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Brain Development, Intelligence and Cognitive Outcome in Children Born Small for Gestational Age

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Abstract
Intrauterine growth restriction (IUGR) can lead to infants being born small for gestational age (SGA). SGA is associated with increased neonatal morbidity and mortality as well as short stature, cardiovascular disease, insulin resistance, diabetes mellitus type 2, dyslipidemia and end-stage renal disease in adulthood. 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 extrauterine factors. Animal and human studies show structural alterations in the brains of individuals with IUGR/SGA. The presence of growth hormone (GH) receptors in the brain implies 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 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 infants being born small for gestational age (SGA) [1]. SGA is associated with increased neonatal morbidity and mortality. Also at later ages, these children are often smaller than children born appropriate for gestational age (AGA) [1]. Furthermore, SGA children are at risk for cardiovascular disease, insulin resistance, diabetes mellitus type 2, dyslipidemia and end-stage renal disease in adulthood [1]. In addition to a negative influence on these physical and metabolic parameters, decreased levels of intelligence and cognition have been described in SGA children. However, the nature and severity of these intellectual and cognitive vulnerabilities differ widely between study populations [2].

Intelligence comprises a set of abilities to understand, learn and apply knowledge and can be expressed in terms of an intelligence quotient (IQ). Cognition is the knowledge-handling aspect of behavior and can be discerned in the following cognitive domains: speech and language, visuospatial and visuoconstructive skills, motor skills, learning and memory, attention and executive functions such as planning, problem-solving and self-monitoring [3].

Both intelligence and cognition are determined by genetic diversity and variations in the pre- and postnatal

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environment. Intelligence and cognition can be regarded as functions of the brain [3]. 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 in this topic has increased since the approval of growth hormone (GH) therapy for treatment of SGA children [4]. The effect of GH therapy on height has been carefully documented [1]. Interestingly, one group described an effect of GH on intelligence and cognition in SGA children [5], whereas another group did not find any significant effect of GH on intelligence [6].

In this review, we summarize the literature on brain development after IUGR in animals and 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

IUGR is defined as a process of reduced fetal growth velocity resulting in a failure of the fetus to attain its growth potential. It is a prenatal diagnosis, based on serial ultrasound measurements during pregnancy [7]. Unfortunately, for most pregnancies multiple ultrasound measurements are not available. SGA is defined as a birth weight and/or length below a predefined cutoff limit [7]. A group of SGA children therefore will not only include children born small due to IUGR, but also constitutionally small children. When, for example, the 5th percentile is taken as the cutoff limit, approximately 20% of the children termed SGA will not be growth restricted but constitutionally small [8]. To study the effects of IUGR, in most studies a predefined cutoff limit is used, although from a methodological point the use of serial ultrasounds is preferable [7].

Brain Development after IUGR

Studies in Animals

Since it is very difficult to obtain specimens for histopathological study of human IUGR brains, most of the knowledge of the 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 on the brain of IUGR in mid- or late gestation. Frequently used methods are uterine artery ligation, embolization or malnutrition [9]. The cerebral cortex, hippocampus and cerebellum are 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 [10]. When investigated, both hippocampus and cerebellum have reduced volume compared to controls [11–13]. Histopathological studies demonstrate a reduced cortical thickness and a reduced number of neurons in IUGR animals [11, 12, 14–16]. Neuronal migration to the cortex can be delayed [17], and dendritic and axonal outgrowth is retarded [12, 18, 19]. In addition, delayed and reduced myelination was evident [12, 18, 20, 21]. There are many factors that contribute to the 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 [22]. In summary, IUGR animal experiments demonstrate that IUGR results in variable outcomes of abnormal fetal brain development.

Studies in Humans

There are very few postmortem studies of human brains of SGA children [23]. In a small group of term SGA infants without documented IUGR, reduced brain weight and cell number in the brain were found compared to normal birth weight controls of similar age [23]. In addition, the total amount and concentration of myelin lipids was reduced in SGA infants. With magnetic resonance imaging 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 [24]. Several studies in premature infants with documented IUGR and children born SGA have shown a reduction of total brain volume, most pronounced in cerebral cortical gray matter [25–27]. The degree of volume reduction was well correlated with both head circumference and functional outcome at term, especially attention [26]. In contrast to brain volume, cortical gyrus and sulcus formation is less affected [25].

Unfortunately, there are no longitudinal magnetic resonance imaging studies of brain development in SGA children from birth onwards. In adolescents born SGA at term with postnatal catch-up growth, a trend towards smaller cerebral cortical volume was found compared to control adolescents, but this difference was not signifi-

Table 1. Intelligence and cognition in children born SGA, compared to children born AGA (matched for gestational age)

Report	Definition of SGA	Sample size (SGA)	Age at assessment (years)	IQ	Cognitive domains				
					speech and language	visuospatial and visuoconstructive skills	manual dexterity and motor skills	learning and memory	executive function and attention
Children born at term									
Westwood et al., 1983 [33]	P2.3	33	19	↓[1]					
Viggedal et al., 2004 [34]	P2.3	17	1.5, 24	↓[1]		↓		↓	
Fitzhardinge and Steven, 1972 [35]	P3	96	4, 6, 8	↓[1]	↓				
Paz et al., 1995 [36]	P3	64	17	↓[1]					
Paz et al., 2001 [37]	P3/ P10	944	17	↓[1]					
Strauss and Dietz, 1998 [38]	P5	2,719	7	↓[1]	↓				
Strauss, 2000 [39]	P5	1,064	5, 16		↓	↓[1]			
O'Keeffe et al., 2003 [40]	P10	596	14	=	↓				↓
Theodore et al., 2009 [41]	P10	385	7	=					
Kulseng et al., 2006 [42]	P10	60	14	=					=
Harvey et al., 1982 [43]	P10	51	5	↓[1], ↓[2]		↓[2]	↓[2]		
Sommerfelt et al., 2000, 2002 [44, 45]	P15	311	5	↓[1], ↓[3]	=	=	↓	=	
Children born preterm									
McCarton et al., 1996 [46]	P3	129	6	↓					
Gutbrod et al., 2000[4] [32]	P10	115	4.7	↓[1]	=				
Feldman et al., 2006 [47]	P10	40	2	↓					
Sung et al., 1993 [48]	P10	27	1, 2, 3	↓					
Children born at term and preterm (mixed groups)									
Lundgren et al., 2007 [31]	P2.3	5,890	18	↓					
Frisk et al., 2002 [49]	P2.3	71	8	↓	↓[5]	↓[5]			↓[5]
Tideman et al., 2007 [50]	P2.3	19	18	↓					↓
Hollo et al., 2002 [51]	P2.5	118	10	↓					
Fattal-Valevski et al., 1999 [52]	P5	85	3	=					
Leitner et al., 2007 [53]	P10	123	9–10	↓[1], ↓[3]					
Geva et al., 2006[4], 2006[4], 2008[4] [54–56]	P10	123–138	9–10	↓[1]	↓	=	↓	↓	↓
Silva et al., 1984 [57]	P10	96	3, 5, 7, 9	↓[1]					

P2.3 = Below the 2.3rd percentile; P2.5 = below the 2.5th percentile; P3 = below the 3rd percentile; P5 = below the 5th percentile; P10 = below the 10th percentile; P15 = below the 15th percentile; ↓ = significantly lower than the control group; = = equal to the control group.

[1] Significant difference but within the normal range.

[2] In children born SGA with onset of slow head growth before 26 weeks of gestation.

[3] Performance IQ only.

[4] With prematurity as a covariate.

[5] Only in children with prenatal head growth compromise.

cant [28, 29]. 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 criterion 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 in intelligence and cognition [30–32], studies were grouped according to gestational age into term children or preterm children (table 1) [31–57].

Children Born at Term

For the studies included in table 1, the birth weight cutoff for defining SGA varied widely, ranging from below the 2.3rd percentile to below the 15th percentile. The group size also differed considerably. In most studies, IQ was assessed only once, but in some studies children were tested repeatedly with several years in between.

From table 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 1 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 cutoff. 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, considerably fewer 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 various cognitive domains. This is exemplified by the fact that SGA children have poorer school performance and experience more learning difficulties [31, 51, 55].

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 significantly lower IQ in preterm children born SGA compared to preterm children born AGA.

Conceptual Model of Intelligence and Cognition in Children Born SGA

Being born SGA places 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 visualized in figure 1. Some of these factors operate independently, while others are associated with being born SGA, i.e. perinatal morbidity and lower socioeconomic status [31, 32, 41, 46, 51, 52].

Intrauterine factors that determine growth and growth restriction can be divided into fetal, maternal and placental factors [58]. The severity of growth restriction [40], prenatal head growth pattern [31, 43, 49] and perinatal complications including prematurity [31, 33, 52] are key players in determining the outcome of the SGA child at birth.

After birth, postnatal catch-up growth of both the body and head can follow various patterns. Good catch-up growth is associated with better outcome at later ages with respect to IQ and cognition [31, 49, 55]. Remaining factors determining the final outcome in SGA children are psychosocial and genetic factors. The most important factors are the home and school environment, socioeconomic status and parental intelligence [33, 41, 44].

GH and the Brain

Distribution of GH Receptors

From animal studies, it is known that GH receptors (GHRs) 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 [59]. 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 GHRs on neurons of the cerebral cortex [60]. Studies in human adults demonstrate the presence of GHRs and IGF-I receptors in different areas of the human brain but mainly concentrated in the choroid plexus, pituitary, hippocampus, putamen and hypothalamus [61].

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 [62]. Although the blood-brain barrier was generally considered to be impermeable to peripheral (or pituitary) GH, both animal and human studies have demonstrated that peripheral GH can pass the blood-brain barrier [61, 63, 64]. During pregnancy, human placental GH, also named GH2 or GH-V, is secreted by the placenta and gradually replaces maternal pituitary GH [65].

Action of GH in the Brain

The presence of GHRs in the developing brain suggests a role for GH in neural development and neural function. Using cell culture systems, it was found that GH

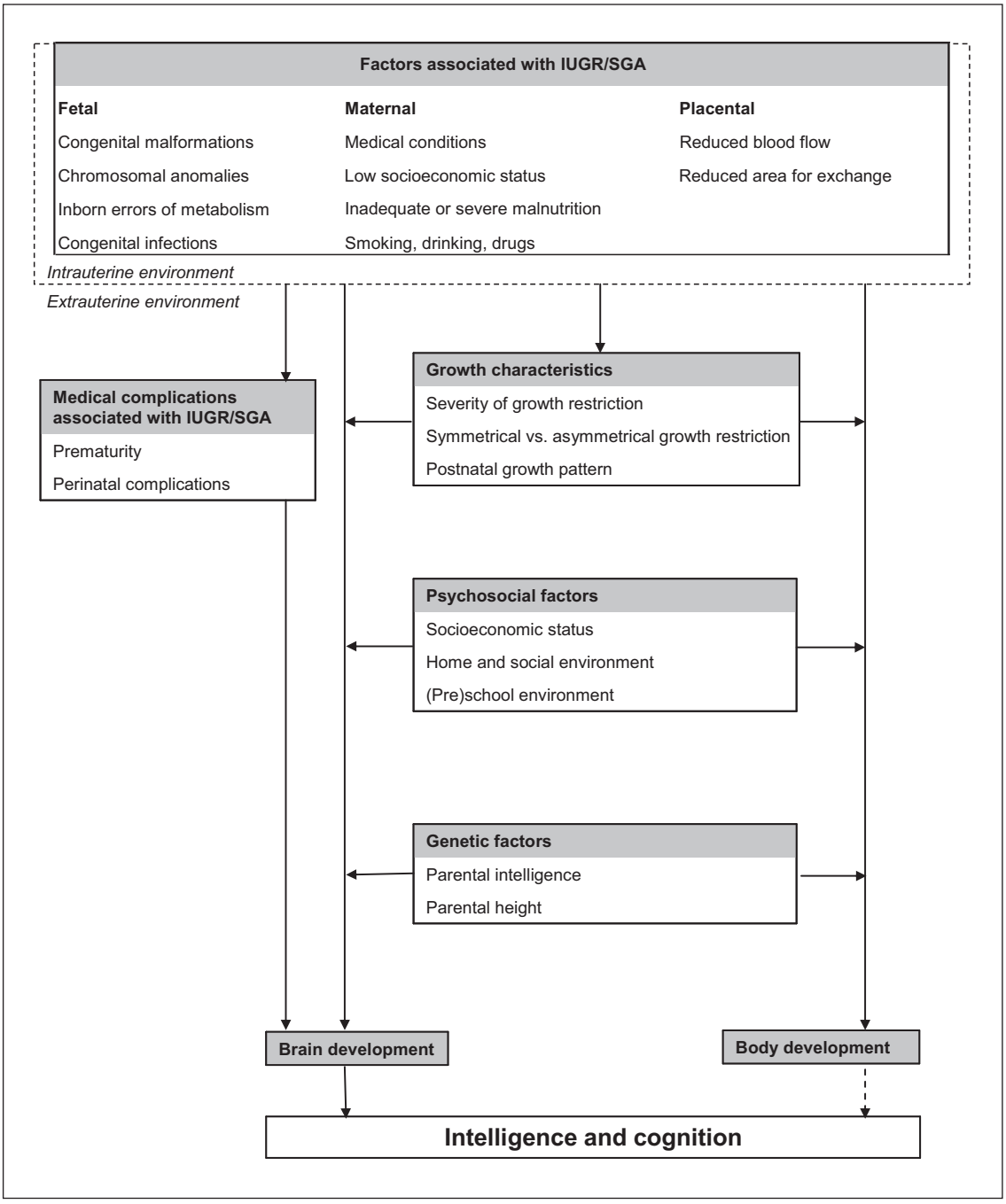

Fig. 1. Conceptual model of intelligence and cognition in children born SGA. Adapted from Noeker [2], with permission.

induces neuronal and glial proliferation and differentiation [61, 66]. 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 [61, 67]. Animal studies further demonstrate that GH has a neuroprotective effect following hypoxic-ischemic injury [68, 69].

Some but not all the effects of GH are thought to be mediated via IGF-I [59, 66, 70]. Animal studies show an

important role of IGF-I in brain growth and development, with demonstrated effects on the proliferation and differentiation of neurons and glial cells and synaptogenesis [70–74]. IGF-I knockout mice have reduced brain size, whereas mice with transgenic overexpression of IGF-I have increased brain size [75, 76]. In addition, IGF-I promotes cell survival through antiapoptotic actions [77]. 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 [78, 79].

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 GHRs 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 has been studied in children with GH deficiency, idiopathic short stature and Prader-Willi and Turner syndromes. 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 [80, 81]. Adults with GH deficiency have IQs within the normal range. Several studies indicate that GH deficiency can lead to minor but clinically relevant cognitive impairment. Most extensively studied are memory, processing speed and attention [82]. In contrast with the lack of effect of exogenous GH in children, GH therapy has been shown to have a beneficial effect on cognition in adults [82].

GH Therapy in Children Born SGA

There are 2 cohorts of SGA children in which the effect of GH therapy on intelligence and cognition has been evaluated [5, 6, 83, 84].

In the Netherlands, children born SGA without catch-up growth were evaluated after 2 and 8 years of GH treatment [5, 83, 84]. In 53 treated children, a positive effect of GH treatment on performance and total IQ scores as well as attention was found. After 8 years of GH treatment, estimated IQ scores of SGA children had increased by 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 randomized controlled trial, no beneficial effect of GH treatment on IQ scores could be observed after 2 years of treatment [6]. A remarkable finding in this study was an increase in IQ scores of about 8 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. Firstly, in the Dutch study, an estimated IQ score was reported that was based on 2 out of 12 subscales of the Wechsler Intelligence Scale for Children-Revised. Secondly, the changes in IQ scores after 8 years may have been influenced by the Flynn effect, i.e. an increase in IQ over generations. This problem can be overcome by using an appropriate control group. Thirdly, changes in test instruments (from preschool children to school children) may have influenced 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 on the effect of exogenous GH on brain development and cognition in IUGR models are lacking. Exogenous GH improves learning processes in rats, but this type of experiment has not been performed in IUGR animals [85, 86].

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 extrauterine factors. The presence of GHRs in the brain implies 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.

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