ORIGINAL ARTICLE

Are there critical periods for brain growth in children born preterm?

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Background: Children born very preterm who attend mainstream schools have a high prevalence of minor motor, behavioural, and learning disorders. These appear to be associated with reduced postnatal growth, particularly of the head. It is unclear when this poor growth occurs and whether growth restriction during different periods has different effects on later function.
Objective: To identify periods during early development, in children born preterm, when impaired head growth may influence minor motor and cognitive function.
Population: A geographically defined cohort of 194 infants born in Merseyside during 1980–81 and weighing less than 1500 g.
Methods: Measurements of head circumference (occipitofrontal circumference (OFC)) were available at birth, hospital discharge, 4 years, and 15 years of age. Assessments of intelligence (intelligence quotient (IQ)) and minor motor impairment (test of motor impairment (TOMI)) were made at 8 years of age. Clinical, social, and demographic variables were obtained from the clinical record and maternal interviews.
Results: IQ correlated significantly with OFC at 4 and 15 years of age after correction for growth restriction at birth (intrauterine growth restriction (IUGR)) and social class. TOMI scores correlated significantly with OFC at all four times, but especially with OFC at discharge and with change in OFC between birth and discharge. They were not affected by correction for social class or IUGR.
Conclusion: Although both IQ and minor motor impairments correlate strongly with each other at school age in very low birthweight children, the factors determining them and their timing of operation are different. Interventions designed to improve IQ in this population would need to reduce IUGR and improve later childhood growth. Those aimed to improve motor ability need to be targeted more at brain protection during the neonatal period.

Very preterm infants show a range of major neurodevelopmental sequelae in 10–15% during infancy, and 30–40% have minor motor, behavioural, and learning disorders at school age.[1] Although imaging studies have indicated white matter damage in the perinatal period as the likely cause of most major neuromotor problems, the origin of the later learning, motor, and behavioural difficulties is not so clear. Follow up studies of children in mainstream schools have shown an association between height and head circumference and intelligence, but it is not known if it is causal.[2] As most of these children were not growth restricted at birth, the poor growth must have been postnatal, either in the neonatal period or during infancy or early childhood. Postnatal growth could be affected by antenatal factors, perinatal illness, drugs, or nutrition, or subsequent childhood illness or nutrition.[3–5] It may be that only poor growth during certain critical periods has an effect on later cognitive and behavioural development. Knowledge of the timing and factors associated with postnatal growth failure would allow further improvements in later outcomes in this vulnerable group of children.

The late intrauterine and early postnatal periods in human development are characterised by high growth velocity, particularly of the brain.[6] In older children, the size of the brain is broadly related to cognitive function, as is height.[2 7 8 9] The head circumference correlates well with brain volume and so can be used as a measure of brain growth.[10] The size of the head at birth is poorly related to later intelligence, suggesting that it is postnatal rather than antenatal growth failure that leads to a smaller head later.[11] Others have shown in preterm infants that it is the course of postnatal growth rather than appropriateness of weight for gestational age that determines later neurodevelopmental outcome, although they have not identified which postnatal period.[7 12 13] Although the timing of impaired growth in the postnatal period has not been examined in detail in preterm children, it has in an unselected group of normal 9 year olds.[14] Growth rates both in infancy and early childhood were related to intelligence quotient (IQ), but the effect was greater in childhood.

The aim of this study was to identify periods during early development, in children born preterm, when impaired head growth may influence minor motor and cognitive function.

POPULATION AND METHODS

A cohort study of a population of very low birthweight infants was carried out. The cohort was obtained from birth notifications and comprised all infants of birth weight 1500 g or less born in 1980 and 1981, to mothers whose place of residence at the time of birth was the county of Merseyside. The obstetric and neonatal records were abstracted for general and clinical details of mother and child. The children were examined at age 4 years and again at age 8 years to determine the prevalence of clinical disability. They were reassessed aged 15 years when at secondary school. Details of these assessments have been published.[15–20] For the purposes of this study, by measuring the head circumference in these children at birth, near term at discharge, and at 4 and 15

Abbreviations: IQ, intelligence quotient; IUGR, intrauterine growth restriction; OFC, occipitofrontal circumference; TOMI, test of motor impairment, Henderson revision

years of age, four periods of growth could be examined: antenatal, immediate postnatal, infancy, and early childhood. The occipitofrontal circumference (OFC) was extracted from the clinical record for each time point and converted into a standard deviation score (z score) taking in to account the sex and age at the time of measurement. The standards used for these computations were from those published by the Child Growth Foundation from 1990.[21] The z score at birth (zOFCB) gave an indication of antenatal growth restriction. Standardised measurements at discharge from hospital (zOFCD) and 4 years (zOFC4) and 15 years (zOFC15) of age indicated growth restriction at those times. Changes in z score between the four measurement times indicated whether growth was normal or impaired in the three periods between measurements (dzOFC1, dzOFC2, dzOFC3).

General, social, and clinical details were available at 8 years of age together with the results of a test of cognitive ability (Wechsler intelligence scales for children)[22] and minor motor impairment (test of motor impairment, Henderson revision (TOMI)).[23] It should be noted that the latter is an impairment scale, higher scores indicating poorer rather than better performance in eight simple motor tasks.

The z score for birth weight allowing for gestation at birth and sex was also computed, again using weight standards from the Child growth Foundation.

The protocols for the original studies were approved by the local research ethics committee.

RESULTS

There were 40 321 live births in Merseyside in 1980–81; 399 were very low birth weight of whom 229 survived to age 15 years. Ten survivors refused assessment, were abroad, or could not be traced. Twenty five had cerebral palsy or major visual or hearing deficits, and were excluded further from the study. This left 194 subjects available for the study.

The cohort comprised 107 (55%) male subjects and included 40 (21%) twins. The mean (SD) birth weight was 1230 (195) g and mean gestational age 30.8 (2.8) weeks. Median (interquartile range) birth weight ratio was 0.79 (0.65–0.97). They received respiratory support for a median of 0 (0–2) days and added oxygen for a median of 2 (0–6) days. Eleven (6%) developed a pneumothorax, 49 (25%) a clinically significant persistent ductus arteriosus, seven (4%) a positive blood culture, eight (4%) necrotising enterocolitis, and 29 (15%) cranial ultrasound evidence of periventricular haemorrhage of which four (2%) were parenchymal in extent. Not all infants in the cohort would have had cranial ultrasound scans in 1980–81, so the true incidence of periventricular lesions may have been higher. Full oral feeding was achieved at a median of 3 (1–8) days after birth. Table 1 shows mean (SD) head circumferences for boys and girls.

Mean (SD) head circumferences expressed as z scores and standardised for sex, gestation, or age were −1.20 (1.69) at birth, −0.90 (1.32) at discharge, −0.19 (1.37) at 4 years, and 0.21 (1.47) at 15 years. The median change in z scores between birth and discharge was 0.31 (1.07), between discharge and 4 years 0.59 (1.27), and between 4 and 15 years 0.41 (1.02). At 8 years, the mean full IQ was 93.6 (13.6), verbal IQ 93.6 (14.3), and performance IQ 93.7 (14.0). The median TOMI score was 3.0 (1–5). TOMI scores correlated significantly with IQ scores (IQ full, −0.38, $p<0.001$; IQ verbal, −0.28, $p<0.001$; IQ performance, −0.41, $p<0.001$). Table 2 shows correlations between the head circumference variables and IQ and TOMI scores.

Table 1 Head circumferences (cm) at birth, discharge from hospital, and 4 and 15 years of age, by sex

	OFCB	OFCD	OFC4	OFC15
Male	27.8 (1.9)	33.3 (1.2)	50.6 (1.8)	55.1 (2.1)
Female	27.2 (2.0)	32.5 (1.1)	49.6 (1.7)	54.4 (1.6)

Values are mean (SD).
OFCB, Occipitofrontal circumference at birth; OFCD, OFC at discharge; OFC4, OFC at 4 years of age; OFC15, OFC at 15 years of age.

Table 2 Correlations between occipitofrontal circumference z scores (zOFC) at four different ages, and change in zOFC between those ages, and intelligence quotient (IQ) and test of motor impairment (TOMI) scores

	IQ full	IQ verbal	IQ perform	TOMI
zOFCB	0.20*	0.17*	0.20*	−0.19*
zOFCD	0.12	0.10	0.12	−0.29**
zOFC4	0.20*	0.16*	0.19*	−0.21**
zOFC15	0.24**	0.25**	0.18*	−0.16*
dzOFC1	−0.04	−0.03	−0.04	−0.21*
dzOFC2	−0.03	−0.02	−0.04	0.01
dzOFC3	0.07	0.14	−0.02	0.11

Significant correlation indicated: *$p<0.05$, **$p<0.01$.
OFCB, Occipitofrontal circumference at birth; OFCD, OFC at discharge; OFC4, OFC at 4 years of age; OFC15, OFC at 15 years of age; dzOFC1, change in OFC between birth and discharge; dzOFC2, change in OFC between discharge and 4 years; dzOFC3, change in OFC between 4 and 15 years.

IQ correlated significantly with zOFCB, zOFC4 and zOFC15, but not with zOFCD. On the other hand, TOMI scores correlated significantly with OFC at all four times, but most strongly at the time of discharge. Only the change in OFC between birth and discharge (dzOFC1) correlated significantly with the TOMI score. IQ scores correlated significantly with social class (Registrar General's classification) (−0.39 full, −0.41 verbal, −0.28 performance, $p<0.001$), but TOMI scores did not (0.04, $p = 0.59$). After correction for social class, the correlations between OFC variables and IQ and TOMI scores remain significant. Because the cohort had been selected by birth weight rather than gestational age, an increasing proportion were growth restricted with higher gestational age. Correcting for birth weight using z score for birth weight (adjusted for gestation and sex) in addition to social class showed that zOFC4 and zOFC15 remained significantly correlated with IQ, and that TOMI scores remained significantly correlated with OFC at all four times and with change in OFC between birth and discharge (dzOFC1) (table 3).

Table 3 Correlations between occipitofrontal circumference z scores (zOFC) at four different ages, and change in zOFC between those ages, and intelligence quotient (IQ) and test of motor impairment (TOMI) scores, corrected for z score birth weight and social class

	IQ full	IQ verbal	IQ perform	TOMI
zOFCB	0.15	0.14	0.14	−0.23**
zOFCD	0.08	0.09	0.06	−0.34***
zOFC4	0.17*	0.14	0.16*	−0.21**
zOFC15	0.18*	0.20*	0.12	−0.15*
dzOFC1	0.04	0.04	0.02	−0.24*
dzOFC2	0.06	0.07	0.04	−0.01
dzOFC3	0.03	0.10	−0.05	0.11

Significant correlation indicated: *$p<0.05$, **$p<0.01$, ***$p<0.001$.
OFCB, Occipitofrontal circumference at birth; OFCD, OFC at discharge; OFC4, OFC at 4 years of age; OFC15, OFC at 15 years of age; dzOFC1, change in OFC between birth and discharge; dzOFC2, change in OFC between discharge and 4 years; dzOFC3, change in OFC between 4 and 15 years.

dzOFC1 correlated significantly with grade of intraventricular haemorrhage on cranial ultrasound scan (−0.22, p<0.01), duration of respiratory support (−0.42, p<0.01), and duration of oxygen therapy (−0.27, p = 0.001).

DISCUSSION

In this study of head growth in infancy and childhood, IQ scores at 8 years of age were significantly related to head size at birth and 4 and 15 years of age. In a similar study of term children, IQ at 9 years was significantly related to head size at 9 months and 9 years and growth between birth and 9 months and 9 months and 9 years, but not to OFC at birth. This suggested that postnatal growth was more important as a determinant of IQ than intrauterine growth. Unlike this mainly preterm study cohort, the term cohort would not have contained many children with significant intrauterine growth restriction (IUGR). Correcting for IUGR using z score birth weight showed that IQ correlated significantly with OFC at 4 and 15 years (r = 0.17, 0.18), confirming that, in the absence of significant IUGR, later growth of the head is a more important determinant of IQ than immediate postnatal growth. However, the similar correlation between IQ and OFC at birth (r = 0.15, p = 0.07) suggests that antenatal head growth is also a determinant of later IQ. Further correction for social class did not alter this relation even though social class correlated with IQ at 8 years. This suggests that, in this cohort, the main effect of social class on IQ is mediated through IUGR, with which it is closely associated. A further point of note is that, although this study cohort consists of very low birth weight infants, it does not include the sickest, who died, nor those who survived with major neurodevelopmental sequelae. There are very few survivors of 26 weeks and below, which makes comparisons with a present day cohort difficult.

The findings with the TOMI at 8 years followed a different pattern. There were significant negative correlations between the TOMI scores and OFC at birth, discharge, 4 years, and 15 years. The strongest correlation was with OFC at discharge, and with the change in OFC between birth and discharge, suggesting that poor growth in the immediate period after preterm birth was most closely responsible for poor TOMI scores. Correction for birthweight ratio and social class did not alter these correlations, indicating that factors such as illness and brain injury in the perinatal period may be more important than social and nutritional factors in causing minor motor impairments in these children. Antenatal clinical factors that could affect postnatal growth but allow a normal size at birth include chorioamnionitis or other causes of perinatal brain injury. Chorioamnionitis has been shown to be linked to both periventricular leucomalacia and later cerebral palsy,[24] but no data on this variable were available for this cohort. White matter damage appears to be strongly linked to poor later growth of the brain in terms of both white and grey matter.[25] Preterm infants in the neonatal period suffer frequent illnesses related to systemic immaturity. Several authors have associated illness severity at this time with later poor growth and outcomes, showing it to be a stronger factor than gestational age.[26 27] Drug treatments in the neonatal period such as corticosteroids have a pronounced effect on growth and have been associated with subsequent cerebral palsy and lower IQ,[28] although were rarely if ever used in this cohort. Low nutritional intakes are common in preterm infants after birth, and cumulative deficits can account for a substantial part of postnatal growth failure,[4] although in this cohort the median time to full feed was only three days. Randomised controlled trials of high energy feeds at this time have shown improvements in growth, and, in another non-randomised historically controlled study, improved cognitive outcomes.[29 30] In infancy, many born very preterm may have chronic lung disease, which is also associated with poor early growth and poorer cognitive outcomes later, either through lower energy intakes or higher requirements.[31] In early childhood, atopic and infective respiratory diseases and social and environmental factors may combine to impair growth.

In this study, factors such as grade of intraventricular haemorrhage on cranial ultrasound scan, duration of respiratory support, and duration of added inspired oxygen all correlated highly significantly with growth between birth and discharge. Magnetic resonance imaging studies have shown that signs of white matter damage are associated with poorer later myelination[32] and also reduced brain volume.[33] Magnetic resonance imaging evidence for white matter damage has also been associated with poorer Movement ABC scores (similar to TOMI) in 7 year olds born preterm.[34]

Limitations of this study include the age of the data sets, the quality of the data, the use of birth weight rather than gestation to define the cohort, and the use of OFC at 15 years rather than 8 years when IQ was determined. If data from a more recent cohort had been available, the proportion of extremely preterm survivors may have been greater, probably increasing the differences seen. As the cohort was initially geographically selected, it contained data from several different hospitals of varying quality and completeness. Only variables that were reasonably robust were used in this analysis. The use of birth weight to define the cohort meant that infants growth restricted at birth were over-represented and had to be corrected for by using the birth weight ratio. The OFC had not been measured at 8 years when the cognitive and motor outcomes were determined, and OFC at 15 years had to be substituted. It is likely that most growth would have occurred by 8 years anyway, and that OFC at 8 and 15 years would have been similar.

In conclusion, it would seem that, although IQ and minor motor impairments correlate strongly at school age in very low birthweight children, the factors determining them and the timing of their operation are different. Whereas interventions designed to improve IQ in very low birthweight children would need to reduce IUGR and improve later childhood growth, interventions to improve motor ability would need to be targeted at brain protection during the neonatal period.

What is already known on this topic

- Preterm infants without major neurodevelopmental sequelae nonetheless have a high incidence of behavioural, cognitive, and minor motor deficits at school age
- Head circumference in childhood correlates significantly with these problems; smaller head circumferences are related to postnatal growth failure as well as intrauterine growth restriction

What this study adds

- The timing of poor head growth differs depending on whether motor or cognitive deficits are considered
- This may imply different aetiologies and the need for different preventive strategies in the preterm

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