Neurodevelopment at Age 10 Years of Children Born <28 Weeks With Fetal Growth Restriction

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abstract

OBJECTIVES: We sought to evaluate the relationships between fetal growth restriction (FGR) (both severe and less severe) and assessments of cognitive, academic, and adaptive behavior brain function at age 10 years.

METHODS: At age 10 years, the Extremely Low Gestational Age Newborns Cohort Study assessed the cognitive function, academic achievement, social-communicative function, psychiatric symptoms, and overall quality of life of 889 children born before 28 weeks' gestation. A pediatric epileptologist also interviewed parents as part of a seizure evaluation. The 52 children whose birth weight *z* scores were <−2 were classified as having severe FGR, and the 113 whose birth weight *z* scores were between −2 and −1 were considered to have less severe FGR.

RESULTS: The more severe the growth restriction in utero, the lower the level of function on multiple cognitive and academic achievement assessments performed at age 10 years. Growth-restricted children were also more likely than their extremely preterm peers to have social awareness impairments, autistic mannerisms, autism spectrum diagnoses, difficulty with semantics and speech coherence, and diminished social and psychosocial functioning. They also more frequently had phobias, obsessions, and compulsions (according to teacher, but not parent, report).

CONCLUSIONS: Among children born extremely preterm, those with severe FGR appear to be at increased risk of multiple cognitive and behavioral dysfunctions at age 10 years, raising the possibility that whatever adversely affected their intrauterine growth also adversely affected multiple domains of cognitive and neurobehavioral development.

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WHAT'S KNOWN ON THIS SUBJECT: No cohort study of later school-aged children born extremely preterm has examined the relationship between fetal growth restriction and executive function, adaptive behaviors, or quality of life.

WHAT THIS STUDY ADDS: Among children born extremely preterm, those born with fetal growth restriction appear to be at increased risk of multiple cognitive and behavioral dysfunctions at age 10 years.

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Children born at term weighing much less than expected for their gestational age are at greater risk of developmental limitations than their peers with birth weights appropriate for gestational age (AGA),[1–4] seemingly even into adulthood.[5–9] Children born very preterm are also at increased risk of developmental disorders.[10–13] The combination of severe growth restriction and extremely preterm birth might result in so-called double jeopardy,[14] placing children with both characteristics at especially high risk of developmental problems.[15–19]

Researchers in follow-up studies of children born extremely preterm have used just a handful of instruments and questionnaires to assess motor, cognitive, speech and language, hearing, vision, academic, and some behavioral problems or other symptoms typically at ~5 years of age.[11,20,21] Whereas motor function appears stable by ~5 years old,[22–26] deficits in other domains involving higher-order cognitive processes do not.[27,28] No researchers in cohort studies of later school-aged children born extremely preterm have examined the relationship between fetal growth restriction (FGR) and executive function, adaptive behaviors, or quality of life. The large Extremely Low Gestational Age Newborns (ELGAN) Study cohort of infants born before 28 weeks' gestation provided us opportunities to fill this void and evaluate the relationships between FGR (both severe and less severe) and assessments of cognitive, academic, and behavioral functioning at age 10 years.

METHODS

Participants

The ELGAN Study is a multicenter, prospective, observational study of the risk of structural and functional neurologic disorders in extremely preterm infants.[29] All women delivering before 28 weeks' gestation at 1 of 14 participating institutions were asked to enroll in the study during years 2002 to 2004. All the children they delivered who survived to have a cranial ultrasound scan were included. A total of 1506 infants born before 28 weeks' gestation were enrolled, and 1200 survived to 2 years, when 1102 of them had a developmental assessment.[30] At age 10 years, of the 966 children who were eligible to be recruited for follow-up (because of the availability of data on inflammation-related proteins in blood samples from their first postnatal month), 889 (92%) returned for an assessment of cognition, executive functioning, behaviors, and achievement. Children who survived but did not participate were more likely at the time of birth than participants to have indicators of social disadvantage (lower maternal education and receipt of public health insurance), but there were no differences on sex, gestational age, or birth weight *z* score. Enrollment and consent procedures for this follow-up study were approved by the institutional review boards of all participating institutions. Our previous publications provide additional information about the ELGAN Study design,[29] pregnancy disorders,[31] microbiologic and histologic characteristics of the placenta,[32] systemic inflammation in children born with FGR,[33] and the age 10 years assessments.[34]

Newborn Variables

The gestational age estimates were based on a hierarchy of the quality of available information. The most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before the 14th week (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks (29%), last menstrual period (LMP) without fetal ultrasound (7%), and gestational age recorded in the log of the NICU (1%). The birth weight *z* score is the number of SDs an infant's birth weight is above or below the mean weight of infants of the same gestational age in referent samples not delivered for preeclampsia or fetal indications.[35,36] Three study groups were formed according to birth weight *z* score category: <-2, ≥ -2 and <-1, and ≥ -1.

Procedures

Families who were willing to participate were scheduled for 1 visit, during which all of the measures reported here were administered in 3 to 4 hours, including breaks. The assessments were selected to provide the most comprehensive information about cognitive and academic function in 1 testing session. While the child was being tested, the parent or caregiver completed questionnaires regarding the child's medical and neurologic status, language, behavior, and quality of life.

Cognitive Measures

We selected cognitive measures that are well validated and provide recently normed standard scores, allowing for comparison with US population norms. Details about the assessments of cognition and executive function (the Differential Ability Scales–II [DAS-II][37]), Developmental Neuropsychological Assessment-II [NEPSY-II][38]), language (Oral and Written Language Scales [OWLS][39]), social and communication function (Social Communication Questionnaire [SCQ][40]), and autism spectrum disorder (ASD) diagnosis are provided in our previous publications.[34,41,42] Each cognitive subtest is described elsewhere.

Academic Function

The Wechsler Individual Achievement Test-III (WIAT-III [C]) provides standard scores in word recognition and decoding, spelling, and numeric operations.[43] We report the scores from the WIAT-III Numeric Operations, Word Reading, Pseudoword Decoding, and Spelling subtests.

Autism Assessment

Children determined to be at risk on the SCQ (see parent-completed questionnaires below) were assessed with the Autism Diagnostic Interview–Revised (ADI-R) and an in-depth parent interview.[42,44] Children who met ADI-R modified criteria for ASD[45] were administered the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2).[46] All children who met standardized research criteria for ASD on both the ADI-R and ADOS-2 were classified as having ASD. In addition, 11 children were included who met ADOS-2 criteria but did not have an ADI-R assessment; of these children, 9 who had a previous clinical diagnosis of ASD or who the site psychologist thought were likely to meet diagnostic criteria for ASD were assessed with the ADOS-2, whereas the parents of the remaining 2 children did not complete the ADI-R interview.

Gross Motor Function

The children's motor function was assessed with the Gross Motor Function Classification System.[47] A child was classified as level 3 or higher if he or she needed mobility assistance (level 3, walks using a handheld mobility device; level 4, self-mobility with limitations, may use powered mobility; and level 5, transported in a manual wheelchair).

Manual Ability Classification System

The classification assigns a single level for the collaborative use of both hands when handling objects in daily life (level 1, handles objects easily and successfully; level 2, some reduction of quality and/or speed; level 3, handles objects with difficulty; level 4, significant limitations; and level 5, requires total assistance).[48]

Communication Function Classification System

The Communication Function Classification System allocates children to 1 of 5 levels of communication performance (level 1, effective with unfamiliar and familiar partners; level 2, effective but slower paced; level 3, effective with familiar partners but less so with unfamiliar partners; level 4, inconsistent with familiar partners; and level 5, seldomly effective with familiar partners).[49] The system assesses speech, gestures, behaviors, eye gaze, facial expressions, and such augmentative and alternative communication systems as manual signs, pictures, communication boards, communication books, and speech-generating devices.

Parent-Completed Questionnaires

While the child was being tested, the parent or caregiver was asked to complete the following questionnaires regarding the child's medical and neurologic status and behavior.

Child Symptom Inventory-4

While the child was being tested, the parent or caregiver completed questionnaires regarding the child's medical and neurologic status and behavior, including the Child Symptom Inventory-4 (CSI-4) Parent Checklist.[50] The child's current teacher was also asked to complete the CSI-4 Teacher Checklist. Although the parent checklist has 20 more items than the teacher version (97 vs 77), both include the same 18 items specific to attention-deficit/hyperactivity disorder symptoms (9 for the inattentive domain and 9 for the hyperactive and/or impulsive domain) that are each rated on a scale from 0 (never) to 3 (often). Teachers and parents did not make any *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis. Rather, the CSI-4 program identified children as screening positive for these diagnoses on the basis of the parents' or teachers' acknowledgment of selected child characteristics.

Social Responsiveness Scale

The Social Responsiveness Scale (SRS) is a short, parent-completed questionnaire designed to evaluate a child's social ability.[51,52] This 65-item instrument was designed as a quantitative trait measure for ASD-related deficits that do not warrant a formal diagnosis in the general population.[53,54] It provides a total score reflecting the severity of social deficits on the autism spectrum as well as 5 subscale scores: social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behavior.

SCQ

All children were screened for an autism disorder by the parent-completed SCQ.[55] We used the current version, which is composed of 40 yes-or-no questions about the child's behavior over the last 3 months.

Children' s Communication Checklist-2

The Children's Communication Checklist-2 (CCC-2) has 70 items that are used to assess speech, vocabulary, sentence structure, and social language skills.[56] The 10 subscales are discourse, syntax, semantics, coherence, inadequate initiation, stereotyped language, use of context, nonverbal communication, social relations, and interests. We calculated *z* scores using normative data.[57]

Data Analyses

We evaluated the null hypothesis that among children born before 28 weeks' gestation, those who had severe and less severe intrauterine growth restriction do not differ from their peers who had higher weight for gestation on assessments of cognitive and executive function, behavior, language, and communication at age 10 years. We also described motor function, the frequencies of parent and teacher responses on CSI-4 items, the occurrence of seizures, and quality of life among children who were born growth restricted and children who were not.

Frequencies and proportions were calculated to describe the

characteristics of each study group. For assessments that yield a continuous outcome, we used normative data described by the authors of the assessment[37,58,59] to derive *z* scores. Associations with *z* scores <−2 or *z* scores ≥−2 and <−1 were evaluated for cognition and academic outcomes, as well as those measured by the SRS, SCQ, and CCC-2. We used logistic regression models to estimate odds ratios (ORs) with 95% confidence intervals (CIs) adjusting for potential confounders (sex and racial identity) that were selected a priori and were associated with the independent and dependent variables (see Supplemental Fig 5). ORs with 95% CIs that exclude 1.0 are statistically significant at P <.05.

RESULTS

Correlates of Birth Weight *Z* Score Categories

The mothers of severely growth-restricted newborns were more likely than the mothers of other children to identify as neither white nor African American (Supplemental Fig 5). Most (69%) children who were delivered because of preeclampsia were growth restricted, as were half of those who were delivered for a fetal indication. Girls were more frequently growth restricted than boys.

Distributions of Age 10 Years Assessment Scores

Figure 1 shows box plots for each measure; the 3 horizontal lines in the box plots correspond to the normative population 25th, 50th, and 75th percentile values for each measure. The distributions of scores on every assessment were lower than was expected on the basis of the distributions in the normative sample (ie, the medians lie below the horizontal line at 0).

Compared with their peers who were not born with FGR, the most severely and the less severely growth-restricted newborns had relatively

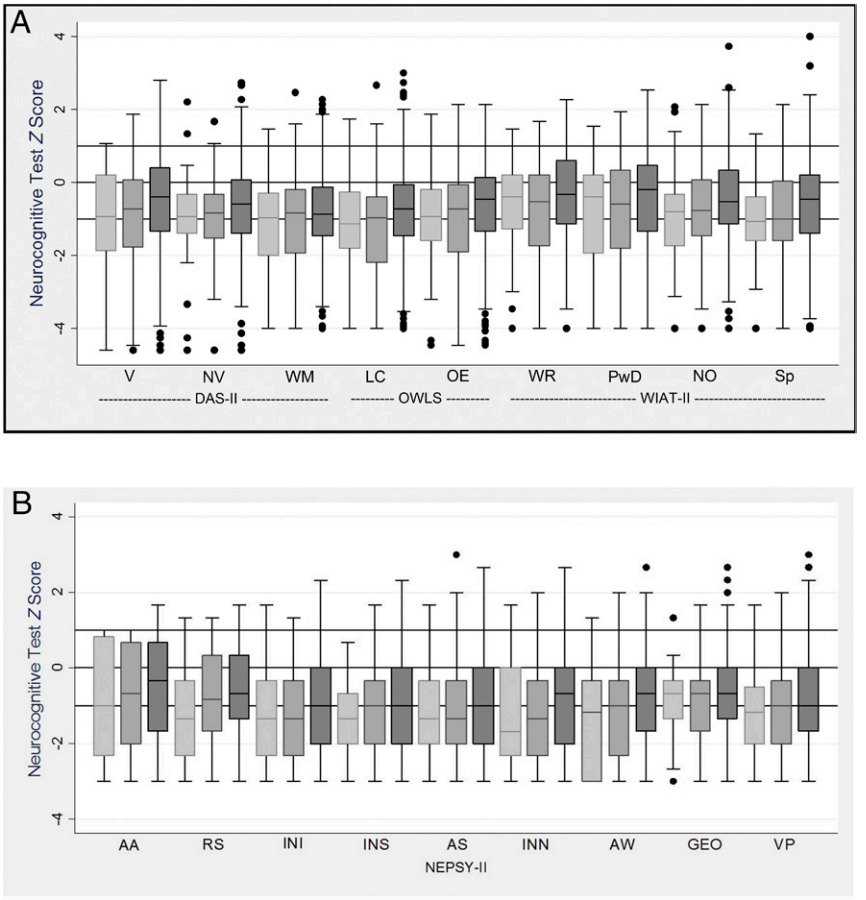

FIGURE 1

Box-and-whisker plots (A and B) of each cognitive subtest by birth weight *z* score category. All *z* scores are adjusted to population norms. Light gray is <−2; medium gray is ≥−2, <−1; and dark gray is ≥−1. The central line in the box indicates the median (50th percentile), whereas the top of the box indicates the 75th percentile, and the bottom of the box indicates the 25th percentile. If ELGAN had the expected normal distribution of term children, the middle of the box would be at *z* score = 0, and the upper and lower ends of the box would be at *z* score = 1 and *z* score = −1, respectively. AA, auditory attention; AS, animal sorting; AW, arrows; GEO, geometric puzzles; INI, inhibition inhibition; INN, inhibition naming; INS, inhibition switching; LC, listening comprehension; NO, numerical operations; NV, nonverbal reasoning; OE, oral expression; PwD, pseudoword decoding; RS, auditory response set; Sp, spelling; V, verbal; VP, visuomotor precision; WM, working memory; WR, word reading.

similar percentages of low scores on the DAS-II Verbal Reasoning, OWLS Listening Comprehension, NEPSY-II Visuomotor Precision, and WIAT-III Word Reading, Pseudoword Decoding, and Spelling subtests. In contrast, the more severe the growth restriction, the lower the scores for auditory attention, auditory response, inhibition inhibition, inhibition switching, inhibition naming, and arrows assessments. Differences in scores for the remaining assessments across the 3 study groups were minor, although median and 25th percentile scores generally tended to be higher among the AGA group than among their growth-restricted peers.

General Cognition and Achievement

In analyses that were adjusted for race and sex, children born severely or less severely growth restricted were 1.5- to twofold more likely than their peers who were born with higher birth weight *z* scores to have low scores on the OWLS Oral Expression subtest, the DAS-II Working Memory subtest, the NEPSY-II Auditory Response subtest, and the WIAT-II

Numeric Operations subtest (Fig 2, Supplemental Tables 1 and 2).

Children who were less severely growth restricted at birth were also at increased risk of low scores on the OWLS Oral Expression subtest and the DAS-II Working Memory subtest. These children also had higher risks of low scores on the DAS-II Verbal subtest, the NEPSY-II Animal Sorting subtest, and the WIAT-II Word Reading, Pseudoword Decoding, and Spelling subtest scores.

SRS

Clinically significant impairment (score of ≥60) at age 10 years on the social awareness and social cognition components of the SRS occurred more frequently among children who were severely growth restricted at birth than among children who were not growth restricted (Fig 3, Supplemental Table 3). The ORs of clinically significant impairment as defined by the total SRS score and the remaining SRS components (social cognition, social communication, social motivation, and autistic mannerisms) were not statistically different from 1.

Children who were severely growth restricted at birth were also at increased risk of a rigorously defined ASD. Their increased risk of screening positive on the SCQ was not statistically significant, although they were considerably more likely than others to have been described as using odd phrases, socially inappropriate questions, and made-up words.

Children whose growth restriction at birth was less severe were not at increased risk of high scores on the SRS, screening positive on the SCQ, or positive ADOS-2.

CCC-2

Children with severe FGR were at increased risk of a *z* score ≤−1 on the CCC-2 subtests of coherence, context, nonverbal communication, and interests (Fig 4, Supplemental Tables 4). Children who were less severely growth restricted at birth were not at increased risk of a low score on any subtest of the CCC-2.

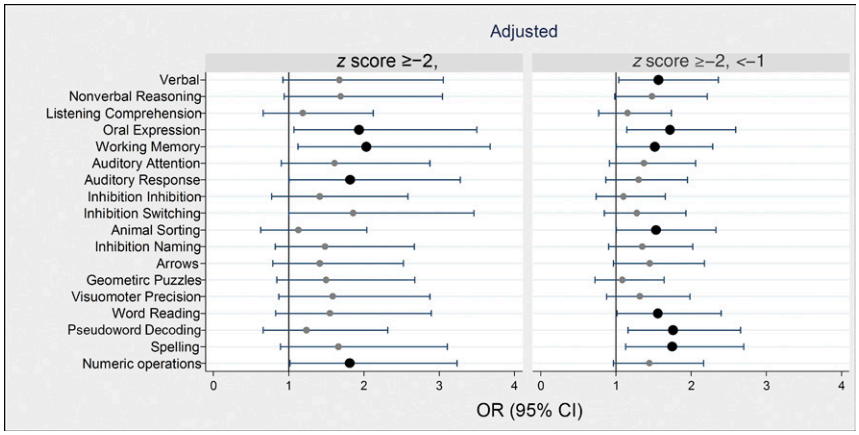

FIGURE 2
Forest plots of ORs and 95% CIs of a *z* score ≤−1 on each DAS-II and NEPSY-II cognitive assessment at age 10 years associated with birth weight *z* score category <−2 (on left) and ≥−2, <−1 (on right). ORs are adjusted for racial identity and sex. BW, birth weight.

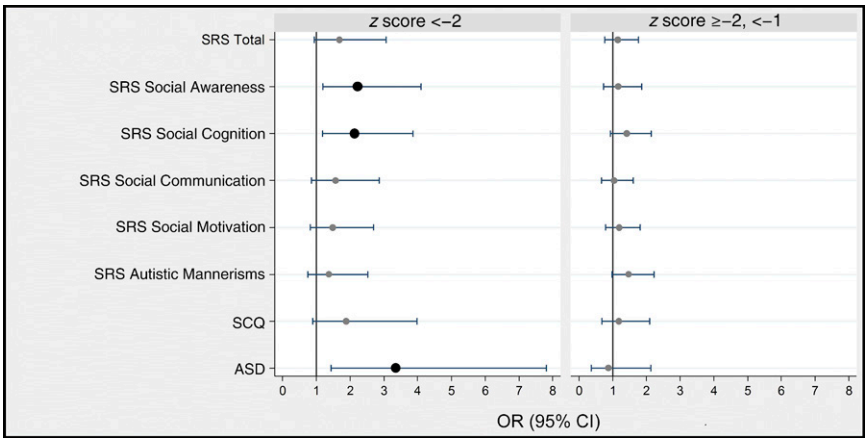

FIGURE 3
Forest plots of ORs and 95% CIs of a T score ≥60 on the SRS subtests, of a positive screening result on the SCQ, and of documented characteristics of ASD on the basis of the ADOS-2 at age 10 years associated with birth weight *z* score category <−2 (on left) and ≥−2, <−1 (on right). ORs are adjusted for racial identity and sex. BW, birth weight.

CSI-4 Identified Behavioral Disorders

According to both parents and teachers, children who were born severely growth restricted screened positive for posttraumatic stress at age 10 years more frequently than their AGA peers (Supplemental Fig 6). Parents, but not teachers, also reported a higher frequency of vocal tics among children who were born severely growth restricted. In contrast, teachers, but not parents, reported higher frequencies of symptoms of specific phobia, obsessions, compulsions, and social phobia among the severely growth restricted than among those who were not growth restricted. The less severely growth restricted children were remarkably similar to their peers who had higher birth weight for gestation.

Other Dysfunctions

Inconsistent or seldom effective communication with familiar partners was more common among severely growth restricted than among

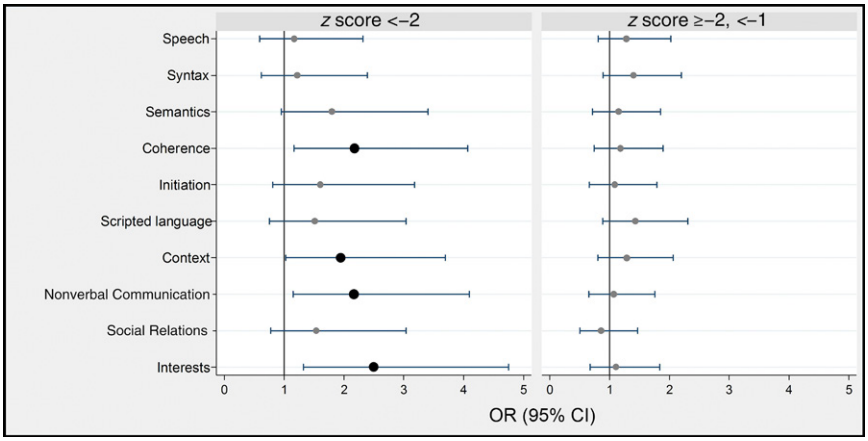

FIGURE 4

Forest plots of ORs and 95% CIs of a *z* score ≤−1 on the CCC-2 subtests at age 10 years associated with birth weight *z* score category <−2 (on left) and ≥−2, <−1 (on right). ORs are adjusted for racial identity and sex. BW, birth weight.

children who were not born with FGR (Supplemental Fig 7). However, less severely growth-restricted children did not have such severe communication limitations. Children who were severely growth restricted at birth were also more likely than others to be strongly right-handed, but they were no more likely to have seizures or a limitation of manual ability or gross motor function.

The more severe the FGR, the higher the proportion of children who had limited quality of life in school functioning. Limited quality of life in social functioning and psychosocial functioning were also more common among children born severely growth restricted but not among those who were born less severely growth restricted.

DISCUSSION

Our main finding is that by and large, the more severe the growth restriction in utero, the lower the scores on multiple neurodevelopmental assessments at age 10 years. Severely growth-restricted children were more likely than their extremely preterm peers to have social awareness impairments and autistic mannerisms (according to the SRS), a rigorously defined ASD, and difficulty with speech coherence, context, nonverbal communication, and interests (according to the CCC-2). These severely growth-restricted children also had diminished social and psychosocial function and quality of life (according to the Pediatric Quality of Life Inventory) compared with their peers who were not growth restricted. Children who were less severely growth restricted at birth were at increased risk of low scores on the OWLS Oral Expression subtest and the DAS-II Working Memory subtest.

Synthesis With Previous Studies

Some of the social and communication deficits we studied were particularly pronounced in children born extremely preterm who had severe FGR, as were some cognitive functioning deficits, but not all. We do not know if FGR at low gestational ages is associated with general deficits across most cognitive domains or with selective deficits in only some domains of brain function.[11,20,21] Our search of PubMed identified no large study of associations between FGR (or being small for gestational age [SGA]) and cognitive and behavioral outcomes in children born before 28 weeks' gestation. However, such associations have been assessed in 3 studies involving children who were born before 30 weeks' gestation. In the first, excluding children who had cerebral palsy and/or sensory impairment, 6-year-old SGA children were more likely to have an IQ <75 than were their AGA peers (35%, 7 of 20 vs 14.6%, 12 of 82).[60] The second included 8-year-olds who were born before 28 weeks' gestation, but only 4 children were SGA. Nonetheless, birth weight *z* score was moderately correlated with IQ.[61] In the third study, SGA children who also had absent or reversed end diastolic blood flow were compared with AGA controls and matched for sex, gestational age at birth, and year of birth. At 5 years to 8 years of age, a full-scale IQ <70 was more common (10 of 34 vs 2 of 34), and the mean verbal IQ was lower in the SGA group.[62]

Our findings are also generally consistent with those of 2 population-based cohorts of children born very preterm (ie, before the 32nd week). In a Dutch cohort of school-aged children who were born very preterm or very low birth weight (<1500 g), SGA children were more likely to have a speech and language abnormality and to receive special education.[63] Similarly, in the Etude Epidémiologique sur les Petits Ages Gestationnels (EPIPAGE) cohort, 5- to 8-year-olds who were SGA were more likely to have minor cognitive difficulties, inattention-hyperactivity symptoms, and school difficulties (OR: 1.74; 95% CI 1.07–3).

The most likely explanation for the observation that girls are more likely than boys to be growth restricted at birth is based on the observation that preterm preeclampsia occurs more commonly among pregnancies with a female fetus than among pregnancies with a male fetus.[64]

FGR and the Brain

Some of the brain structure characteristics of growth-restricted children born preterm might account for some of the dysfunctions evident

at age 10 years in children who were growth restricted at birth,[65–70] although some morphologic correlates might be below current clinical MRI resolution.[71] These brain structure abnormalities might, in turn, be a consequence of epigenetic phenomena that sensitize the brain,[72–75] making it vulnerable to inflammatory phenomena that appear to increase the risk of brain damage in very preterm newborns.[76] Indeed, the risk of brain damage in severely growth-restricted neonates born very preterm appears further heightened by their tendency to have more intense systemic inflammatory responses than their peers who were not growth restricted,[33] perhaps acting in a 2-hit model[77] (in which growth restriction is the first hit, and intermittent or sustained systemic inflammation is the second hit). Likewise, inflammation appears to account for some of the brain abnormalities in rats with FGR.[78]

Growth Restriction Might Be a First Hit Because of Impaired Placentation

In the ELGAN Study, almost two-thirds of all severely growth-restricted infants were born to women who had preeclampsia. Both of these disorders are characterized by impaired placentation[79,80] and deficiencies of growth factors[81,82] apparently involved in the regulation of intravillous or fetomaternal angiogenesis.[83–86] Although the stimulus responsible for altered placental release of the molecules is not known,[87–89] dysregulation of angiogenic-related factors is thought to affect pregnancy either by failing to promote growth[90] or limiting the availability of nutrients.[91] Both mechanisms have the potential to limit brain growth and maturation.[15,92,93]

A paucity of the enzyme heme oxygenase (HO) might also contribute to impaired fetal brain development.[94,95] It helps regulate not only angiogenesis but also vascular tone, inflammation, apoptosis, and oxidation. Deficiencies of HO additionally appear to characterize preeclampsia,[96–100] although not all researchers agree.[101] The deletion of the gene HO-1 in mice leads to inadequate remodeling of spiral arteries and suboptimal placentation followed by intrauterine growth restriction.[102] Consistent findings have been shown in rats.[103]

HO also modulates innate and adaptive immune responses,[104–109] can contribute to the resolution of inflammation,[110–112] and can also reduce oxidative stress.[113,114] Moreover, an HO-1 inducer promotes preconditioning,[115] perhaps thereby protecting the vulnerable brain.[116–119] Consequently, the brains of very preterm children born to women who have severe preeclampsia might be more vulnerable than the brains of their peers who are delivered for spontaneous indications.[120] Such vulnerability might explain the increased risk for cognitive impairment reported among children who were born to mothers affected by preeclampsia (and its correlates).[121–124]

Methodologic Issues

Defining FGR is not as simple as it might seem. This is reflected in the wide variation in terms and methods across studies.[125–127] Not all infants whose weight is near the lower end of the spectrum have had disordered growth. Some will be small in part because of the tendency for children of his or her genetic predisposition to be small at birth.[128] However, the contribution of such tendencies is thought to be small relative to the contributions of phenomena that lead to severe growth restriction.[129] Consequently, customized percentiles based on maternal characteristics are not recommended.[130,131]

Some argue that growth restriction and SGA are not synonymous.[127,132] We use the term FGR in light of the ongoing challenge to discern pathologically from constitutionally small newborns[3,133,134] and because we prefer to avoid the impression that we used a cutoff of the lowest decile (which would define SGA). Indeed, our finding that some children who were relatively but not severely growth restricted at birth had cognitive limitation leads to this inference that growth restriction can be a continuum and not an either/or phenomenon.

Clinical Implications

The cognitive, social, and other behavioral impairments we and others have observed call for efforts to prevent and ameliorate these impairments among children with FGR born extremely preterm. Low-dose aspirin administered in early gestation has therapeutic benefits for some women who are at increased risk of preeclampsia (and its correlates [ie, FGR][135]), and trials are underway to test additional strategies.[135–140] Placental and other stem cells,[141–148] proton-pump inhibitors,[149] low-molecular-weight heparin[150] and other molecules[151–153] might also have therapeutic benefits. Indeed, compelling studies of rodents[154–157] and nonhuman primates[158] support the possibility of a therapeutic benefit from exogenous angiotrophins during gestation.

Interventions aiming to improve maternal diet and its correlates (eg, the mHealth coaching program[159]) would likely be more beneficial than a narrow focus on maternal weight gain.[160–163] Postnatal care plans that were not specifically developed for children with FGR might nevertheless help minimize some of the limitations identified.[164–175]

Strengths and Limitations

The strengths of our study are the large number of infants, the enrollment of infants based on gestational age and not birth weight,[176] the outcome assessments by

individuals who did not know which study participants had a history of FGR, and the large number of instruments used to assess cognitive and other functions at age 10 years. To avoid the error of inappropriately drawing the inference that FGR has no influence, we did not adjust for multiple comparisons; it is possible that this increased type I error.[177] However, we found 5 times as many statistically significant ORs than was expected by chance alone; this prompts us to infer that our findings are unlikely to reflect random phenomena. As with all observational studies, we are limited in our ability to infer causation from associations; ie, we cannot rule out the possibility that the observed association between FGR and increased risk of neurodevelopmental deficits was explained by alternative unmeasured or measured factors (eg, neonatal morbidities).

CONCLUSIONS

Among children born extremely preterm, those with severe FGR are at increased risk of a wide variety of neurodevelopmental dysfunctions and low achievement scores assessed at age 10 years.

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ABBREVIATIONS

ADI-R: Autism Diagnostic Interview–Revised
ADOS-2: Autism Diagnostic Observation Schedule, Second Edition
AGA: appropriate for gestational age
ASD: autism spectrum disorder
CCC-2: Children's Communication Checklist-2
CI: confidence interval
CSI-4: Child Symptom Inventory-4
DAS-II: Differential Ability Scales–II
ELGAN: Extremely Low Gestational Age Newborns
FGR: fetal growth restriction
HO: heme oxygenase
NEPSY-II: Developmental Neuropsychological Assessment-II
OR: odds ratio
OWLS: Oral and Written Language Scales
SCQ: Social Communication Questionnaire
SGA: small for gestational age
SRS: Social Responsiveness Scale
WIAT-III: Wechsler Individual Achievement Test-III

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