Developmental Profiles and Mentality in Preschool Children with Prader-Willi Syndrome: A Preliminary Study

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Background: A majority of the children with Prader-Willi syndrome (PWS) have global developmental delay and mental delay. The aim of this study was to investigate the developmental profiles and mental assessments among preschool children with PWS.

Methods: Ten children with PWS between the ages of 15 months to 6 years, and 11 children with typical development were enrolled. Developmental profiles in terms of their developmental quotient (DQ) for the eight domains of the Chinese Children Developmental Inventory (CCDI) and mental assessments in terms of intelligence quotient (IQ) and developmental index (DI) were carried out for all children.

Results: The DQs of all eight domains, including gross motor, fine motor, expressive language, concept comprehension, situation comprehension, self help, personal-social and general development, in the PWS group were lower than the DQs of the children from the typical development group ($p < 0.01$). Children with PWS had better DQs in the fine motor domain than in the gross motor domain and in the receptive language domain than in the expressive language domain. Furthermore, their verbal IQ were better than their performance IQ and their mental DI was better than their psychomotor DI.

Conclusions: These findings suggest that the children with PWS show an uneven global developmental delay together with an uneven mental delay. The results of this study should allow clinicians to better understand the developmental functioning of children with PWS and this will help with the planning of treatment strategies.

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Key words: Prader-Willi Syndrome, intelligence quotient, developmental quotient

Prader-Willi syndrome (PWS) was first described in 1956.(1) This syndrome is a genetic disorder that results from the deletion of chromosome 15q, maternal uniparental disomy, deletion in the imprinting center or an imprinting defect.(2) This syndrome is characterized by neonatal and infantile central hypotonia, feeding problems in infancy, excessive or rapid weight gain after 12 months but before 6 years

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of age, facial dolichocephaly in infancy, hypogonadism, global developmental delay, mental retardation, and hyperphagia.[3] The incidence of PWS is about 1 in 25,000 live births,[4-6] and the population prevalence is 1 in 50,000 to 80,000.[6,7]

According to the latest revision of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR),[8] mental retardation is characterized by the following three criteria: a subaverage general intellectual function, significant limitations in two or more skill areas of adaptive function, and onset before 18 years of age. Subaverage general intellectual function or mental delay is defined as an intelligence quotient (IQ) of about 70 or lower. Many genetic etiologies of mental retardation, such as large chromosome abnormalities, microdeletions, copy number changes, coding abnormalities, and X chromosome-linked single genes have been identified over the years.[9] In one review article that covered 43 original articles, the prevalence of mental retardation was found to be around 3.8/1000 for children with an IQ < 50, and 29.8/1000 for children with an IQ between 50 and 70.[10] A number of articles have indicated that most individuals with PWS have mild mental retardation (full-scale IQ between 55-70).[11-15]

Majority of the children with PWS have global developmental delay.[3,16] Up to the present, there has been very little research on the developmental profiles of preschool children with PWS that takes into consideration the full spectrum of developmental functions across a wide range of domains. Elucidating developmental profiles of children with PWS will enable clinicians to understand the developmental patterns and help them determine more flexible strategies when treating these children. The aim of our study is to investigate the features of the developmental profiles and mental assessments among preschool children with PWS.

METHODS

Participants

We recruited 10 children with PWS between the ages of 15 months to 6 years who had visited the outpatient rehabilitation clinic. The diagnosis of PWS was confirmed on the basis of a genetic analysis performed by pediatric geneticists at our hospital. We classified the genotypes of the 10 children with PWS and found that 8 children had a deletion and 2 children had maternal uniparental disomy. An additional 11 children with typical development (TD), matched for age and gender, were selected as a comparison group. The Institutional Review Board for Human Studies at our hospital approved the study protocol.

Assessment procedures

The intelligence and developmental profiles of all children were assessed. The Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R, Taiwanese version) or the Bayley Scales of Infant Development-Second Edition (BSID-II) were used for the mental assessments, depending on the age of the individual.

The Taiwanese version of the WPPSI-R was selected for children between the ages of 3 to 6 years, and the BSID-II was selected for children below 3 years of age. The Taiwanese version of the WPPSI-R was translated from the WPPSI-R,[17] and was norm sample standardized.[18] The Verbal Intelligence Quotient (VIQ) and the Performance Intelligence Quotient (PIQ), which contribute to the Full Scale Intelligence Quotient (FSIQ). VIQ and PIQ, are designed to examine specific skills, while the FSIQ can be used to evaluate global intelligence. The three measures have been proven to have high reliability (0.89~0.95) and validity.[17,18] The WPPSI-R scale is suitable for testing subjects from 3 years up to 7 years 3 months of age.

The BSID-II is a norm-referenced test suitable for infants between 1 to 42 months of age.[19] The mental and motor scales of the BSID-II yield standardized scores; these are the Mental Development Index (MDI) and the Psychomotor Development Index (PDI), respectively. The mean MDI and PDI score is 100 ± 15.[19] An MDI or PDI score of 85~114 is considered to be within normal limits. Between 70 and 84 is considered to indicate mildly delayed performance and 69 or below is considered to indicate significantly delayed performance. The BSID-II is a highly reliable developmental instrument with high internal consistency (Cronbach $\alpha >$ 0.95) that has been widely used in Taiwan.[20] In our study, the WPPSI-R was used to test children who were between 3-6 years old and the BSID-II was used to test children who were < 3 years old.

The developmental profiles were assessed by the Chinese Children Developmental Inventory

(CCDI),[21] which is widely used in Taiwan to assess developmental profiles in children with developmental delay.[22-24] The CCDI is a 320-item questionnaire that consists of statements that describe particular behaviors in children. Parents/caregivers have to provide "yes" or "no" answers as a response to each statement depending on whether the child has or has not displayed that specific behavior. The CCDI contains a normative score, which yields age equivalents for eight domains of developmental function. These eight domains include gross motor (34 items), fine motor (44 items), expressive language (54 items), concept comprehension (67 items), situation comprehension (44 items), self help (36 items), personal-social (34 items), and general development domains (131 items). The general development domain is made up of 7 specific items and 124 items selected from the other 7 domains. The CCDI comprises a total of 320 items. The gross motor domain is useful when evaluating locomotion and related balance/coordination movements. The fine motor domain assesses visual-motor coordination The expressive language domain measures ability to expressing self in interpersonal relationships. The concept comprehension domain assesses the child's ability to comprehend language and abstract concepts. The situation comprehension domain investigates the child's comprehension of certain situations, but language is not included. The self help domain looks at the development of the ability to manage personal daily activities. Finally, the personal-social domain looks at interpersonal relationships in the child's social life. The validity and reliability of the CCDI are greater than 0.83 and 0.88, respectively.[21] The development quotient (DQ) was then calculated as a percentage of developmental age divided by chronological age. In addition to the above, the following demographic data were recorded: age, body height, body weight, and gender.

Statistical analysis

Differences in gender between the two groups were determined using the Fisher's exact test. Differences in some demographic data (age, body weight, and body height) together with the DQ of developmental profile (CCDI), VIQ, PIQ, FSIQ, MDI, and PDI of the two groups were compared by Mann-Whitney *U* test. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

There were no significant differences between the demographic data of the two groups (Table 1). The children with PWS consisted of slightly more females (60%), while children within the typical development group consisted of slightly more males (54.5%). The body weights in the PWS group were higher than those in the TD group but there is no significant difference ($p = 0.078$, Table 1).

The average DQs for all developmental functions among the children with PWS (gross motor ability, 52.6%; fine motor ability, 68.4%; expressive language function, 46.9%; concept comprehension function, 57.5%; situation comprehension function, 57.3%; self help, 60.6%; personal–social development, 54.6%; general development, 61.4%) were lower than those among the children in the TD group. All domains were significantly different between the two groups (Fig. 1). The discrepancy between the DQs for gross motor and fine motor domains in the PWS group was about 16%. The DQ for expressive language functions (47%) in the PWS group was poorer than the concept comprehension functions (57%) by 10%.

In total, 14 children (7 children in the PWS

Table 1. Demographic and Birth Data of the Children with Prader-Willi Syndrome and the Children with Typical Development

	Children with Prader-Willi syndrome (n = 10)	Children with typical development (n = 11)	*p* value
Demographic data			
Age (months)	45.6 ± 14.5	40.2 ± 16.4	0.398†
Body height (cm)	96.4 ± 9.8	95.3 ± 13.8	0.972†
Body weight (kg)	19.6 ± 7.80	14.0 ± 3.50	0.078†
Gender			0.670*
Male	4 (40%)	6 (60%)	
Female	6 (54.5%)	5 (45.5%)	

Values are expressed as numbers (%) for gender and as mean ± standard deviation for age, body height, and body weight.

*: *p* values for the comparisons of the Prader-Willi syndrome children and the children with typical development groups were obtained by Fisher's exact test; †: *p* values for comparisons of the Prader-Willi syndrome children and children with typical development groups were obtained by Mann-Whitney *U* test.

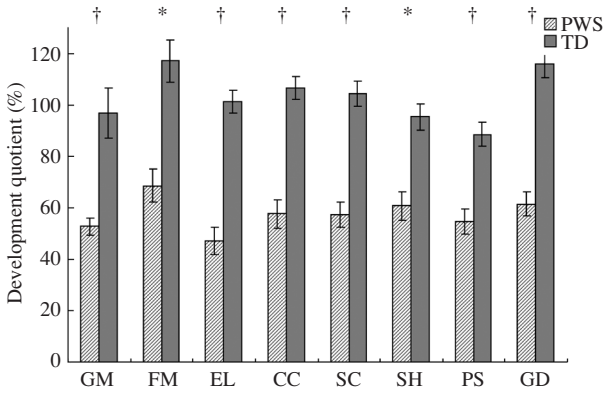

Fig. 1 Comparisons of the DQs measured using the Chinese Children Developmental Inventory of the children with Prader-Willi syndrome and the children with typical development compared using the Mann-Whitney U test. All values are mean ± standard error. Abbreviations used: PWS: Prader-Willi syndrome; TD: typical development; GM: gross motor; FM: fine motor; EL: expressive language; CC: concept comprehension; SC: situation comprehension; SH: self help; PS: personal-social; GD: general development. *: $p = 0.001$; †: $p < 0.001$.

Table 2. IQs Measured Using the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) and Developmental Indices Measured Using Bayley Scales of Infant Development-Second Edition (BSID-II) for the Children with the Prader-Willi Syndrome and the Children with Typical Development

	Children with Prader-Willi syndrome (n = 10)	Children with typical development (n = 11)	*p* value
Case Number (3~6 years)	7	7	
Intelligence Quotient			
Verbal	64.4 ± 13.1	96.6 ± 10.6	0.002
Performance	57.7 ± 8.2	92.4 ± 14.7	0.002
Full Scale	57.9 ± 9.7	93.9 ± 13.2	0.002
Case Number (< 3 years)	3	4	
Developmental Index			
Mental	63.3 ± 14.7	104.5 ± 8.1	0.034
Psychomotor	59.7 ± 25.9	107.5 ± 9.0	0.034

Data are presented as mean value ± standard deviation.

group, and 7 children in the TD group) were assessed using the WPPSI-R. The average VIQ in both the PWS group was greater than 60; however, the average PIQ and FSIQ was less than 60. The average VIQ, PIQ and FSIQ were significantly higher in the children from the typical development group than those from the PWS group ($p = 0.002$, Table 2). The average VIQ (64) was higher than the PIQ (58) and FSIQ (58) by a score of 6 in the PWS group. Overall, 7 patients (3 children in the PWS group, and 4 children in the TD group) were assessed using the BSID-II. The discrepancy between the average MDI and PDI in the PWS group was 3.6 (Table 2). The average MDI and PDI in the PWS group were significantly lower than that of the TD group ($p = 0.034$).

DISCUSSION

Children with PWS demonstrated uneven global developmental delay pattern. In this study, the developmental profiles of all eight domains in children with PWS were lower than those of children with typical development. The DQ of the gross motor domain was lower than that of the fine motor domain in the PWS group. One previous study indicated that the hypotonic characteristics of the disorder could interfere with the development of postural control.[25] Another study showed that children with PWS undergo excessive and/or rapid weight gain between the ages of 1 to 6 years.[3] We suspect that the hypotonia and rapid weight gain may compromise development in locomotion and balance. Nevertheless, there is a need for more evidence to prove that hypotonia and rapid weight gain do compromise locomotion and balance development more than visual-motor coordination. Overall, these findings may indicate the motor intervention, especially gross motor training, may benefit children with PWS.

Expressive language was found to be more impaired than receptive language in the children with PWS. In this study, the discrepancy between the DQs for the expressive and receptive language domains in the PWS group was 10%. This discrepancy between expressive and receptive language in children with PWS may be related to cognition, language, and oromotor impairment in these children. In a previous study, 11 individuals with PWS were analyzed and it was found that the voice, speech, and language of such individuals were generally impaired.[26] Yet another study found that articulation in children with PWS is usually impaired and that the overall error rate for articulation was negatively correlated with

the children's full scale IQ.[12] Children with PWS demonstrate poor articulation and development of speech. Language expression involves a complicated integration of various functions including coordination of the central nervous system and oromotor control. We suspected that the intelligence level of these children may interfere with central nervous system coordination. In addition, hypotonia of the speech-related muscles might disturb oromotor control. Based on these findings, we suggest that speech therapy ought to be provided for children with PWS and should include training in verbal comprehension, especially expression training.

The average VIQ, PIQ, and FSIQ in the PWS group were lower than those of children from the typical development group. Children with PWS had better verbal intelligence than performance intelligence and the discrepancy between the average VIQ and PIQ in the PWS group was 6.7. Our results are consistent with previous studies,[12,14] which showed that children with PWS had a higher VIQ than PIQ. Therefore, we suggest that treatment strategies for children with PWS should focus on visual perception, visual spatial, and visual cognition training in addition to verbal cognition training.

Toddlers with PWS had better mental development than psychomotor development. In this study, the average MDI score (63) was found to be higher than the average PDI score (60) for children with PWS. This result is consistent with a previous study in which 43 PWS infants, where their mean MDI and PDI scores were 71.6 and 56.8, respectively.[27] These findings imply that toddlers with PWS have better in MDI scores, which are measures of visual and auditory information processing, language development, memory, eye-hand coordination, imitation, and problem solving, than PDI scores, which are measures of gross and fine motor skills. Based on these findings, it is suggested that any therapeutic strategies during this period should focus not only on mental functions but also on psychomotor functions.

Due to the limited sample size and the characteristics of the analyzed subjects, the correlations between genotype and phenotype have not been discussed in this study. In addition, the developmental profiles in relation to age between the two groups have not been investigated. Despite these limitations, this study provides baseline information on the developmental profiles of children with PWS.

Conclusions

In conclusion, children with PWS show uneven global developmental delay and an uneven mental delay. Children with PWS have better fine motor ability than gross motor ability, and have better receptive language ability than expressive language ability. Furthermore, children with PWS have a better Verbal Intelligence Quotient than Performance Intelligence Quotient and a better Mental Developmental Index than Psychomotor Developmental Index. The results from this study should help clinicians understand better the developmental profiles and mental functioning of children with PWS, and this should help them create better treatment strategies for them. Future studies ought to focus on longitudinal follow-up and the effect of early intervention strategies on children with PWS across the various genotypes.

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患有小胖威利症候群的學齡前孩童其發展概況與心智狀況：初步研究

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背 景： 大多數患有小胖威利症候群 (Prader-Willi syndrome) 的小孩均有整體發展遲緩 (global developmental delay) 與心智功能遲緩 (mental delay) 的情況。我們這個研究的目標主要是研究患有小胖威利症候群的學齡前孩童其發展概況與心智狀況。

方 法： 我們收集了 10 位年齡分布從 15 個月大到 6 歲大患有小胖威利症候群的孩童；另外也收集了 11 位正常的孩童作爲比較組。在評估工具方面，發展概況主要是評估學齡前兒童行爲發展量表中 8 個分項目的發展商數 (developmental quotient) 而心智功能主要是評估智能商數 (intelligence quotient) 與發展指數 (developmental index)。

結 果： 小胖威利這一組所有 8 個分項目的發展商數，包括粗動作 (gross motor)、精細動作 (fine motor)、溝通表達 (expressive language)、概念理解 (concept comprehension)、環境理解 (situation comprehension)、身邊處理 (self help)、人際社會行爲 (personal-social) 和一般發展 (general development) 均比正常組孩童這一組分數更低，達顯著差異 ($p < 0.01$)。此外，在小胖威利這一組中總括來看，其細動作 (fine motor) 表現比粗動作更好；語言的接受能力比表達能力更好；語文智能商數 (verbal intelligence quotient) 比操作智能商數 (performance intelligence quotient) 更好；智力發展指數 (mental developmental index) 比運動發展指數 (psychomotor developmental index) 更好。

結 論： 我們的研究發現患有小胖威利症候群的這一組孩童有整體發展遲緩與心智遲緩的情況。在發展概況與心智功能各分項的差異可以幫助臨床醫師針對小胖威利症候群的孩童擬定治療方向。

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關鍵詞： 小胖威利症候群，智能商數，發展商數

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