一、 請參考以下版面，寫出：(20 分)
1. 期刊名稱(3 分)； 2. 研究題目(3 分)； 3. 作者及通訊作者(6 分)
4. 以 APA 參考書目的格式寫出本篇期刊 (2011 年出版, 53 卷，第 35-39 頁) (8 分)

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Neurodevelopmental outcome in preterm infants

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二、 請看完本試卷之研究內容（第 1～4 頁），以中文簡要寫出下列各段落之重點：(50 分)
1. 前言(10 分)； 2. 結果(10 分)； 3. 討論與結論(20 分)； 4. 你對本篇研究的評論(10 分)

三、 請協助作者以英文寫出本篇的摘要，分別包含：(1)Aim, (2)Method, (3)Results, 與(4)Discussion 四部分，每部分以 1 至 5 句爲原則。 (30 分)

In recent decades, major advances have been made in neonatal intensive care. Survival rates of preterm born infants have improved considerably. Unfortunately, the prevalence of developmental disabilities in preterm survivors is still high.1 Although the rates of major handicaps have remained relatively constant over the past decade, the prevalence of milder dysfunctions seems to be increasing. Cognitive, behavioural, and mild motor problems without major motor deficits are now the most dominant neurodevelopmental sequelae in children born preterm.2,3 These include learning problems, borderline to low IQ scores, attention deficit, and specific neuropsychological deficits affecting visuomotor integration and executive function.4 They occur in more than 50% of children born preterm with very low birthweight (below 1500g) and are often not in isolation.3 The pathogenesis of these so-called 'high prevalence, low severity' impairments in children born very preterm is still largely unclear, although a lower gestational age is a prominent factor.3 As yet, it is unclear whether the prevalence of impairments and low developmental scores are also related to decreasing gestational age when the infant is born very preterm (i.e. before 32wks' gestation).

Models of pathogenesis include changes related to developmental disruptions and brain injury.5 A lower gestational age, in particular below 28 weeks, is associated with brain lesions such as higher grades of germinal matrix and intraventricular haemorrhages, periventricular haemorrhagic infarction, and periventricular leukomalacia.5 Developmental disruptions that are common in preterm infants include diffuse white matter injury accompanied by neuronal and axonal disruption.5 In the developing preterm brain, maturation of oligodendroglia precursors and genetically programmed changes in cortical connectivity are particularly vulnerable to injury.6

The distinction between developmental disruptions, involving nearly all infants, and overt brain injury, involving a few infants, may be hinted at based on the distribution of scores and disabilities among infants born very preterm.

We were able to provide such data on cognition and motor function in a group of children, born very preterm and assessed between 6 and 12 years. The aim was to determine the prevalence of cognitive and motor impairments in children born very preterm. We were particularly interested in the distribution of cognitive and motor scores, and the influence of decreasing gestational age and brain lesions thereon.

(背面仍有題目,請繼續作答)

Method

Participants

We selected 106 children, born at a gestational age below 32 weeks between January 1995 and December 2002, and admitted to the Neonatal Intensive Care Unit of the Beatrix Children's Hospital in Groningen, the Netherlands. They were participating in an ongoing study on the functional outcome of very preterm children at risk for neurodevelopmental impairments. Risk factors of interest were periventricular haemorrhagic infarction, late-onset sepsis, intrauterine growth restriction, and bronchopulmonary dysplasia.[7,8] Preterm children with an uneventful clinical course in the neonatal period also were part of the study group. We excluded children who had cerebral palsy (CP) with functional limitations (Gross Motor Function Classification System [GMFCS] level 2 or more), determined at school age. Of the selected children, nine (8%) were classified as having CP in GMFCS level 1. The perinatal and neonatal characteristics of the included children are presented in Table I. Compared with representative samples of very preterm children admitted to third-level neonatal intensive care units in the 1990s, our study group had a slightly lower gestational age (28.6wk compared with 29.2–29.7wk) and birthweight (1043g compared with 1250–1283g), with more children with intrauterine growth restriction (32% compared with 12–23%) and a higher prevalence of late-onset sepsis (44% compared with 20–28%).[9,10]

The children were invited prospectively to participate in an extension of the routine follow-up programme at the age of 6 to 12 years. Parents gave their written informed consent to participate in the follow-up programme. The study was approved by the Medical Ethical Committee of the University Medical Center Groningen.

We tested the children's cognition and motor outcome. We assessed total, verbal, and performance IQ using a shortened version of the Wechsler Intelligence Scale for Children, third edition, Dutch version.[11] To assess the children's motor outcome we administered the Movement Assessment Battery for Children (Movement ABC), a standardized test of motor skills for children.[12] This test yields a total motor performance score that is based on subscores for manual dexterity (fine motor skills), ball skills, and static and dynamic balance (coordination). The higher the score, the poorer the performance. The tasks composing the Movement ABC are representative of the motor skills that are required of children attending elementary school and are adapted to the child's age.

Statistical analysis

To analyse the data we used SPSS for Windows version 16.0 (SPSS, Chicago, IL, USA). We classified the IQs as normal (IQ≥85), borderline (IQ 70–85), and abnormal (IQ<70). We used the centiles on the standardization samples of the Movement ABC to classify raw scores into normal (>15th centile), borderline (5–15th centiles), and abnormal (<5th centile). Next we displayed the distribution of total, performance, and verbal IQ, and z-scores of the Movement ABC graphically by histograms and Q–Q plots. Visual inspections of the histograms and Q–Q plots determined which outcome measures were normally distributed, which were also statistically tested using the Kolmogorov–Smirnov test.[13] We determined the correlation between outcome measures (IQ and Movement ABC scores), gestational age, and age of testing with Spearman's rank correlation coefficient. Finally, we used the Mann–Whitney *U* test to determine whether outcome measures differed between children with and without cerebral lesions, between children with and without CP, and between children born at 24 to 25 weeks compared with 26 weeks or more. A p value <0.05 was considered statistically significant.

Table I. Perinatal and neonatal characteristics

Males/females	63/43
Gestational age (wk)	28.6 (24.0–31.6)
Birthweight (g)	1043 (480–2275)
Socioeconomic status[a]	
Below average	26 (25)
Average	51 (50)
Above average	26 (25)
Neonatal complications	
IUGR (<10th centile)	34 (32)
Apgar at 5min	8 (7–9)
Ventilatory support (IPPV or HFO)	67 (63)
Cerebral pathology	
GMH–IVH grade I or II	22 (21)
GMH–IVH grade III or PVHI	10 (9)
Periventricular echodensities >1wk	59 (56)
Cystic PVL	–
Late-onset morbidity	
Late-onset sepsis	47 (44)
Bronchopulmonary dysplasia	19 (18)

Data are median (minimum–maximum) or numbers (percentage). [a]According to the standard Dutch profession classification.[24] IUGR, intrauterine growth restriction; IPPV, intermittent positive pressure ventilation; HFO, high-frequency oscillation; GMH–IVH, germinal matrix haemorrhage–intraventricular haemorrhage; PVHI, periventricular haemorrhagic infarction; PVL, periventricular leukomalacia.

Table II. Intelligence and motor skills of the preterm children, classified into normal, borderline, and abnormal

	Normal	Borderline	Abnormal
Intelligence[a]	77 (73)	25 (24)	4 (4)
Total IQ (n=106)	82 (77)	19 (18)	5 (5)
Verbal IQ (n=106)	72 (68)	26 (25)	8 (8)
Performance IQ (n=106)	40 (40)	25 (25)	36 (36)
Motor skills[b]			
M-ABC total score (n=101)	40 (40)	25 (25)	36 (36)
M-ABC static and dynamic balance (n=102)	58 (57)	14 (14)	30 (29)
M-ABC manual dexterity (n=102)	44 (43)	33 (32)	25 (25)
M-ABC, ball skills (n=101)	63 (62)	24 (24)	14 (14)

Data are numbers (percentage). [a]Normal, IQ>85; borderline, IQ 70–85; abnormal, IQ<70. [b]Normal, >15th centile; borderline, 5–15th centiles; abnormal, <5th centile.

Results

The children were tested at an age of 8 years 8 months (median, range 6y 0mo to 12y 10mo). The number and percentages of children classified as normal, borderline and abnormal, regarding IQ and Movement ABC scores are presented in Table II.

The IQs were normally distributed (Fig. 1a–c), but shifted to the left (Kolmogorov–Smirnov test not significant: p=0.816 for total IQ; p=0.528 for verbal IQ; p=0.290 for performance IQ). Mean total IQ was 91 (SD 12). This means that the mean total IQ was 0.60 SD below the norm. Mean performance IQ was 89 (SD 13), 0.73 SD below the norm. Verbal IQ was 93 (SD 15), 0.47 SD below the norm.

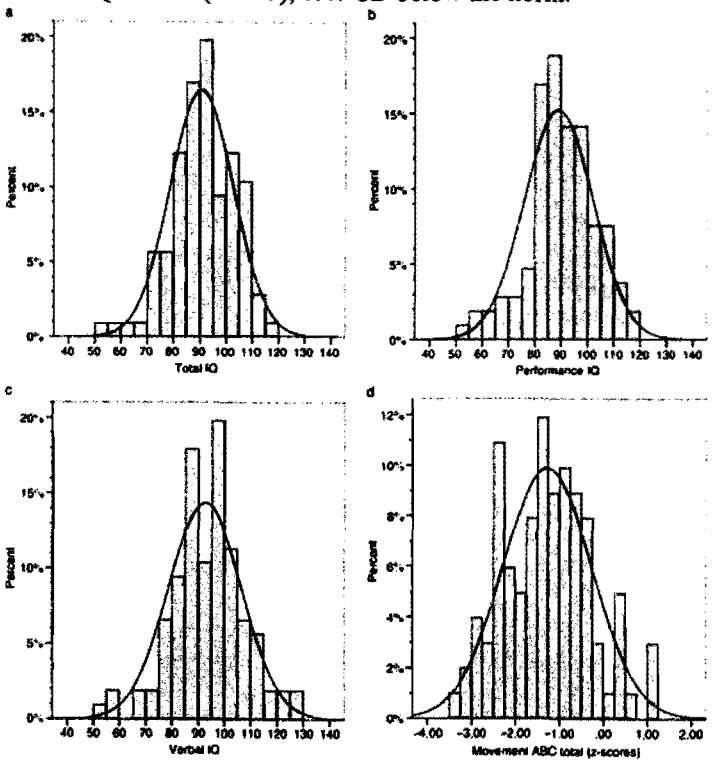

Figure 1. Distribution of (a) total IQ, (b) performance IQ, (c) verbal IQ, and (d) z-scores of total Movement Assessment Battery for Children scores in 106 very preterm children.

IQ scores did not correlate with gestational age (Spearman's *rho*=0.082, 95% confidence interval [CI] −0.111 to 0.267, p=0.406 for total IQ; *rho*=0.123, 95% CI −0.069 to 0.306, p=0.211 for verbal IQ; *rho*=−0.006, 95% CI −0.247 to 0.132, p=0.955 for performance IQ). Total IQ of the children born at 24 to 25 weeks' gestation (n=5) had a median of 83 (range 71–96), verbal IQ 78 (68–98), and performance IQ 83 (75–93). Compared with children born at 26 weeks or more, total IQ and verbal IQ were lower, but the difference just failed to reach significance (p=0.067 and p=0.093 respectively).

Total Movement ABC scores were normal in a minority of the children (Table II). The z-scores of the total Movement ABC scores in the group were again normally distributed (Fig. 1d), with a mean z-score −1.27 below the norm scores (SD of the mean 1.01; Kolmogorov–Smirnov test p=0.833). Again, z-scores of the Movement ABC did not correlate with gestational age (*rho*=0.126, 95% CI −0.071 to 0.313, p=0.210). The same was found for the scores on the various domains of the Movement ABC (*rho*=−0.157, 95% CI −0.341 to 0.038, p=0.115 for static and dynamic balance; *rho*=−0.082, 95% CI −0.273 to 0.115, p=0.412 for ball skills; *rho*=−0.076, 95% CI −0.266 to 0.120, p=0.450 for manual dexterity). Movement ABC z-scores of the children born at 24–25 weeks had a median of −1.28 (range −2.43 to −0.88), which was not different from the z-scores of those born at 26 weeks or more (p=0.486).

The children with cerebral lesions (grade III germinal matrix haemorrhage–intraventricular haemorrhage and periventricular haemorrhagic infarction) had similar scores to those without cerebral lesions on total IQ and the Movement ABC (Mann–Whitney U test, p=0.140 and p=0.122, respectively), and the various subdomains of cognitive (p=0.091 for verbal IQ and p=0.346 for performance IQ) and motor functioning (p=0.444 for static and dynamic balance, p=0.255 for ball skills, and p=0.312 for manual dexterity). For the nine children with CP, total IQ was 88 (range 73–93), verbal IQ 85 (75–100), and performance IQ was 83 (68–95). This was not different from the IQ scores of the children without CP, although the children with CP tended to have a lower total IQ and performance IQ (Mann–Whitney U test, p=0.071 for total IQ, p=0.218 for verbal IQ, and p=0.065 for performance IQ). We obtained Movement ABC z-scores in only five of the nine children with CP. We do not report those data, as too much information is missing.

The age of testing correlated with total IQ and performance IQ. The higher the age of testing, the lower the IQ (for total IQ, Spearman's *rho*=−0.206, 95% CI −0.381 to −0.016, p=0.034; for performance IQ, *rho*=−0.200, 95% CI −0.376 to −0.010, p=0.040). Age of testing did not correlate with verbal IQ (p=0.150) and Movement ABC scores (p=0.365).

Discussion

Our study indicates that the 'normal' distribution curve for cognition and motor outcome at school age is shifted to the left in our sample of children born very preterm, with an effect size of approximately 0.60 SD for IQ (nine IQ points) and 1.27 SD for motor outcome. We could not demonstrate that children with overt brain lesions performed worse than those without lesions, on motor and intelligence tests. In this small study we were also not able to identify an effect of decreasing gestational age, which may have been because the number of children born at 24

and 25 weeks was very small. Nevertheless, our data are in line with previous studies indicating that so-called 'high prevalence, low severity' impairments are common in children born before 32 weeks gestational age.[2,7,14,15] This suggests that complex destructive and developmental mechanisms may be the basis of these impairments in preterm infants, rather than overt brain injury such as is seen in germinal matrix haemorrhage, periventricular haemorrhagic infarction, and periventricular leukomalacia. The exact mechanism, however, remains to be elucidated.

One of the proposed models of pathogenesis includes white matter damage. Global white matter damage revealed by ultrasound and magnetic resonance imaging (MRI) is quite common in children born preterm, and relations with motor function have been found in the short term.[16,17] However, until now, clear associations of cognition with pathological changes on neuroimaging have not been demonstrated beyond doubt.[18] The same is true for mild motor impairments in the long term. New imaging techniques may provide insights into microstructural changes in the developing preterm brain by studying diffusion properties of water among different brain regions.

White matter damage may occur as the result of systemic derangements of the circulation, but also of increased inflammatory cytokines and activation of microglia, for example in the event of bacterial infections, hyperoxia, and surgery.[5,19] Oligodendroglia precursors in particular are highly vulnerable to these events.

In addition to global white matter changes, other aspects of brain development, such as decreased total brain volume and a lesser degree of cortical folding, may be involved in the pathogenesis of these 'high prevalence, low severity' impairments among preterm infants.[6] Axonal and neuronal injury frequently accompanies white matter injury, leading to decreased volumes of the corpus callosum, thalamus, basal ganglia, and cerebral cortex.[5,6] This may be intermediated by the subplate and the subventricular zone, which are brain structures that both reach their maximum size between 24 and 32 weeks' gestation.[5] The subplate neuron is located in the subplate, with its efferent motor connections running through the white matter in the preterm period. It plays a key role in both cortical and thalamic development. Between 24 and 32 weeks, thalamocortical afferents accumulate within the superficial subplate and grow into the cortical plate developing synapses.[20] After 32 weeks, the resolution of the subplate and growth of cortico-cortical fibres into the cortical plate occur simultaneously with gyration.[20] It has been speculated that subplate neurons are selectively vulnerable to hypoxia–ischemia, because they contain excitatory amino-acid receptors.[5] The subventricular zone has only recently been recognized in the human brain as a potentially important developmental structure for cortical development. It is neurogenic up to 27 weeks of gestation, and gives rise to interneurons of the expanded upper cortical layers.[5] Although the exact pathogenetic mechanisms remain to be elucidated, disruptions due to very preterm birth in the subplate and subventricular zone may lead to altered thalamic and cortical development.

A final potential pathogenetic mechanism is cerebellar injury.[21] The cerebellum grows rapidly during the last trimester of pregnancy, until a few weeks post-term. Particularly in very preterm children, pathological changes of the cerebellum are increasingly recognized.[22] Furthermore, the role of the cerebellum in motor, cognitive, and behavioural development has become increasingly recognized.[23]

The strength of our study is that we included preterm children with and without brain lesions, who did not develop severe CP. We also recognize several limitations. Firstly, the sample size of our cohort was small. Secondly, this was a single-centre study, which raises the question of how far the results can be generalized to the broader population of children born preterm. Thirdly, neuroimaging was confined to brain ultrasound scans. It might be that using MRI would have revealed more subtle lesions. Nevertheless, clear associations of motor skills and cognition with pathological changes on MRI have not been demonstrated previously. Perhaps more sophisticated MRI techniques are required to elucidate the underlying pathogenetic mechanisms.

Conclusion

Our data indicate that the shift of the 'normal' distribution curve for cognition and motor outcome to the left in this sample of very preterm children is not clearly associated with overt brain injury: rather, it is based on developmental disruptions specific in preterm brain maturation, affecting the cerebral white matter, cortex, cerebellum, and thalamus. Note that our sample is selective and that the findings cannot be generalized to all very preterm infants. A better understanding of underlying mechanisms is needed to develop optimal ways of intervention.