VARIABLE EXPRESSION OF CLINICAL FEATURES OF MARTIN BELL SYNDROME IN YOUNGER PATIENTS

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ABSTRACT

The clinical features of 20 patients of Martin Bell syndrome were analyzed in order to derive diagnostic features in younger patients. The characteristic clinical features comprising long face, large ears and macro-orchidism were commoner in children more than 10 years old than in prepubertal children. This study shows that younger the patient, fewer the classical features exhibited. Hyperactivity was the most useful feature for diagnosis of the younger patient with Martin Bell syndrome.

Keywords: *Fragile X-syndrome, Martin Bell syndrome.*

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Martin Bell syndrome or fragile X-syndrome is the second commonest genetic cause of mental retardation(l-5). Better appreciation of the clinical profile of this syndrome is important for early diagnosis, for better management and for identification of the high risk families in order to avoid the burden of another affected child. It is easier to diagnose the Martin Bell syndrome in post-pubertal patients, as the clinical features are better defined as compared with those in younger children(3,4,6-9). The present study analyses the clinical features ift 20 patients with Martin Bell syndrome, and examines their relationship to age.

Material and Methods

Patients with mental retardation attending the Genetic clinic of the Pediatric Department, All India Institute of Medical Sciences, New Delhi, between January 1986 and November 1989, were screened for fragile X-syndrome. The selection criteria and the methodology for cytogenetic screening using culture media deficient in folk acid and thymidine, are described elsewhere(10). *Figure 1* shows the fragile site on Xchromoosome at the end of long arm (Xq27.3). Fifty five patients with non-specific mental retardation with or without dysmorphic features of fragile X-syndrome were selected for cytogenetic studies, and of these 20 patients were confirmed to have fragile X-syndrome. Their demographic data and clinical features were recorded and analyzed.

Results

Of the 20 patients with fragile X-syndrome, 13 (65%) were below 10 years in age, and 7 (35%) were above 10 years. Eight children were below 5 years in age, while one set of twin brothers were 22 years old.

Table I compares the clinical features observed in patients of Martin Bell syndrome with those present in patients who were screened cytogenetically but did not have the MBS. Among the 27 non-MBS male patients, common clinical features

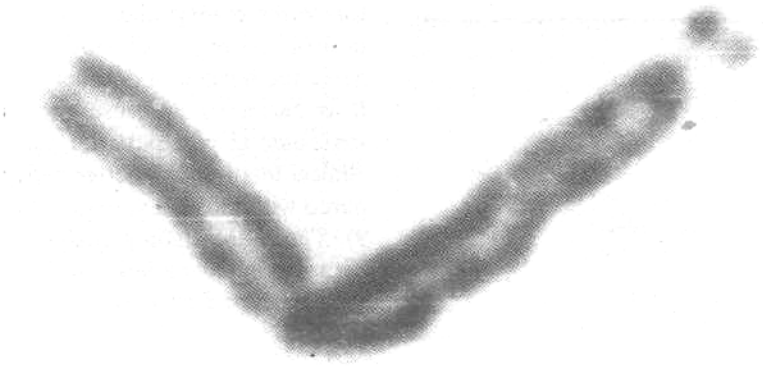

Fig. 1. Enlarged view of the X chromosome in metaphase after culture of lymphocytes in medium deficient in folic acid and thymidine. The fragile site is present at the distal end of the long arm (Xq 27.3).

TABLE I–*Frequency of the Clinical Features of Patients in the Study Group*

Clinical features	Non-MBS MR				MBS	
	Male		Female			
	(n=27)		(n=8)		(n=20)	
	No.	(%)	No.	(%)	No.	(%)
Long face*	2	(07.4)	0		12	(60)
Facial asymmetry	3	(11.1)	1	(12.5)	0	
Large/prominent ears	10	(37.0)	2	(25)	12	(60)
High forehead	3	(11.1)	1	(12.5)	5	(25)
Macro-orchidism**	1	(03.7)	-		6	(30)
Hypotonia	3	(11.1)	2	(25)	2	(10)
Hyperactivity #	5	(18.5)	1	(12.5)	14	(70)
Low set ears	13	(48.1)	2	(25)	7	(35)
High arched palate	5	(18.5)	6	(75)	4	(20)
Large/bulbous nose	1	(03.7)	0		5	(25)

Test of significance: Fisher's exact test.
MBS *vs* Non MBS Male M.R.: * p = 0.000007, ** p=0.0231, # p = 0.0009. Rest of the clinical features showed insignificant differences (p>0.05).
MBS = Martin Bell syndrome; MR = Mentally retarded.

observed were low set ears (13, 48.1%) and large/prominent ears (10, 37.0%). Among the 8 non-MBS female patients, 6 (75%) showed high arched palate, while 2 (25%) had low set and large ears, and 2 (25%) had hypotonia.

In patients with Martin Bell syndrome hyperactivity (14, 70%) was the commonest feature. Long face and large/prominent ears were the next common clinical features seen in 12 (60%) of the boys with Martin Bell syndrome. The features which most clearly differentiated fragile X-syndrome patients from others with nonspecific mental retardation were long face, hyperactivity and macro-orchidism. *Figure 2* depicts the clinical features of two patients with MBS. The prominent ears and bulbous nose are evident in both the boys.

Table II shows the presence of common features of fragile X-syndrome according to age (below and above 10 years). In younger

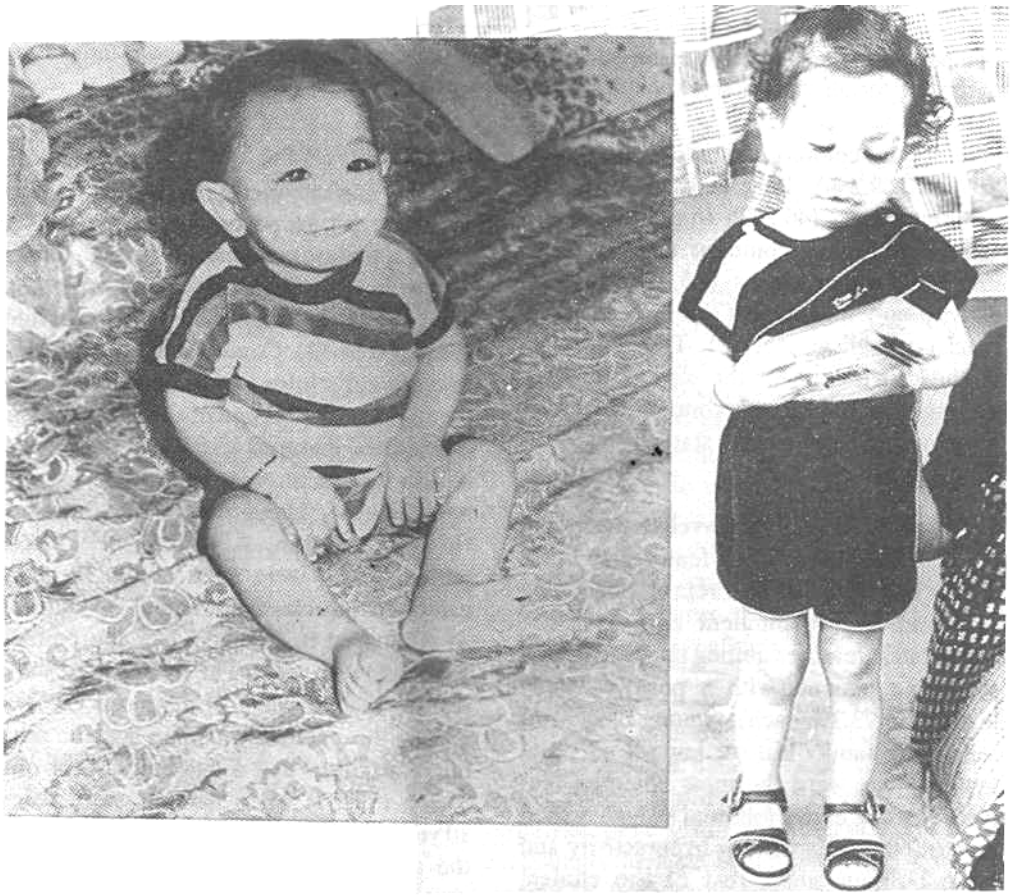

Fig. 2. Clinical features of two young boys with Martin Bell syndrome. Note prominent and lowset ears in the 1-year-old boy on the left. Prominent ears and bulbous nose are obvious in the 2½-year-old boy on the right.

TABLE II–*Variability of Clinical Features with Age of the Fragile X-Syndrome Patients (n=20)*

Clinical features*	Above 10 years (n = 7)		Below 10 years (n = 13)	
	No.	%	No.	%
Long face	5	71.4	7	53.9
Prominent ears	6	85.7	6	46.2
High fore-head	1	14.3	4	30.8
Macro-orchidism	4	57.1	2	15.4
Hyperactivity	5	71.4	9	69.2
Hypotonia	0	00.0	2	15.4
Mental retardation	7	100.0	13	100.0

Comparison of the presence of features in those below and above 10 years in age showed insignificant difference for all the features ($p>0.05$) on Fisher's exact test.

patients the common features were hyperactivity (69.2%), long face (53.9%) and prominent ears (46.2%). In the older boys (above 10 years) common features were large/prominent ears (85.7%), hyperactivity and long face (71.4% each), and macro-orchidism (57.1%). The difference in the distribution of the clinical features among the older and younger patients, however, did not reach statistical significance ($p>0.05$).

Table III depicts the correlation between the distribution of clinical features and past family history of mental retardation. Long face and large/prominent ears were the commonest features among the Martin Bell syndrome patients with a positive family history (in 73.3% each). Among those with a negative family history, low set ears and hyperactivity were the most common features (in 80% each), followed by high arched palate (60%). Except for hyperactivity and large/bulbous nose, rest of the clinical features did not show statistically significant difference in those with and without a positive family history ($p>0.05$).

Discussion

The clinical picture of MBS is fairly characteristic in post-pubertal males. The classical features comprise a "triad" consisting of long face with large and prominent ears, mental retardation and macro-orchidism(3,5,6,ll-13). Clinical diagnosis of MBS in younger children is hindered by the inconsistent expression of the characteristic craniofacial features(4,5,8,9,14,15). Presence of different features is reported to vary with age'(4,6,9,14). The present study supports this observation. All the four (100%) patients, who were aged above 12 years, exhibited the classical "triad" of features as compared to 2 (12.5%) of the patients aged below 12 years. The present study also reveals that the clinical diagnosis of MBS among the patients with non-specific mental retardation had a success rate of only 35.1% (13/37) when patients were below 10 years, and increased to 70% (7/10) when the age of the patient was more than 10 years.

Consistently observed feature among the patients with MBS in the present study was

TABLE III—*Correlation between the Clinical Features of MBS and Past Family History of MR*

Clinical features	Family history of MR			
	Positive (n=15)		Negative (n=5)	
	n	%	n	%
Long face	11	(73.4)	1	(20) *
large/prominent ears	11	(73.3)	1	(20) *
Hyperactivity	10	(66.7)	4	(80) NS#
Macro-orchidism	6	(40.0)	0	(0) NT
Large/bulbous nose	4	(26.7)	1	(20) NS##
Low set ears	3	(20.0)	4	(80) *
High forehead	3	(20.0)	2	(40) **
High arched palate	1	(6.67)	3	(60) *
Hypotonia	1	(6.67)	0	(0) NT

χ^2 test: *p = 0.000001; **p = 0.0034;
NS# = Not significant (p = 0.0545);
NS## = Not significant (p = 0.3170); NT = Not tested.

hyperactivity (70%), irrespective of age. This feature was seen in only 18.5% and 12.5% of the male and female patients with non- , specific mental retardation is. the study (p=0.0009 and 0.0007, respectively). This observation is consistent with a previous study by Simko, *et al.(9).* This indicates that behavioral abnormalities are the key to early diagnosis of MBS, in addition to the physical features.

Macro-orchidism is an important diagnostic clue although it is usually present in post-pubertal patients with MBS(3,4, 7,14,16). The present study also supports this observation as 6 (86.7%) of the 7 patients who had macro-orchidism were diagnosed as MBS patients. Four (57%) of them were above 10 years old and 2 (15.4%) were below 10 years of age.

Features of MBS like long face (p = 0.000001), large and prominent ears (p = 0.000001) and macro-orchidism were seen more commonly in those MBS patients with a positive family history than in sporadic cases. Soudek *et* of. (17) reported that almost 22.4% of the MBS patients did not show the characteristic features of the syndrome. We do not know how many of these patients were with or without a positive family history. It is likely that in the presence of positive family history, mild dysmorphic features are more likely to be detected than in patients with a negative family history.

In conclusion, the present study reveals that the younger patients with MBS show fewer clinical features characteristic of the syndrome. The key to diagnosis of the MBS in younger patients is the consistent observation of behavioral abnormalities rather than the presence of abnormal physical features. The present study confirms the weak

association between phenotypic expression of the clinical features of fragile X-syndrome with the age of patient. Presence of positive family history helps in the detection of the syndrome.

REFERENCES

1. Sutherland GR. Heritable fragile sites on human chromosomes. II. Distribution, phenotypic effects and cytogenetics. Am J Hum Genet 1979, 31: 136-148.
2. Sutherland GR. Heritable fragile sites on human chromosomes. XII. Poulation cytogenetics. Ann Hum Genet 1985,49:153-161.
3. Fiyns JP, Kleczkowska A, Kubien E, vanden Berghe H. Cytogenetic findings in moderate and severe mentally retarded: A study of an institutionalized population of 1991 patients. Acta Pediatr Scand 1984, 313: 1-23.
4. Fryns JP. X-linked mental retardation and the fragile X-syndrome: A clinical approach. *In:* The Fragile X-syndrome. Molecular Medicine Series 2. Ed Davies, KE. Oxford, UK. Oxford University Press, 1989, pp 1-39.
5. Nussbaum RL, Ledbetter DH. The fragile X-syndrome. *In:* "The Metabolic Basis of Inherited Disease", Vol. I, 6th edn.' Eds Scriver CR, Beaudet AL,, Sly WS, Valle D. New York, McGraw-Hill Information Services Co, USA. 1989, pp 327-342.
6. Largo RH, Schinzel A. Developmental and behavioral disturbances in 13 boys with fragile X-syndrome. Europ J Pediatr 1985, 143: 269-275.
7. Sutherland GR, Hecht F. Fragile Sites of Human Chromosomes. New York, Oxford University Press. 1985.
8. Hockey A, Crowhurst J. Early manifestations of the Martin Bell syndrome based on a series of both sexes from infancy. Am J Med Genet 1988, 30: 61-71.
9. Simko A, Hornstein L, Soukup S, Bagamery N. Fragile X-syndrome: Recognition in young children. Pediatrics 1989, 83: 547-552.
10. Elango R. Chromosomal fragile sites in the etiology of mental retardation. PhD Thesis. All India Institute of Medical Sciences, New Delhi. 1990.
11. Carpenter NJ. The fragile X-chromosome and its clinical manifestations. *In:* Cytogenetics of the Mammalian X-chromosome, Part B: X-chromosome Anomalies and Their Clinical Manifestations. Ed Sandberg AA. New York, Alan R Liss Inc, 1983, pp 399-414.
12. Nussbaum RL, Ledbetter DH. Fragile X-syndrome: A unique mutation in man. Ann Rev Genet 1986, 20: 109-146.
13. Chudley AE, Hagerman RJ. Fragile X-syndrome. J Pediatr 1987, 110: 821-831.
14. Fryns JP. The fragile X-syndrome. A study of 83 families. Clin Genet 1984, 26: 497-528.
15. Partington MW. The fragile X-syndrome. II. Preliminary data on growth and development in males. Am J Med Genet 1984, 17: 175-194.
16. Howard-Peebles PN, Finley WH. Screening of mentally retarded males for macroorchidism and the fragile X-chromosome. Am J Med Genet 1983,15:631-635.
17. Soudek M, Partington MW, Lawson JS. The fragile X-syndrome. I. Familial variation in the proportion of lymphocytes with the fragile sites in males. Am J Hum Genet 1984, 17: 241-252.