Yonago Acta Medica 2021;64(1):30–33 doi: 10.33160/yam.2021.02.005

Clinical Characteristics of Fragile X Syndrome Patients in Japan

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ABSTRACT

Background Fragile X syndrome (FXS) is a well-known X-linked disorder clinically characterized by intellectual disability and autistic features. However, diagnosed Japanese FXS cases have been fewer than expected, and clinical features of Japanese FXS patients remain unknown.

Methods We evaluated the clinical features of Japanese FXS patients using the results of a questionnaire-based survey.

Results We presented the characteristics of seven patients aged 6 to 20 years. Long face and large ears were observed in five of seven patients. Macrocephaly was observed in four of five patients. The meaningful word was first seen at a certain time point between 18 and 72 months (median = 60 months). Developmental quotient or intellectual quotient ranged between 20 and 48 (median = 29). Behavioral disorders were seen in all patients (autistic spectrum disorder in six patients, hyperactivity in five patients). Five patients were diagnosed by polymerase chain reaction analysis, and two patients were diagnosed by the cytogenetic study. All physicians ordered FXS genetic testing for suspicious cases because of clinical manifestations.

Conclusion In the present study, a long face, large ears, macrocephaly, autistic spectrum disorder, and hyperactivity were observed in almost cases, and these characteristics might be common features in Japanese FXS patients. Our finding indicated the importance of clinical manifestations to diagnosis FXS. However, the sample size of the present study is small, and these features are also seen to patients with other disorders. We consider that genetic testing for FXS should be performed on a wider range of intellectually disabled cases.

Key words CGG repeat expansion; *FMR1* gene; fragile X syndrome; genetic testing; intellectual disability

Fragile X syndrome (FXS) (OMIM #300624) is a well-known X-linked disorder clinically characterized by intellectual disability and autistic features. In Japan, FXS (no. 206) and the related disorders (FXTAS and FXPOI) (no. 205) was authorized as designated intractable diseases in July 2015, and the genetic testing was accepted as national health insurance in April 2016. Well-known physical phenotypes of FXS are the long face, macrocephaly, mandibular prognathism, and large ears.[1] However, these physical features are manifested mostly in boys and tend to become more marked with age.[1] Additionally, these features may not be clinically noticeable in every patient. The FXS phenotype is caused by inactivation of the *FMR1* gene, which consists, in an expansion above 200 CGG at the 5' untranslated region (5′ UTR) repeat and subsequent methylation of the CGG triplets and CpG island in the promotor region of the gene.[1] Because disease-specific clinical features are unknown, genetic testing to detect more than 200 CGG repeat expansion (full mutation) of *FMR1* gene is necessary for the diagnosis of FXS, except for the rare patients with the intragenic pathogenic variant in *FMR1* gene.[2, 3]

Prevalence of the *FMR1* full mutation in male is 1 in 7,143 and in female is 1 in 11,111. Prevalence of FXS is varied by ethnicity.[4] In Asian countries, the prevalence of FXS patients is thought to be smaller than that of Western countries.[5, 6] The prevalence of Japanese FXS patients in males is estimated to be approximately 1 in 10,000, and this predicted prevalence of FXS in Japan is lower than Caucasian populations.[4] In Japan, several reports have been published about Japanese FXS patients.[7–9] However, the detailed clinical features

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Received 2020 October 30
Accepted 2020 December 7
Online published 2021 January 6
Abbreviations: DQ, developmental quotient; FXS, fragile X syndrome; IQ, intellectual quotient

Table 1. Clinical features of Japanese patients with fragile X syndrome

Family	A		B	C		D	E
Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age	9 y	8 y	8 y	20 y	20 y	6 y	9 y
Age at assessment	9 y 0 m	5 y 11 m	7 y 1 m	20 y	20 y	5 y 0 m	6 y 8 m
Sex	Male	Male	Male	Male	Male	Male	Male
Macrocephaly	+	+	–	Unknown	Unknown	+	+
Facial features	Prominent forehead, long face, large ear	Prominent forehead, long face, large ear	Unknown	Long face, large ear, mandibular prognathia	Long face, large ear, mandibular prognathia	Long face, mandibular prognathia	Large ear, mandibular prognathia
Epilepsy	–	–	–	–	–	–	+
Meaningful words	1 y 6 m	4 y	6 y	6 y	6 y	3 y	-
Walking	1 y 7 m	2 y 6 m	1 y 6 m	1 y 5 m	1 y 5 m	1 y 0 m	1 y 6 m
Abnormal behavior	ASD, hyper activity	ASD, hyper activity harm to others	Hyper activity ASD	ASD	ASD	Hyper activity ASD	Hyper activity euphoria
DQ/IQ	DQ 43	DQ 20	IQ 48	IQ 20	IQ 29	DQ 37	DQ 17
Other symptoms	None	Talipes equinovarus, Kawasaki disease	Serous otitis media, bronchial asthma	None	None	Hypospadias	None
Genetic diagnosis	PCR	PCR	PCR	PCR	PCR	Cytogenetic study	Cytogenetic study

DQ was assessed by the Kyoto Scale of Psychological Development 2001. IQ was assessed by Tanaka–Binet Intelligence Test. ASD, autistic spectrum disorder; DQ, developmental quotient; IQ, intellectual quotient; m, month(s); y, year(s).

of Japanese FXS patients are unknown. This is the first case series of the phenotypes in Japanese FXS cases.

SUBJECTS AND METHODS

To elucidate the clinical characteristics of Japanese FXS patients, we analyzed the results of a nationwide questionnaire-based survey in Japan. The first set of questionnaires, which focused on the experience of patients with FXS, was sent to Japanese specialists for pediatrics and pediatric neurology. The second set of questionnaires, which focused on the clinical information of patients with FXS, was sent to their attending physicians. The clinical data collected from the secondary questionnaire included developmental, behavioral, and physical assessment (Patient 3, 4, 5, 6 and 7 in Table 1). The clinical information of Family A (Patients 1 and 2 in Table 1) was not collected from nationwide questionnaire survey, and we collected the clinical information from the attending physician using the same questionnaire.

Macrocephaly was defined as a head circumference of more than 2 standard deviations based on age and gender, or subjective findings by the attending physician. PCR-based genetic testing of *FMR1* gene was performed as previously described at a Tottori University (Patient 1, 2 and 3).[7] PCR-based genetic testing of Patient 4 and 5 was performed using FragilEase^{TM} PCR assay at a registered clinical laboratory. Cytogenetic study was performed at registered clinical laboratory (Patient 6 and 7). All surveys and experiments performed in this study were approved by the Ethical Committee of Tottori University (approval number G81, G170, and G171).

RESULTS

Table 1 shows a clinical summary of the patients in our series. The seven patients from five families were male, participated from 2011 to 2016. The age at the time of examination ranged from 6 to 20 years old. The following facial features were observed in almost all patients: macrocephaly (four patients), long face (five patients), large ears (five patients), and mandibular prognathism (four patients). The head circumstance was accessed by the scale of Japanese standard head circumstances, and macrocephaly was observed in Patient 6. Additionally, subjective findings of macrocephaly were observed in Patient 1, 2 and 7. Epilepsy was observed in Patient 7. Walking was first seen at a certain time point between

Table 2. Comparison between clinical features of present fragile X syndrome case series and recent review

Clinical characteristics	Prevalence	
	Present series	Recent review (Ciaccio et al. 2017)[10]
Macrocephaly	4/5 (80%)	81%
Long face	5/6 (83%)	83%
Large ears	5/6 (83%)	72–78%
Mandibular prognathia	4/6 (66%)	80%
ADHD/hyperactivity	5/7 (71%)	50–66%
ASD	6/7 (86%)	30–50%
Intellectual disability	7/7 (100%)	~100%
Seizure	1/7 (14%)	10–20%

ADHD, attention deficit–hyperactivity disorder; ASD, autistic spectrum disorder.

12 and 18 months (median = 18 months). The meaningful word was first observed at a certain time point between 18 and 72 months (median = 60 months). Patient 7 did not utter any meaningful word at the age of 18. Developmental quotient (DQ) and intellectual quotient (IQ) were assessed by the Kyoto Scale of Psychological Development 2001 and Tanaka–Binet Intelligence Test, respectively. IQ/DQ ranged between 20 and 48 (median = 29). Behavioral disorders were seen in all seven patients (hyperactivity in five patients, autistic spectrum disorder in six patients, harm to others in one patient, euphoria in one patient). Five patients were diagnosed by polymerase chain reaction analysis, and two patients were diagnosed by the cytogenetic study. The reason why each physician ordered the testing was as follows. In five families, three families (Family C, D and E) have patients with facial features and abnormal behavior, one family (Family A) has patients with facial features, abnormal behavior and family history (Patient 1 and 2), and one family (Family B) has a patient with abnormal behavior and family history (an uncle has an intellectual disability).

DISCUSSION

We show a comparison between clinical features of present FXS case series and description in recent review collected from 15 articles,[10] showing the prevalence according to phenotypes, facial features, behavioral features, intellectual disability, and epilepsy (Table 2). In FXS patients, facial phenotypes are seen more commonly in adult patients.[1] However, these features were manifested in all four pediatric patients (Patients 1, 2, 6, and 7 in Table 1). The evident variability of clinical features due to ethnicity differences is unknown. Charalsawadi *et al*.[6] described the elongated face of FXS patients in Korea and Thailand was less significant than that of the American population. Conversely, large ears were more significant in FXS patients in Korea and Thailand. Both the elongated face and large ears were equally seen in our patients. However, in the present study, most attending physicians suspected FXS based on the patient's facial features, and this high frequency of facial features in the present series might not reflect certain features of every Japanese FXS patient. Macrocephaly is also a well-known feature in FXS patients, was also common in our case series. Prevalence of epilepsy (Patient 7) is compatible with those described in the previous report.[10]

The IQ of male FXS ranges between 35 and 55 with a mean around 40.[11] In the present case series, four of seven patients have DQ/IQ under 35. Japanese FXS patients have lower IQ/DQ scores, which may be due to a small sample size and that physicians conduct FXS genetic testing for patients with more severe intellectual disability than those in other countries. Hyperactivity and autistic spectrum disorders symptoms, which are well-known behavioral features in FXS patients, were also common in our case series. Generalizability was limited because of the small sample size, but the clinical features in Japanese FXS patients might have the same well-known features in previous reports on FXS patients in other countries.

The sample size of the present study is small; thus, this may not reflect every Japanese FXS patient. However, this is the first clinical case series conducted in Japan. In the present study, most physicians ordered FXS genetic testing for suspicious cases because of clinical manifestations. Clinical features such as the macrocephaly, long face, large ears, and hyperactivity may be common features in Japanese FXS patients, but these features are also seen in patients with other disorders. In many countries, FXS genetic testing is first-tier

testing for patients with intellectual disabilities.[12, 13] Genetic testing should be performed on a wider range of intellectually disabled cases to diagnose more FXS patients in Japan. FXS genetic testing has been accepted as national health insurance and has been widely used in Japan now. The knowledge of the clinical features of FXS patients obtained in this study might be useful for increasing the diagnostic rate and understanding of FXS patients.

Acknowledgments: We would like to express our gratitude to the patients and their parents for their cooperation. This work was supported by Research on Measures for Intractable Diseases from the Ministry of Health, Labor and Welfare for E.N. This work was also supposed by AMED under Grant Number JP17ek0109111 for K.A.

The authors declare no conflict of interest.

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