Features of Developmental Functions and Autistic Profiles in Children with Fragile X Syndrome

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Background: In this study, we investigated the developmental functions and autistic profiles in children with Fragile X syndrome (FXS). In addition, we established the relationships between developmental and autistic profiles in these children.

Methods: The medical records of 12 children with FXS, aged 2 to 7 years, were collected. Fifteen children with autism, without FXS, who were age- and sex-matched were selected as the comparison group. All children underwent assessments of developmental functions according to the Chinese Child Development Inventory (CCDI), and autistic profiles according to the Childhood Autism Rating Scale (CARS). Differences in genders between the two groups were determined with the Fisher's exact test. Differences in developmental functions (CCDI) and autistic profiles (CARS) between the two groups were compared using Mann-Whitney U test and Bonferroni adjustment. The Spearman's rho correlation was used to determine the relationship of developmental functions and autistic profiles.

Results: All developmental functions in children with FXS were better than those with autism except for gross motor, fine motor and expressive language functions. Children with FXS had the worst expressive language function (56% Development Quotient, DQ) as compared with other developmental functions (> 70% DQ). The major difference between the children with FXS and those with autism was personal social function with a difference of 33% DQ. The average total CARS score were lower in children with FXS (average score, 28) than children with autism (average score, 34). Spearman's correlation demonstrated the CARS total score were negatively correlated with all developmental functions, except for gross motor function.

Conclusions: Our findings suggest that the FXS children had multifaceted and disproportional development patterns in motor, speech and social domains when compared with the autism children without FXS. The developmental functions were inversely correlated with autistic profiles. Therefore, when applying comprehensive assessment, we were able to identify the special developmental features in children with FXS.

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Key words: Fragile X syndrome, autism, development delay, communication disorder, autistic behavior.

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The ability of humans to interact with the other people develops gradually from birth, for example, recognition of his mother face, eye contact, and utilization of body movements and verbal skills to develop the ability to communicate.[1,2] However, these abilities are impaired in children with certain types of conditions, such as children with Fragile X syndrome (FXS) or autism. The development of social behavior and communication skills may be restrained in children with these conditions. FXS is diagnosed based on the mutation of X chromosome.[3] The diagnosis of autism is mostly based on clinical behavior.[4] At present, the most commonly used basis for the diagnosis of autism is the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV).[5]

The first description of FXS was published by Martin and Bell in 1943.[6] FXS is a genetic disease. The gene causing FXS was discovered in 1991.[7] The Cytosine-Guanine-Guanine (CGG) sequential repetition takes place at the q27.3 location of the X chromosome long arm, while abnormal methylation occurs due to the over expansion of the repeated CGG.[7] Thus, the fragile X mental retardation protein (FMRP) is not produced by the fragile X mental retardation 1 (FMR1) gene, which ultimately causes the clinical symptoms in children with FXS.[8] The main clinical symptoms of FXS is developmental delay, low intelligence and behavior disorders, such as autistic behavior.[9] Aside from the clinical symptoms, children with FXS always have some unique physical manifestations such as: elongated face, long ears, macro-orchidism, etc.[10] However, until now, most researchers have discussed the diagnostic and screening tools for FXS in Taiwan.[11,12] No detailed developmental functions and autistic profiles in children with FXS in Taiwan have been reported.

Autism is a special mental disease that covers different aspects, such as: recognition capabilities, verbal communication and social interaction. Autism causes the children to encounter difficulties in their social abilities, as well as disruption in their general development.[4] In 1943, Doctor Kanner adopted the term “early infantile autism” to describe such cases.[13] The primary characteristics included deficits in sociability, lack of a drive to communicate or the withholding of speech, and impairment of interests and activities.[4]

Therapy to promote the functional development of children with FXS is based on the understanding the autistic profiles of these children. In this study, we investigated the developmental and autistic profiles in children with FXS. In addition, we established the relationships between the developmental and autistic profiles in these children. The aim of this study is to provide information for clinicians who are planning the therapeutic strategies for these children.

METHODS

The medical records of 12 children with the diagnosis of FXS, aged 2 to 7 years, were collected. Children with FXS were confirmed using results of chromosome studies. Fifteen children with autism, that were age- and sex-matched and excluded from the FXS using results of chromosome studies, were selected as the comparison group. The children with autism met the DSM- IV criteria (qualitative impairment in social interaction, qualitative impairments in communication, restricted, repetitive, and stereotyped patterns of behavior, interests, and activities). All children underwent the assessment of developmental functions and autistic profiles.

To assess the developmental functions, we used the Chinese Children Developmental Inventory (CCDI) to assess eight functional domains including gross motor (GM), fine motor (FM), expressive language (EL), concept comprehension (CC), social comprehension (SC), self help (SH), personal social (PS) and general development (GD).[14] The development quotient (DQ) was determined as a percentage of development age divided by chronological age. Childhood Autism Rating Scale (CARS), which is composed of 15 categories, was used to determine autistic profiles.[15] The 15 categories included: relating to people, imitation, emotional response, body use, object use, adaptation to changes, visual response, listening response, taste/smell/touch response and use, fear or nervousness, verbal communication, non-verbal communication, activity level, level and consistency of intellectual response, and general impressions. Each category was scored on a seven-point rating scale. Those with age appropriate reactions scored 1, mildly abnormal reactions scored 1.5 or 2, moderately abnormal reactions scored 2.5 or 3, and severely abnormal reactions scored 3.5 or 4. The total score for each child was measured from the summation of all scores in each

category. The child was defined as non-autistic if the total score was less than 30, as mildly to moderately autistic if the total score ranged from 30 to 36.5, and as severely autistic if the total score was equal to or greater than 37.

Differences in the genders between the two groups were determined using the Fisher's exact test. The Spearman's rho correlation was used to determine the relationship of developmental functions and autistic profiles. The Mann-Whitney U test was used to compare some demographic data (age, body height, body weight). A value of $p < 0.05$ was considered statistically significant. Differences in the developmental functions (CCDI) and autistic profiles (CARS) between the two groups were compared using the Mann-Whitney U test. To avoid the inflation of type I errors due to multiple comparisons, a Bonferroni adjustment was applied, raising the significance threshold to 0.006 and 0.003 for this part of the analysis.

RESULTS

We found the children with FXS (83%) and autism (53%) were male dominant. There were no significant differences of the demographic data between the two groups (Table 1). The DQs of all developmental functions in the children with FXS (GM: 73.2%; FM: 81.5%; EL: 56.6%; CC: 73.8%; SC: 75.8%; SH: 80.9%; PS: 70.3%; GD: 77.2%) were higher than in those with autism (GM: 59.7%; FM: 57.9%; EL: 41.4%; CC: 44.9%; SC: 49.1%; SH: 50.2%; PS: 37.4%; GD: 54.9%) (Fig. 1). All developmental functions showed significant differences between the two groups except for gross motor, fine motor, and expressive language functions. Children

Table 1. Demographic Data of Children with Fragile X Syndrome (FXS) and Autism

	Children with FXS (n = 12)	Children with Autism (n = 15)	*p* value
Gender			0.108*
Male	10 (83.3%)	8 (53.3%)	
Female	2 (16.7%)	7 (46.7%)	
Age (years)	4.3 ± 1.2	3.8 ± 1.5	0.380†
Body height (cm)	105.7 ± 11.0	98.3 ± 14.3	0.181†
Body weighty (Kg)	16.0 ± 3.4	17.0 ± 9.34	0.656†

Values are expressed as mean ± SD, or n (%).

* *p* values for comparisons of FXS with autism, based on Fisher's exact test.

† *p* values for comparisons of FXS with autism, based on Mann-Whitney U test.

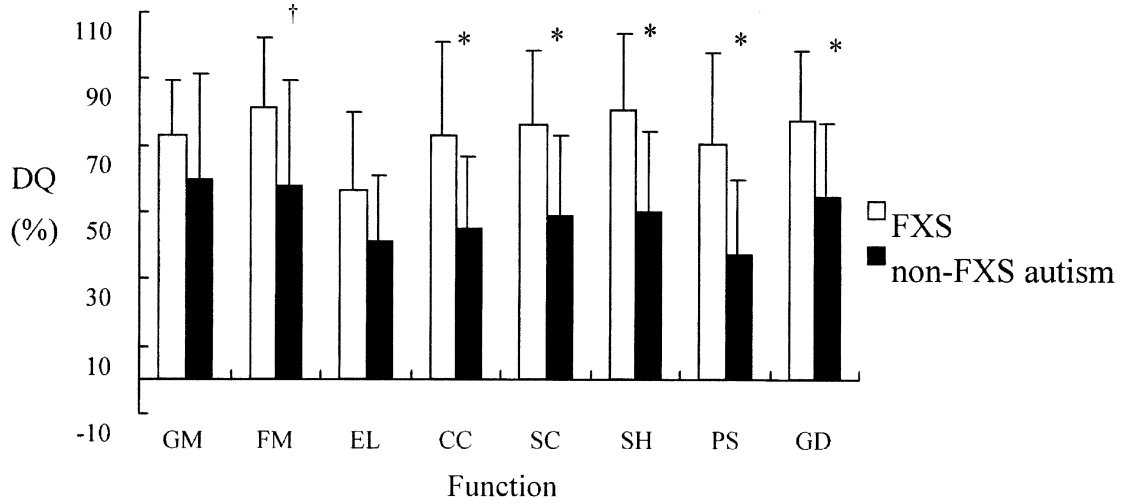

Fig.1 Chinese Child Development Inventory development quotient of children with autism and Fragile X syndrome.
GM: gross motor; FM: fine motor; EL: expressive language; CC: concept comprehension; SC: social comprehension; SL: self help; PS: personal social; GD: general development; DQ: Development Quotient.
* $p < 0.006$
† $p < 0.05$

with FXS showed that expressive language functions were worse than the other developmental functions by 14 to 25%. Children with autism showed that expressive language and personal social functions were worse than gross motor and fine motor functions by 17 to 22%.

Based on the CARS assessment, approximately 92% of children with FXS were classified as non-autistic or mildly/moderately autistic. However, 80% of the children with autism were classified as mildly/moderately or severely autistic. The average total CARS score were greater in children with autism (average score, 34) than in children with FXS (average score, 28; Table 2). The average score of the autistic profiles in children with autism were greater than in children with FXS (Table 2). After correction for multiple statistical comparisons, when autistic profiles were compared for FXS and autism, no significant differences were present. The average score in most categories of autistic profiles was less than 2 in children with FXS, except for verbal communication, activity level, level and consistency of intellectual response, and general impressions. The average score in most categories of autistic profiles was greater than 2 in children with autism, except for adaptation to changes, listening response, and taste/smell/touch response and use.

Spearman's correlation coefficient demonstrated the CARS total scores were negatively correlated with all developmental functions (rho = -0.30 to -0.54, $p < 0.05$), except for gross motor (Table 3). All developmental functions had positive relationships with each other (rho = 0.45 to 0.87, $p < 0.01$).

Table 2. Childhood Autism Rating Scale (CARS) of Children with Fragile X Syndrome (FXS) and Autism

Categories of CARS	Children with FXS (n = 12)	Children with autism (n = 15)	*p** value
Total scores	28.53 ± 6.44	34.43 ± 6.38	0.016
relating to people	1.79 ± 0.54	2.56 ± 0.72	0.007
Imitation	1.75 ± 0.65	2.36 ± 0.71	0.032
listening response	1.37 ± 0.48	1.90 ± 0.73	0.057
taste, smell and touch response and use	1.37 ± 0.52	1.96 ± 0.95	0.063
emotional response	1.95 ± 0.72	2.50 ± 0.62	0.063
visual response	1.62 ± 0.88	2.30 ± 0.97	0.066
fear or nervousness	1.66 ± 0.68	2.16 ± 0.72	0.105
verbal communication	2.50 ± 0.90	2.93 ± 0.84	0.128
nonverbal communication	1.79 ± 1.05	2.13 ± 0.74	0.136
object use	1.79 ± 0.72	2.10 ± 0.89	0.343
activity level	2.58 ± 0.79	2.83 ± 0.79	0.462
general impressions	2.37 ± 0.74	2.60 ± 0.57	0.487
body use	1.87 ± 0.82	2.10 ± 0.80	0.510
intellectual response	2.50 ± 0.76	2.30 ± 0.64	0.542
adaptation to change	1.62 ± 0.80	1.66 ± 0.52	0.559

* *p* values for comparisons of FXS with autism, based on Mann-Whitney U test.

DISCUSSION

Children with FXS and autism had disproportional development patterns in motor, speech and

Table 3. The Spearman's Correlation Coefficient between Autistic Profile, Measured by Childhood Autism Rating Scale (CARS) Total Score, and Developmental Functions, Measured by Chinese Children Developmental Inventory

	CARS	DQGM	DQFM	DQEL	DQCC	DQSC	DQSH	DQPS	DQGD
CARS	1								
DQGM	-0.17	1							
DQFM	-0.30*	.74†	1						
DQEL	-0.43†	.51†	.60†	1					
DQCC	-0.44†	.35*	.60†	0.77†	1				
DQSC	-0.46†	.75†	.80†	0.71†	.66†	1			
DQSH	-0.38*	.51†	.69†	0.45†	.611†	0.70†	1		
DQPS	-0.54†	.62†	.64†	0.81†	.729†	0.87†	.59†	1	
DQGD	-0.46†	.57†	.71†	0.80†	.671†	0.71†	.46†	0.69†	1

Abbreviations: GM: gross motor; FM: fine motor; EL: expressive language; CC: concept comprehension; SC: social comprehension; SL: self help; PS: personal social; GD: general development; DQ: Development Quotient; CARS: The Childhood Autism Rating Scale.
* $p < 0.01$
† $p < 0.05$

social domains. The developmental profiles in children with FXS were different from those in children with autism, although both of these children had communication and behavioral disorders. Most developmental functions in children with FXS were better than in those with autism. In this study, children with FXS had the worst expressive language function (56% DQ) as compared with other developmental functions (> 70% DQ). Children with autism showed that expressive language and personal social functions (approximately 40%) were worse than gross motor and fine motor functions by 17 to 22%. Our findings were compatible with the findings reported in earlier studies.[16] Bailey et al found that the development functions of children with FXS was superior to those with autism based on the Battle Developmental Inventory assessment scores.[17] Burack and Volkmar and Freeman et al also showed that the personal social aspects of children with FXS were better than those in children with autism.[18,19]

Children with FXS had better personal social functions than children with autism, although both groups demonstrated delays in personal social functions. In this study, we found the major discrepancy between children with FXS and autism was personal social functions (FXS DQ: 70%; autism DQ: 37%). The reasons may be that children with FXS had less autistic behaviors than children with autism based on the autistic profiles, especially in terms of relating to people and imitation. Fisch and Hagerman indicated that the causes of the abnormal behavior were different in children with FXS and autism, although both groups had difficulties in personal social aspects.[3,20,21] For example, both groups demonstrated gaze avoidance and reduced social interactions. However, the reasons for these symptoms were different: anxiety and hyperarousal for children with FXS, and reduced interest in society for children with autism.[3,20,21]

The developmental functions were inversely correlated with autistic profiles. That is, the more severe the autistic behaviors, the more delayed the developmental functions. In this study, we demonstrated that the CARS total scores were negatively correlated with all developmental functions (rho = -0.30 to -0.54), except for gross motor. Previous works documented varying results regarding the relationships of developmental functions and autistic behavior. Bailey et al indicated that developmental functions, evaluated by Battle Developmental Inventory, were related to autistic behavior, evaluated by CARS, for children with FXS, aged 3 to 7 years old.[17] Reiss and Freund found that the developmental functions had no relationship with autistic behavior, as assessed by DSM-III-R, for children with FXS or autism, aged 3 to 18 years old.[22] The conflicting findings may be due to the varieties in assessment tools, age, or study groups among the studies.

There were high positive relationships among language, social comprehension, and personal social functions in children with FXS and autism. Social comprehension may play major factors in determining the personal social and language functions.[16] In this study, we found all developmental functions had positive relationships with each other (rho = 0.45 to 0.87). The correlation coefficients were greater than 0.8 between expressive language and personal social functions as well as between personal social functions and social comprehensions. Previous researchers illustrated that the expressive language disorder in children with autism included non-oral expression, delays in the development of oral expression, and inability to start or maintain a conversation.[23] They are completely at a loss in the use of eye contact, facial expression, and body position that prevented them from being able to express their desires and share their thoughts with other people.[24-26] Tanguay et al pointed out that social comprehension includes joint attention, affective reciprocity and theory of mind.[27,28] A disorder in social comprehension prevents the individual from participating in any normal activity leading to a severe lack of social interaction. Children with autism show lack of social knowledge and fail to acquire social knowledge, which is shown by the inability to engage in spontaneous symbolic play, form context-relevant communicative intentions, or generate original actions in play.[29-31] The impaired social functions in these children further deprived their experiences of social communication and social motor functions, such as competitive or playing activities.

In this study, children with FXS and autism not only had speech and social delays, but also had motor delays. Our findings were compatible with the findings from earlier investigations.[16] Some researchers suggested these children had the muscle weakness.[4,32] Children with FXS were associated

with orthopedic problems, such as flat feet, scoliosis, which further impaired physical balance and stability.[33] Children with autism showed gross motor and fine motor disorders, and increased joint laxity.[4] Furthermore, repeated self-stimulating actions like shaking fingers, hands and body, may also have compromised motor development and balance. Thus, therapeutic strategies of promoting motor functions should be integrated into early intervention programs for children with FXS or autism, in addition to the therapeutic strategies to improve other functions, such as speech or personal social functions.

In conclusion, we found that most developmental functions of children with FXS were better than the functions of those with autism. Children with FXS had the worst expressive language functions (56% DQ) as compared with other developmental functions (> 70% DQ). The major difference between children with FXS and autism was personal social functions (by 33% DQ). The developmental functions were inversely correlated with autistic profiles. There were highly positive relationships among language, social comprehension, and personal social functions in children with FXS and autism. Our findings suggest that children with FXS and autism had multifaceted and disproportional development patterns in motor, speech and social domains. The more severe the autistic behaviors, the more delayed the developmental functions. Social comprehension may play the major factor in determining the personal social and language functions. Therefore, when applying a comprehensive assessment, we identified the special developmental features in children with FXS. Early intervention should integrate motor, speech and social functions. Future detailed studies about children with FXS, including genetic and molecular biology, neurophysiological studies, and functional MRI studies are needed to help our understanding of developmental and behavior relationships.

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X 染色體脆折症兒童之發展功能和自閉行爲研究

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背 景： 本研究的目的在評估 X 染色體脆折症兒童之發展功能與自閉行爲，並建立發展功能與自閉行爲的相關性。

方 法： 一共收集了 27 位兒童，包括 12 位 X 染色體脆折症兒童，及 15 位自閉症兒童當比較組。以中華學齡前兒童行爲發展量表來評估其發展功能，以自閉症評量表來評估其自閉行爲。統計使用費雪正確檢定檢測兩組性別差異，曼-惠氏 *U* 檢定及波非朗尼方法檢測兩組發展功能與自閉行爲差異性。另外用斯皮曼等級相關係數檢測發展功能與自閉行爲之相關性。

結 果： X 染色體脆折症兒童之語言表達功能障礙較明顯（發展商數 56%），其它發展商數皆大於 70%。在發展評估中，除了粗動作、精細動作、語言表達外，X 染色體脆折症兒童的發展明顯比自閉症兒童好。X 染色體脆折症兒童及自閉症兒童的發展功能差異則以人際社會功能最明顯，發展商數相差 33%。X 染色體脆折症兒童自閉行爲指數較低（28 分），而自閉症兒童自閉行爲指數較高（34 分）。統計發現，除了粗動作功能外，其餘發展功能和自閉症評量總分呈現負相關。

結 論： X 染色體脆折症兒童在動作、語言及社會功能中，皆有多面向及不對稱發展。自閉行爲越明顯其發展功能則越差。因此對於 X 染色體脆折症兒童，我們可以提供詳細的理解評估及發展功能特點評量。

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關鍵詞： X 染色體脆折症，自閉症，發展遲緩，溝通障礙，自閉行爲。

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