Fetal hemodynamics and language skills in primary school-aged children with fetal growth restriction: a longitudinal study

Running title: Fetal growth restriction and language skills in primary school-age

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Conflict of interest

The authors declare no conflicts of interest.

What`s already known about this topic?

Fetal growth restriction is associated with neurocognitive impairments, including problems with speech, language and literacy skills.

What does this study add?

We demonstrated that increased blood flow resistance in the umbilical artery and cerebral vasodilatation are associated with poor communication, language, and literacy skills at early school age in children born with FGR. These finding indicate the need for follow-up and preventive measures for children who demonstrated abnormal blood flow during fetal life.

Abstract

Aim Long-term follow-up studies on children born with fetal growth restriction (FGR) have revealed a specific profile of neurocognitive difficulties, including problems with speech, language and literacy skills. We hypothesized that problems with communication skills, including language use and literacy skills of FGR children at primary school age are associated with prenatal circulatory changes.

Methods Ultrasonographic assessment of fetoplacental hemodynamics was performed prenatally in 77 fetuses. After a follow-up period of 8-10 years, assessment of reading and spelling skills using standardized tests and the Children`s Communication Questionnaire (CCC-2) was performed to measure different language skills in 37 FGR children and 31 appropriately grown (AGA) controls, matched for gestational age.

Results Increased blood flow resistance in the umbilical artery (UA PI > 2 SD) during fetal life showed odds ratios of 3.9-11.1 for poor literacy skills and need for speech and language therapy. Furthermore, FGR children with prenatal cerebral vasodilatation (cerebroplacental ratio (CPR) <-2 SD) had significantly poorer literacy and communication skills, as shown by the CCC-2, at primary school age compared to the AGA controls. Abnormal CPR demonstrated odds ratios of 4.5-41.2 for poor literacy and communication skills and need for speech and language therapy.

Conclusion Increased blood flow resistance in the umbilical artery and cerebral vasodilatation are associated with poor communication, language, and literacy skills at early school age in children born with FGR. These findings indicate the need for continuous follow-up of this group and timely targeted support to ensure optimal academic outcomes.

Abbreviations

AGA	Appropriate growth for gestational age
CPR	Cerebroplacental ratio
CTG	Cardiotocography
FGR	Fetal growth restriction
MCA	Middle cerebral artery
PI	Pulsatility index
UA	Umbilical artery

Introduction

Fetal growth restriction (FGR) is associated with significant short-term and long-term mortality and morbidity [1,2]. Despite intensive research on FGR, the timing for delivery to ensure optimal long-term outcomes is still under evaluation. In clinical practice, the risks of prematurity are weighed against the deterioration of placental function and fetal distress by using fetal Doppler findings, biophysical profile score, and cardiotocography (CTG) in serial fetal surveillance tests. Placental insufficiency, the most common cause of FGR, may result in chronic fetal hypoxia [3], and as an adaptive mechanism to hypoxia, blood flow in the fetus is redistributed in favor of vital organs, the heart, and the brain [4-6]. Cerebral vasodilatation was earlier regarded as a protective autoregulatory mechanism and referred to as `brain sparing` [7, 8], but recent findings suggest that cerebral redistribution, often assessed clinically using the cerebroplacental blood flow ratio, may not be entirely a protective phenomenon [9]. Adverse neonatal outcomes, reduced neonatal brain volumes, and increased risk for adverse neurocognitive outcomes in early childhood have been associated with fetal cerebral vasodilatation [10-14].

Development of sufficient language and communication skills is essential for a child`s cognitive development and academic performance. Indeed, reading and spelling skills are essential for reading comprehension and later academic and occupational success, and sufficient language and communication skills are needed in order to successfully use language in various situations and social contexts [15-18]. In particular, pragmatic language skills, which are defined as the appropriate use and interpretation of language in relation to the context in which it occurs, play a significant role in effective communication [19]. Previously, the FGR children of this cohort have shown poor performance in reading and writing skills as well as in communication skills at primary school age [20, 21], with a wide variation seen between the individuals. However, detailed data concerning fetal circulatory changes and language skills at early school age are lacking.

In the present study, we hypothesized that poor communication and literacy skills of FGR children at primary school age are associated with fetoplacental hemodynamic changes. Specifically, we were interested in examining the impact of increased umbilical artery pulsatility and the balance between the cerebral and placental circulations on communication and literacy skills at primary school age.

Materials and Methods

The study participants belonged to a prospectively collected cohort (n=77) of growth-restricted fetuses (birth weight < 10^{th} percentile and/or umbilical artery (UA) pulsatility index > 2 SD in a normal population [22, 23]. The mothers were recruited in 1998-2001 from our high-risk prenatal unit, and were later contacted to book a follow-up visit in accordance with the protocol when their children reached 8- 10 years of age (Figure 1). In all cases, gestational age was confirmed by ultrasound before 20 gestational weeks. Pregnancies with major structural and chromosomal abnormalities, and those complicated by chorioamnionitis and/or ruptured membranes were excluded. From the originally collected cohort, 39 children attended the follow-up visit. Two children were excluded from the analyses because of the child`s unwillingness to perform the tests (n=1) and insufficient Finnish language skills (n=1). The control group consisted of 31 children with appropriate growth for gestational age (AGA). The control group was selected from delivery room records and these children were matched for gestational age, gender, and delivery within ±2 weeks of the index FGR neonate. The recruited children included 21 FGR and 17 AGA eight-year-old second graders, 13 FGR and 14 AGA nine-year-old third-graders, and three 10-year-old FGR children, who had recently started the fourth grade. The fourth graders were included presuming that they had only recently achieved third-grade academic skills. The research protocol was approved by the Ethical Committee of the Oulu University Hospital (approval number 8/2008 on February 21, 2008). Study participation required written maternal consent.

Prenatal assessment

Maternal characteristics and obstetric data were collected at the study entry. Maternal hypertensive disorders were categorized according to the guidelines of the American College of Obstetrics and Gynecology [24] and prenatal steroid therapy included two 12 mg betamethasone doses at 24 h apart.

Detailed information concerning placental and fetal hemodynamic assessments collected by a single investigator within a week (median of 2.9 days) prior to delivery has been described earlier [25]. Acuson Sequoia 512 (Acuson, Mountain View, CA, USA) with 4-8 MHz transducers were used for scanning, and the angle of insonation was maintained at <15 degrees in all examinations. Three consecutive cardiac cycles were obtained and the mean values were used in the analyses. The pulsatility index (PI) in the UA was measured from the free loop of the umbilical cord and further categorized as normal, increased (UA PI > 2 SD), or absent/reversed end-diastolic (ARED) flow [23, 26]. The middle cerebral artery (MCA) PI was assessed, and the cerebroplacental ratio (CPR) was calculated as the MCA PI/UA PI [27]. Significant placental insufficiency (UA PI > 2 SD) and redistribution of blood flow (CPR <-2 SD) were determined according to earlier published data [28, 29].

The managing obstetrician was blinded to the study data. During 1998-2001, the indications for delivery were 1) worsening maternal condition, 2) abnormal non-stress test in fetal heart rate monitoring, and 3) abnormal pulsatility in the ductus venosus.

Postnatal outcomes

At birth the mode of delivery, UA blood gas values, Apgar scores, and neonatal morphometric measurements were recorded. The cohort children attended follow-up studies at the mean age of 9.2 years (Table 1). Follow-up studies included evaluations of speech, language, and literacy skills by a licensed speech therapist (LP). The children`s medical charts were reviewed for diagnoses and data from questionnaires completed by the parents were collected. The questionnaires were created specifically for this study and included sections concerning diagnoses and frequent need for intensive preventive measures such as speech and language therapy, physiotherapy, occupational therapy, and special education. Socioeconomic characteristics were also recorded [30].

Assessments of communication and literacy skills

Detailed assessments of communication and literacy skills were performed at the mean age of 9.2 years (Table 1). Communication skills were assessed using the Children`s Communication Checklist-2 (CCC-2) [31], which has been developed to identify children with speech, language, and pragmatic language impairment, and to assist identification of children requiring further assessment of autism spectrum disorder. A Finnish version of the CCC-2 questionnaire [32, 33] for 8-10-year-old children was utilized in the present study, and a questionnaire was completed by the parents after brief verbal instructions were given by the researcher (LP). The General communication composite score (GCC) was calculated by summing the CCC-2 subscales from A to H; low scores (below 69 points according to the Finnish norms) indicated impaired communication skills [31, 34] (Table 2). These assessments are described in full detail in our earlier publication [20].

The assessment of reading and spelling skills included three standardized tests for Finnish-speaking primary school-aged children: the Word Chain test [35] measured word reading skills, the Ytte test [36] evaluated reading fluency, reading accuracy, and reading comprehension, and the Lukilasse test [37] measured spelling. Performance below the 10^{th} percentile of the normal population was considered poor and performance above the 10^{th} percentile was considered normal. The tests used are described in detail in our earlier study [21].

In clinical practice, detailed examinations and speech and language therapy are commonly recommended when problems in several areas of reading, spelling, and communication are identified. In the present study, speech and language therapy was indicated if a child performed below the 10^{th} percentile normal value in >50% of reading and spelling skill subtests and/or in the presence of a compromised (< 15^{th} percentile normal value) score in the GCC.

Statistical analyses

The data were analyzed using the SPSS 22.0 for Windows software package (SPSS Inc., Chicago, IL, USA). The primary outcome measures were poor performance in communication skills (CCC-2), measured by the general communication composite (GCC), poor performance (< 10^{th} percentile of normal population) in literacy skills, measured by comprehensive reading and spelling skills testing, and clinically estimated need for speech and language therapy. Demographic and ultrasonographic variables were analyzed for association with the primary outcome measures using logistic regression analysis. To estimate the OR in the presence of complete quasi separation, we used the brglm package [38] in the R program, version 3.4.2 [39]. The brglm package is based on the method for bias reduction [40] and allows estimation of the OR from sparse data.

Categorical data were compared using Chi-square analysis and the Fisher`s exact test. For continuous variables, the Student`s t-test was used if the data were normally distributed, otherwise the Mann-Whitney U-test was chosen. Data are present as mean (SD), median (range), n (%), and odds ratio (95% confidence interval [CI]). A two-tailed p-value of <0.05 was selected as the level of statistical significance.

Results

The characteristics of the FGR and AGA groups are presented in Table 1. Mothers of the FGR children demonstrated preeclampsia more frequently. In the FGR group, 68% had UA PI value > 2 SD, 22 % (8/37) demonstrated ARED in UA, 27% showed MCA PI <- 2 SD), and 61% had CPR < -2 SD. This cohort was delivered at 24-40 gestational weeks with no differences in gestational age at delivery between the groups, neither did gestational age between the FGR subgroups (FGR UA PI > 2 SD, FGR CPR <-2SD and FGR MCA PI <-2 SD) and the AGA group differ. The FGR neonates had lower birth weights than the AGA group as expected. Although no significant differences were detected in UA pH values at birth between the groups, FGR children demonstrated low 5-minute Apgar scores (< 7) more frequently than the AGA group. However, the number of severe neonatal complications did not differ significantly between the groups.

Prior to the study assessment at the age of 8-10 years, the FGR children had received speech and language therapy more frequently than the AGA children. This was due to poor language skills (10 children vs. 2 children) and articulation problems (12 children vs. 8 children, Table 1), respectively. A total of 70 % of the FGR children and 97 % of the AGA children were studying in mainstream education. One FGR child was in a special education class and nine were receiving assistance in mainstream education, while only one AGA child required assistance in mainstream education classes (Table 1).

Seven (19 %) FGR children performed below the 10^{th} percentile normal values in all three literacy subtests (Ytte test, Word Chain test, Lukilasse test). Ten (27 %) FGR children and four (13 %) AGA children performed below the 10^{th} percentile GCC normal value. According to a speech therapist's evaluation, 15 (41 %) FGR children and five (16 %) AGA children were defined as being in need of speech and language therapy due to compromised performance in literacy skills, communication skills, or both.

The FGR children with prenatal UA PI values of > 2 SD performed below the 10^{th} percentile normal values in literacy skills significantly more often than AGA controls (Table 3). Communication skill testing using the CCC-2 revealed no statistically significant differences between FGR and AGA children in this cohort, but a more frequent need for speech and language therapy was detected among FGR children with UA PI > 2 SD compared to AGA controls (Table 3).

FGR children with significant blood redistribution (CPR < -2 SD) performed significantly more frequently below the 10^{th} percentile normal values in literacy skills, demonstrated significantly poorer communication skills, and also needed speech and language therapy more frequently than the AGA controls (Table 4). At early school age, FGR children with CPR < - 2SD had significantly smaller mean (SD) head circumference (52.0 (1.7) cm) compared to the AGA controls (53.0 (1.1) cm, p=0.01). There were no significant weight and height differences between these subgroups.

In the presence of UA PI > 2 SD, the odds ratios for poor literacy skills, poor communication skills, and the need for speech and language therapy ranged between 3.9 and 11.1 (Table 5). The odds ratio for poor literacy skills was about 41-fold among FGR children with cerebral vasodilatation (CPR < -2 SD) compared to AGA controls, and a 4.5- 5.7 times higher risk for impaired communication skills and a need for speech and language therapy was detected in this group compared to AGA children (Table 5).

Discussion

In the present study, FGR children with significant placental insufficiency and blood flow redistribution in favor of cerebral circulation demonstrated odds ratios of 4.5-41.2 for poor performance in literacy and communication skills and a need for further speech and language therapy. This indicates that placental insufficiency and low CPR during fetal life are associated with a risk of language and communication problems at early school age.

In previous studies, significant placental insufficiency with absent end-diastolic umbilical artery velocity has been associated with adverse neurocognitive outcomes in early childhood and at early school age [13, 41, 30]. In the prospective multicenter PORTO study investigating the impact of brain-sparing on FGR outcomes, the presence of both UA PI > 95^{th} percentile of normal values and abnormal CPR increased the risk of adverse perinatal outcomes [11]. While all FGR children in our study except one with UA PI > 2 SD also had abnormal CPR, we are unable to ubiquitously speculate the impact of a sole UA finding on the outcomes.

About 53% of the FGR children who demonstrated CPR <-2 SD in our study were evaluated as needing speech and language therapy, and one third of these children also showed poor performance in literacy skills. Fetal cerebral vasodilatation, an indicator of fetal blood flow redistribution, seems to be associated with adverse short-term and long-term neurocognitive outcomes in FGR children with normal and increased UA pulsatility, although this has previously been considered as a benign adaptive mechanism [42,10,11,43,14,13]. Moreover, in neonates born prior to 32 weeks, Figueras et al. (2011) reported an association between cerebral vasodilation and short-term neurobehavioral outcomes as measured by the Neonatal Behavioral Assessment Scale (NBAS), while the large randomized TRUFFLE trial detected no significant association between fetal cerebral vasodilatation and 2-year neurodevelopmental outcomes [10, 44]. In the TRUFFLE trial, motor and perception deficits were included in the assessment of impaired neurodevelopment, which was determined as low Bayley Scales mental development score, estimated cognitive delay > 3 months, cerebral palsy, or severe hearing or visual impairment [44]. The authors of the TRUFFLE study concluded that fetal cerebral vasodilatation offered no advantages over birth weight and gestational age in the timing of delivery in FGR pregnancies prior to 32 weeks. However, fetuses with cerebral vasodilatation (abnormal umbilicocerebral ratio Z-score) at the time of the TRUFFLE trial entry, had a higher risk for poor 2-year neurodevelopmental outcomes [44]. Our study cohort included FGR fetuses born at a wide gestational age range (24-40 weeks), including 10 FGR children born prior to 32 weeks. A total of 88% of the preterm born FGR children demonstrated an abnormal CPR prenatally and 60 % of them had problems in language and communication skills, while only 30 % of AGA children born prior to 32 weeks showed impairment in these areas. We speculate that the differences are due to different study populations, study designs, and follow-up times.

Over 40 % of the FGR children, who demonstrated cerebral vasodilatation (CPR <-2SD) prenatally, presented clinically significant impairment of communicative functions in our study. Cerebral vasodilatation, a response to fetal hypoxemia, has been associated with compromised outcomes especially in the areas of communication and executive functions, which depend highly on frontal brain area function [14]. It has been speculated that frontal areas may be exceptionally susceptible even to mild hypoxia [42]. The second half of the pregnancy is essential as regards to formation of critical neuronal connections and myelination of important tracts, and during the third trimester, development of the cortical layers of the brain is accelerated making these parts especially vulnerable to adverse events [45]. Moreover, reduced gray matter volumes, which correlate with suboptimal neurodevelopment, and widespread microstructural changes in white matter have been detected in preterm FGR infants [46-48].

The catch-up growth of FGR children during the early years may have an impact on neurocognitive outcomes. In the large EPIPAGE study, postnatal catch-up growth did not affect neurocognitive outcomes at 5 years of age in children born with FGR [49], but Geva et al. (2006) reported compromised neurocognitive outcomes at 9 years of age in FGR children with poor postnatal head growth [50]. In a recent study on FGR children with prenatal cerebral blood flow redistribution, poor neurocognitive outcomes were associated with incomplete head circumference catch-up growth at 6 years of age [51]. Similarly, in our study, FGR children with cerebral redistribution had significantly smaller head circumferences compared with FGR children without cerebral redistribution, and AGA controls.

The CCC-2 questionnaire has been demonstrated to correctly identify impairments in language and pragmatic language use [52,34, 53]. However, although the GCC is a validated method for identifying those children with clinically marked communication problems from the normal ones, it doesn`t differentiate the type of problem very well [31]. In the present study, all children who scored below the 10^{th} percentile in GCC had low scores (< the 10^{th} percentile of normal values) in more than four subscales of the CCC-2, indicating clinically significant problems in communication skills. Problems in the development of language skills, especially pragmatic language skills, are associated with compromised general intellectual function and behavioral problems [18].

The literacy tests used in the present study are standardized tests that measure different aspects of reading and spelling. These skills are essential for a child to be able to obtain a sufficient level of reading comprehension [17, 15]. Poor performance in all or most of the subtests indicates that a child has marked difficulties in reading and writing, and without support he will most likely also have difficulties in academic performance. Furthermore, difficulties in these areas have proved to be very persistent, indicating that children with poor skills at early school age will most likely have poor skills also in adolescence [54]. In previous studies concerning reading skills in preterm born children, difficulties have been shown to increase with advancing age [55]. Despite our national screening program, conducted prior to school entry as regards to speech and language therapy needs and more frequent speech therapy sessions in the FGR group compared to the AGA group, FGR children showed significant impairments in their linguistic performance. Our results, thus, underline the importance of continuous follow-up and targeted preventive measures in the FGR children, especially those with placental insufficiency and cerebral vasodilatation.

We recognize that the rather small sample-size is a limitation of our study. However, the children studied belong to a well-defined population-based cohort of growth-restricted fetuses. The children lost to follow-up/refusing to participate did not differ from the participants as regards to pre- or perinatal factors (data not shown). Our cohort includes children born at a wide range of gestational ages, but when FGR children were compared to their gestational age matched AGA peers, prenatal circulatory changes have been demonstrated to be a significant risk factor for adverse neurodevelopmental outcomes independent of gestational age [41, 30]. We feel that long-term follow-up and a detailed linguistic and literacy assessment of FGR children in our cohort combined with prenatal hemodynamic evaluation is a significant strength of this study, while previously linguistic skills have been investigated mostly as a part of cognitive assessment [56,57,51].

Conclusion

We conclude that in FGR, increased umbilical artery pulsatility and cerebral vasodilatation are associated with poor communication and literacy skills at early school age, suggesting that these fetal circulatory changes play a significant role in the prediction of later communication and literacy problems. Therefore, preventive measures should be targeted in these FGR children to support the development of their academic abilities.

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