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Original article

Preterm small-for-gestational age children: Predictive role of gestational age for mental development at the age of 2 years

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Abstract

Aim: The aim of the study was to compare the cognitive development of very low birth weight (VLBW) preterm SGA children and preterm AGA children at the age of 2 years. The hypothesis was that SGA children are at an additional risk for deficits in cognitive function. Additionally, the impact of neonatal risk factors and the parents' profession on the early cognitive development was analysed.

Methods: Cognitive function of 107 preterm infants with a gestational age of 24–35 weeks was assessed with the Mental Bayley Scales of Infant Development at the age of 2 years (mean ± SEM). The results of SGA ($n = 38$) and AGA ($n = 69$) children were compared as well as neonatal risk factors and parental education.

Results: There was a linear regression between the Mental Bayley Scales result and gestational age for preterm infants with a gestational age of 24–32 weeks. SGA and AGA children did not differ significantly in their cognitive function at the age of 2 years. A strong association was found between the parents' profession and cognitive development. Among the neonatal risk factors, bronchopulmonary dysplasia was a strong predictor of mental development.

Interpretation: Cognitive development of two-year-old preterm children with a gestational age of 24–32 weeks was mainly related to their gestational age. Being born preterm and small for gestational age was not additionally associated with cognitive deficits at the age of 2 years. The parents' profession had a significant impact on the cognitive development. The role of the parents' profession on the early development of preterm infants should be elucidated in further studies.

Keywords: Preterm infants; Mental development; Gestational age; Parental profession

1. Introduction

Intrauterine growth restriction (IUGR) is considered as an important complication during pregnancy and is associated with fetal abortion or stillbirth in 34–60% [1,2]. The outcome of children born small-for-gestational age (SGA) has been in the focus of several epidemiological investigations during the recent years. These children are supposed to have a higher risk to develop hypertension, diabetes mellitus and psychiatric diseases like schizophrenia [3,4]. A huge study in Great Britain including 14.000 children further proposed that people formerly born small-for-gestational age are less successful academically and are less likely in leading job positions in their later lives [5]. It is unclear whether this

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finding is due to mental deficits in children with small birth weight or an epiphenomenon of small infants who have been born in a greater number in lower social classes and, therefore, have less chances of reaching higher job positions [5]. Studies in which the intellectual abilities of SGA infants were assessed by standardised IQ tests found a lower IQ in the SGA group [6,7]. More specific analyses of the cognitive development showed difficulties in language and social skills [5,7–9]. In contrast, other authors could not find any differences between term SGA and appropriate-for-gestational age (AGA) children [10]. Progress in neonatal intensive care has led to an emerging group of surviving preterm infants and preterm SGA infants with very low birth weight (VLBW). However, a high percentage of preterm children develop neurological or mental impairment [11]. The incidence of cerebral palsy ranges from 9 to 14 percent but does not differ significantly between SGA and AGA (14 vs. 12%) [12,13]. Apart from severe neurological impairment, 32–44% of all preterm children with birth weights <1500 g showed mental developmental deficits when tested at the age of 5 years [11,14]. At the age of 2 years Sung et al. found significant differences in the Mental Development index between SGA and AGA preterm children (98 vs. 116) [12]. Developmental studies using the Griffith-Scales in another study revealed no difference between SGA and AGA preterm children [15]. The EPIPAGE study included 2846 preterm infants and disclosed minor cognitive deficits in 5 and 8 years old children [16].

MRI studies in preterm children suggest that IUGR is associated with a decreased cortical grey matter volume in the neonatal brain [17]. Moreover, structural brain alterations in IUGR newborns have been pointed out by a recent study on the hippocampal volume using 3D MRI [18]. The hippocampus is known to be highly vulnerable to environmental factors as hypoxia and ischemia during brain development [18]. In addition, the number of proliferating neurons and the maturation of neurons in the brain of baboons, which were born IUGR after a maternal diet during pregnancy, were found to be reduced. Possible mechanisms are decreased expression of neuronal growth factors like the brain-derived neurotrophic factor (BDNF) and the glial neurotrophic factor S-100beta [19].

It is unclear whether effects on neuronal proliferation and maturation and changes in MRI are transient or may lead to subtle brain dysfunction like minimal cognitive impairment. As mentioned above, in addition to neonatal complications and changes in brain maturation, the socioeconomic background and the mothers educational level seems to play an important role for the development of preterm infants [20]. Even more, in a study with preterm infants at the age of 6–13 years the maternal background was found to be the strongest predictor of the cognitive outcome [21]. The hypothesis of the present study was that preterm small-for gestational age children are at special risk for cognitive impairment. We considered neonatal risks and the parents' profession as most influencing factors and analysed their impact on mental development.

2. Subjects and methods

2.1. Subjects

107 infants born 2006–2009 between 24 and 35 weeks of gestational age and with a birth weight less than 1500 g took part in a follow-up examination programme and were included in the retrospective study. The follow-up ratio was 68% of preterms with birth weight <1500 g in 2006 and 2007, and 72% in 2008 and 2009. Most of the infants took part in the follow-up at regular intervals of 3, 6, 12 and 24 months. Those who did not take part in the regular examination were invited in written form. Some of the families moved so the invitations were sent back, some of the parents did not respond or refused to participate. There were no SGA infants with a gestational age of less than 26 weeks to be included in the study. One child was excluded because of trisomy 21, one because of a neural tube defect. Small-for-gestational age was defined as gestational weight or length below the 10th percentile using the established reference values of Voigt et al. [22]. Neonatal risk factors were registered as well as the parents' profession, parents' age and bilingualism. The cognitive development of the preterm infants was evaluated with the Mental Bayley Scales of Infant Development Second Edition at the age of 18–24 months corrected age [23]. The Mental Bayley Scales are normalised within a normal population [23]. Normal development is defined as a mental developmental index of 100 ± 2 SD.

2.2. Statistical analyses

The statistical analysis was performed using the SPSS Version19 and the Graph Pad Prism 4 programme. Covariant factors were compared with the Chi^2 test and the Levene test. Small samples were analysed with the fisher test. The relation between the gestational age and mental developmental index (MDI) was analysed by linear regression. The MDIs of SGA and AGA preterm children were compared with the unpaired *t*-test (p value <0.05). The mean MDI was adjusted for the mothers' and the fathers' profession by a univariate analysis of variance. The parents' profession and the MDI were analysed by the one-way-ANOVA and the Kruskal–Wallis test. p values <0.05 were considered significant. A stepwise multiple regression was performed with SPSS Version 19 to analyse the impact of neonatal risk factors.