Longitudinal study of very low birth weight infants until 9 years of age; attention deficit hyperactivity and autistic features are correlated with their cognitive functions

Masayuki Ochiai [a,b,*], Masako Ichiyama [a,b], Mariko Iwayama [a,b], Yasuanri Sakai [a], Keiko Yoshida [c], Toshiro Hara [a,b]

[a] Comprehensive Maternity and Perinatal Care Center, Kyushu University Hospital, Fukuoka, Japan
[b] Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[c] Department of Child Psychiatry, Kyushu University Hospital, Fukuoka, Japan

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ABSTRACT

Background: Increasing attention has been given to neuro-developmental problems of very low birth weight infants (VLBWIs) at school age. However, it remains unknown whether their neuro-cognitive function and psychiatric symptoms are mutually associated.

Aim: The aim of this study was to investigate the characteristics of neuro-cognitive functions in VLBWIs and their relationship with psychiatric symptoms.

Methods: A total of 160 VLBWIs who were born at our institute between 2001 and 2005 were recruited consecutively and followed up until nine years of age. The developmental profiles were obtained from 77 children (45 males and 32 females) at six to nine years of age using the ADHD Rating Scale—Fourth edition (ADHD-RS), Autism Screening Questionnaire—Japanese version (ASQ-J) and the Wechsler Intelligence Scale for Children—Third edition (WISC-III).

Results: The full-scale intelligence quotient did not significantly differ between the male and female VLBWIs (median: 91 vs. 99, p = 0.17). The males had higher total scores (median: 13 vs. 4, p < 0.01) and higher scores on the subscales of Inattention (8 vs. 2, p < 0.01) and Hyperactivity–Impulsivity (5 vs. 1, p < 0.01) of the ADHD-RS compared with the females. The Verbal Comprehension Index (VCI) of the WISC-III was inversely correlated with the total scores of the ASQ-J for all VLBWIs (n = 77, rc: −0.32, 95% CI: −0.19 to −0.01, p = 0.04). We also observed that the Freedom from Distractibility Index (FDI) of the WISC-III was significantly correlated with the Inattentive scores of the ADHD-RS (n = 45, rc: −0.18, 95% CI: −0.35 to −0.02, p = 0.03) in male, but not female VLBWIs.

Conclusions: We herein report that the VCI and FDI of the WISC-III were correlated with the autism spectrum disorder and attention deficit hyperactivity disorder symptoms, respectively, in male VLBWIs.

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1. Introduction

In the last few decades, advances in perinatal medicine have contributed to remarkable improvements in the survival rates and prognoses of very low birth weight infants (VLBWIs), a group of preterm infants weighing less than 1500 g at birth[1,2]. Recent reports showed that 89% of preterm infants delivered at 24 weeks of gestation were safely discharged from perinatal care centers in Japan [3,4]. A prospective registration and follow-up study of VLBWI was initiated in the tertiary level III neonatal intensive care units (NICU) in Japan, which comprised the major part of the NICU-network database [5]. Physical growth, complications, medications and neuro-cognitive development were monitored for all the VLBWIs up to nine years of age [6].The cognitive functioning of VLBWIs at school age was evaluated using the Wechsler Intelligence Scale for Children—Third or Fourth Edition (WISC-III or IV) [7]. The previous related studies in Japan suggested that the long-term outcomes of VLBWIs were not always favorable in terms of cognitive development. In fact, other studies reported that mental retardation or intellectual disability (intelligence quotient (IQ) of <70) occurred at a prevalence of 4–47% in infants who were born at between 22 and 34 weeks of gestational age, or with a birth weight of between 750 and 1500 g[5,8]. These data clearly demonstrated that VLBWIs had an adverse cognitive development.

The autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are neuro-developmental disorders that can

* Corresponding author at: Ochiai Masayuki, Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan, 812-8582. Tel.: +81 92 642 5421; fax: +81 92 642 5435.
E-mail address: ochimasa@pediatr.med.kyushu-u.ac.jp (M. Ochiai).

manifest as disturbances in social relatedness or behavioral regulation that disrupt daily functioning at home or at school. Specifically, ASD is characterized by deficits in social interaction, repetitive behaviors and restricted interests [9], while ADHD results in various externalizing behavioral problems consisting of one or more of the following: inattention, hyperactivity and impulsive symptoms [10]. These psychiatric disorders have been reported to be frequently associated with cognitive impairments [11–13]. Several reports suggested that VLBWIs at school age might present emotional and behavioral problems at higher frequencies than those in the general population [14–16]. However, only limited information was available regarding specific emotional and behavioral profiles of VLBWIs in previous studies [17]. Therefore, the two aims of the present study were as follows: first, to determine the neuro-psychiatric profiles of VLBWIs at six to nine years of age, and second, to investigate their psychiatric symptoms and their relationships with cognitive functioning using parent report rating scales for neuro-developmental disorders. This is the first study to demonstrate the correlations of the specific indices in the Wechsler Intelligence Scale for Children—Third edition (WISC-III) in VLBWIs at school age with their scores on the ADHD Rating Scale—Fourth edition (ADHD-RS) and the Autism Screening Questionnaire-Japanese version (ASQ-J).

2. Methods

2.1. Patient enrollment

A total of 154 VLBWIs, who had been admitted to the neonatal intensive care unit (NICU) of Kyushu University Hospital between April 2001 and March 2005, participated in this study. Four patients with inherited diseases, one with chromosomal abnormalities and one with major constitutional anomalies were excluded from the statistical analysis. Infants with a birth weight below the 10th percentile of the mean Japanese birth size standard data were classified as small-for-gestational age (SGA) [18]. Twenty-three infants (14%) died during hospitalization in our NICU and 42 (26%) dropped out of the study after moving away. The remaining 89 VLBWIs, who grew to six to nine years of age, were subjected to subsequent analyses. From April 2010 to December 2011, the psychiatric symptoms and cognitive functions were assessed for 77 of the 89 children (87%) using the WISC-III [19]. The 12 cases in which the IQ was measured using a different method, e.g., the former version of the WISC-III (WISC-R) or the Tanaka–Binet Intelligence Scale, were excluded from the analysis. There were no statistical differences between the enrolled (n = 77) and non-enrolled groups (n = 54, dropped out: 42 and evaluated by the WISC-R or Tanaka–Binet: 12) in the clinical characteristics including birth weight, gestational age at delivery, number of SGA infants and Apgar scores (data not shown). The protocols used in this study were approved by the Institutional Review Board at Kyushu University Hospital (#19-47). Written informed consent was obtained from all the caretakers of patients prior to their enrollment in this study.

2.2. Intellectual and psychiatric assessments

The full-scale IQ (FIQ) was used as a measure of general intellectual ability, and the four factor index scores were used to examine the specific elements of cognitive function. The Verbal Comprehension Index (VCI) measures verbal reasoning ability, the Perceptual Organization Index (POI) assesses visual–spatial reasoning ability, the Freedom from Distractibility Index (FDI) examines attention and working memory and the Processing Speed Index (PSI) evaluates the speed and accuracy of information processing. These scales were age-standardized to the mean value of 100. The criterion for borderline impairment was a FIQ between 70 and 85, whereas that for mild or greater disability was an IQ below 70 [20].

For the assessments of the neuro-developmental disorders, the ADHD-RS [21,22] and the ASQ-J [23,24] were used. The ADHD-RS is an 18-item questionnaire requiring the respondent to rate the ADHD symptoms of DSM-IV on a four point Likert scale (0–3) [21,22]. This measure yields a total score and two subscale scores, Inattention (IA) and Hyperactivity–Impulsivity (HI). The raw scores for all three scales were used as the independent measures. The ASQ-J consists of 39 questions concerning ASD symptoms based on the Autism-Diagnostic Interview algorithm and is used for the screening and assessment of autism and related disorders[23]. The ASQ-J has good discriminative validity with respect to the separation of pervasive developmental disorders (PDD) from non-PDD diagnoses at all IQ levels; a cut-off score of 13 was recommended in a validation study in Japan [24].

2.3. Statistical analyses

The Spearman's rank sum test was used for the association study involving the continuous variables. The Mann-Whitney U test was used to compare the variables between subgroups. The differences between groups were tested for significance by the Chi-square test. All the dependent variables on a univariate analysis were entered into a forward method of a multilinear regression model. Excel statistics (SSRI, Japan) and SPSS software (ver. 19; SPSS, Chicago, IL, USA) were used for the analyses. Results with p-values of <0.05 were considered to be significant.

3. Results

3.1. Clinical features of the VLBWIs

We first characterized the clinical features of the VLBWIs (n = 77). Table 1 shows the perinatal characteristics and the scores for the WISC-III, ASQ-J and ADHD-RS. We verified that birth weight, gestational age at delivery, number of SGA infants and Apgar scores did not differ between the males and females. One male patient was diagnosed with periventricular leukomalacia. The median IQ was 91 for the males, ranging from 50 to 126, and 99 for the females, ranging from 79 to 126. There were 34 (76%) male and 27 (84%) female VLBWIs with an

Table 1
Clinical features of the VLBWIs (n = 77).

	Male (n = 45)		Female (n = 32)		
	Median	range	Median	range	p-Value
Characteristics					
GA (weeks, days)	30w0d	23w2d–39w4d	29w5d	24w0d–36w2d	0.73
BW (g)	1034	484–1494	1074	534–1476	0.96
SGA[a]	25	55.5	18	56.3	0.95
1-min Apgar	6	0–9	6	1–9	0.97
5-min Apgar	8	3–9	8	5–10	0.70
WISC-III					
FIQ	91	50–126	99	79–126	0.17
VC	97	55–130	100	73–130	0.39
PO	93	56–124	93	80–133	0.66
FD	94	50–129	100	76–118	0.08
PS	86	58–120	96	78–128	**<0.01**
ASQ-J					
Total score	4	0–25	2	0–12	0.15
ADHD-RS					
Total score	13	0–29	4	0–24	**<0.01**
IA	8	0–20	2	0–15	**<0.01**
HI	5	0–11	1	0–11	**<0.01**

[a] Number, percent, GA; gestational age, BW; birth weight, SGA; small-for-gestational age, WISC-III; Wechsler Intelligence Scale for Children—Third Edition, FIQ; full scale intellectual quotients, VC; verbal comprehension, PO; perceptual organization, FD; freedom from distractibility, PS; processing speed, ASQ-J; Autism Spectrum Questionnaire—Japanese version, ADHD-RS; Attentive Deficit Hyperactivity Disorder Rating Scale—Fourth Edition, IA; inattentive, HI; hyperactivity-impulsivity.