention was found. After eight years of GH treatment, estimated IQ scores of SGA children had increased with 5-10 points and were in the same range as the normal population. In addition, the investigators found a relation between the change in head circumference and the improvement of estimated IQ scores during GH treatment. These results are in contrast with the findings in a cohort of SGA children from Belgium. In a randomised controlled trial no beneficial effect of GH treatment on IQ scores could be observed after a period of two years of treatment (Lagrou *et al.*, 2007). A remarkable finding in this study is an increase in IQ scores of about eight points in untreated SGA children. The treated group, consisting of 17 children, did not show an increase in IQ scores, despite a clear effect of GH therapy on head circumference. There are several methodological issues that must be kept in mind when interpreting these IQ-scores. First, in the Dutch study an estimated IQ score was reported that was based on two out of 12 subscales of the Wechsler Intelligence Scale for Children - Revised. Second, the changes in IQ scores after eight years may have been influenced by the Flynn effect, i.e. an increase in IQ over generations. This can be overcome by using an appropriate control group. Third, changes in test instruments (from preschool children to school children) may have influence the IQ scores in the Belgian study, because they were unevenly distributed between treated and untreated groups.

In summary, there is no conclusive evidence that GH treatment in SGA children has an effect on IQ.

Exogenous GH in IUGR animal models

Unfortunately, animal studies about the effect of exogenous GH on brain development and cognition in IUGR models are lacking. Exogenous GH improves learning processes in rats but these type of experiments has not been performed in IUGR animals (Schneider-Rivas *et al.*, 2007; Le Greves *et al.*, 2006).

CONCLUSIONS

IUGR leads to abnormal and delayed brain development. SGA is associated with decreased levels of intelligence and various cognitive problems although the effects are mostly subtle. The overall outcome of each child is the result of a complex interaction between intrauterine and extra uterine factors. The presence of GH receptors in the brain implicates that the brain is also a target for GH. Exogenous GH theoretically has the ability to act on the brain. This is exemplified by the effects of GH treatment on cognition in adult GH deficient patients. Data on the effect of exogenous GH on intelligence and cognition in SGA children are scant and contradictory. Therefore thorough follow up studies in GH treated SGA children are needed to resolve this issue.

ACKNOWLEDGMENTS

We thank Mrs I. Riphagen, University Library, VU University Medical Center for her bibliographic assistance. We thank Ms Boersma for carefully reading the manuscript. This work was funded by an educational grant from Pfizer bv, The Netherlands.