Symptomatic Carriers of Muscular Dystrophy

Pages with reference to book, From 89 To 93

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Abstract

Data of twelve females who were symptomatic carriers of Duchenne muscular dystrophy is being reported here. Age at the time of presentation varied from one year to 17 years. All patients presented with progressive motor disability or delayed development. Six patients were bed ridden and 8 had history of similar disorder in male sibblings. Majority of them had serum creatine kinase levels more than ten times the upper normal limit. Muscle biopsy was consistent with the diagnosis of muscular dystrophy in 4 patients and 1 patient had normal result. Overall prognosis was invariably poor (JPMA 47:89, 1997).

Introduction

The muscular dystrophies are a group of inherited and progressive muscle diseases. Dubhenne muscular dystrophy (DMD) is the most common X-linked disorder in man, with an incidence of about 1 in 3500 live male births and a prevalence rate of about 3 per 100,000 population[1]. Two-third of the mothers of affected boys are thought to be carriers and one-third are due to new mutations. About 10% of carriers have clinical symptoms, sometime also referred as “manifesting carriers”[2]. Serum creatine kinase (CK) activity is raised in 45-70%[3-5] of the carriers and about 70% also have some histological abnormalities on muscle biopsy[6-9]..Until recent past measurement of serum CK was the most commonly used method for detecting at risk females. However, during last few years there has been substantial progress in understanding the molecular basis of DMD. The affected gene (Xp2 1) has been cloned and its protein product named as “dystrophin” by Kunkel et al[10]. Dystrophin, a 400kb protein is localised at the sarcoplasmic membrane of normal skeletal muscle and comprises approximately 0.01-0.001% of total fraction of muscle protein[10-14] Dystmphin is also normally expressed in cardiac muscles, visceral and smooth muscles and brain[15]. Lack of dystrophin causes breakdown of muscle fibres and loss of muscle power. Dystrophin can easily be detected in a small muscle biopsy specimen using antidystmphin antibodies” (Figure 1A).

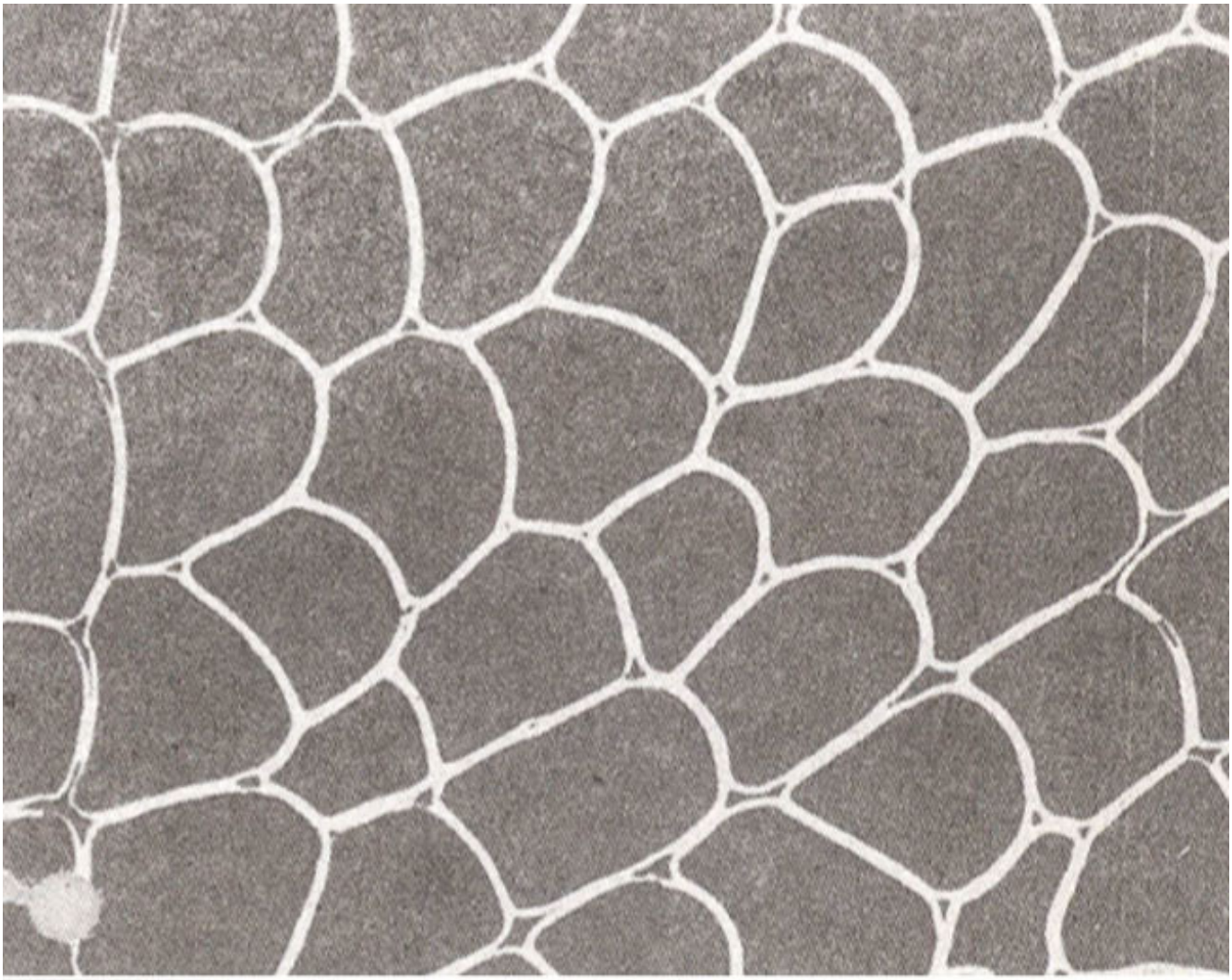

Figure 1 (A). Normal muscle with normal dystrophin. Not clear immunostaining of all surface membranes.

The complete or almost complete abscence of dystrophin is very specific and characteristic of severe Duchenne phenotype whereas, in Becker's muscular dystrophy (BMD), a milder variant, it is usually present but of abnormal size. Symptomatic carriers of DMD have been shown to have patchy involvement of muscle fibres which gives a distinct mosaic pattern (Figure 1B)

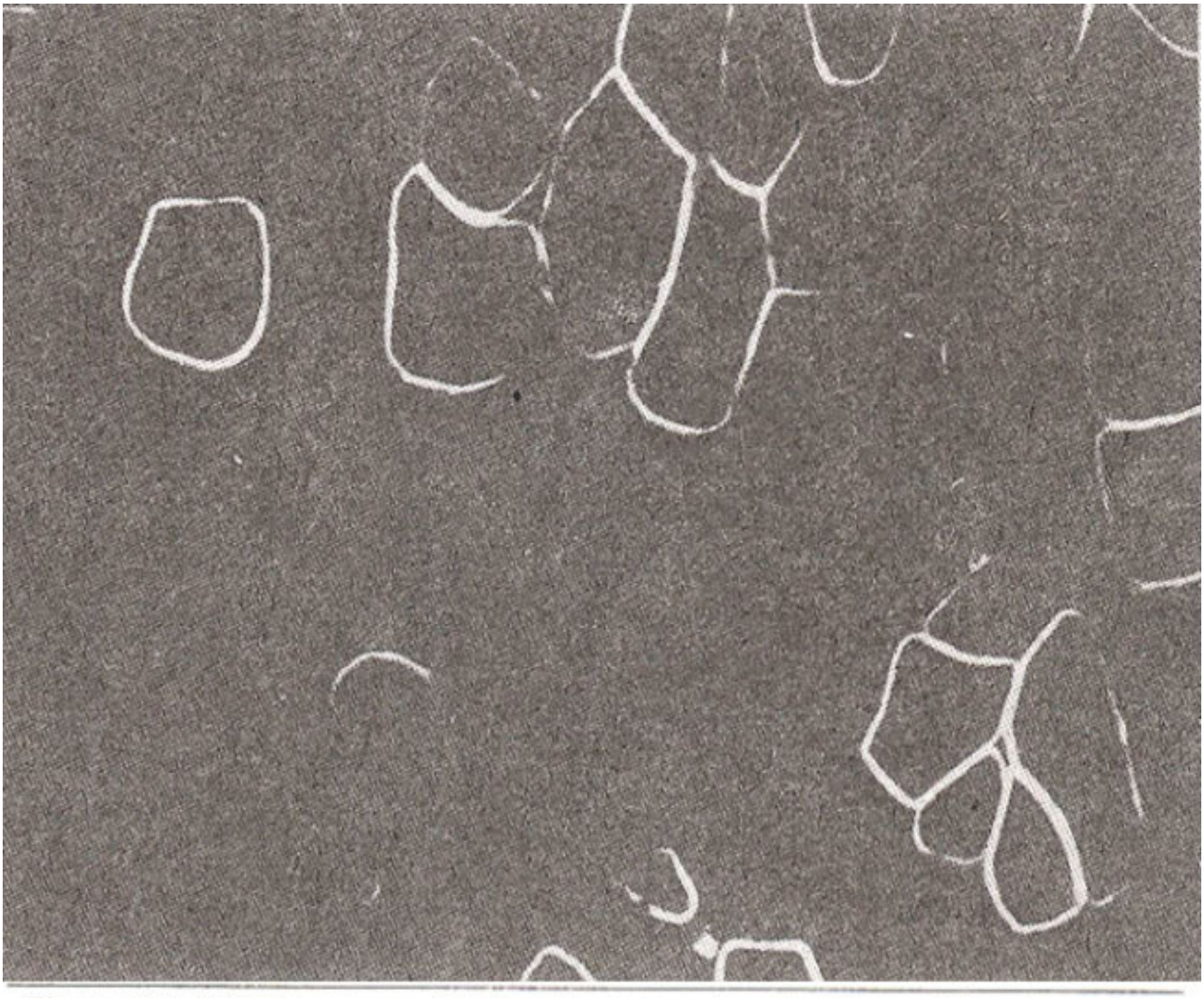

Figure 1(B). Mosaic pattern of dystrophin in symptomatic carriers. Note dystrophin positive and negative muscle fibres. (In DMD all fibres are dystrophin negative slide not shown).

on immunohistochemical staining of skeletal muscle membrane[16]. The diagnosis of DMD is usually stmightfozward. A typical patient is a small boy who presents with abnormal/waddling gait and frequent falls, has markedly raised semmCK; EMG is myopathic andbiopsy has typical findings[17] (Figure 2).

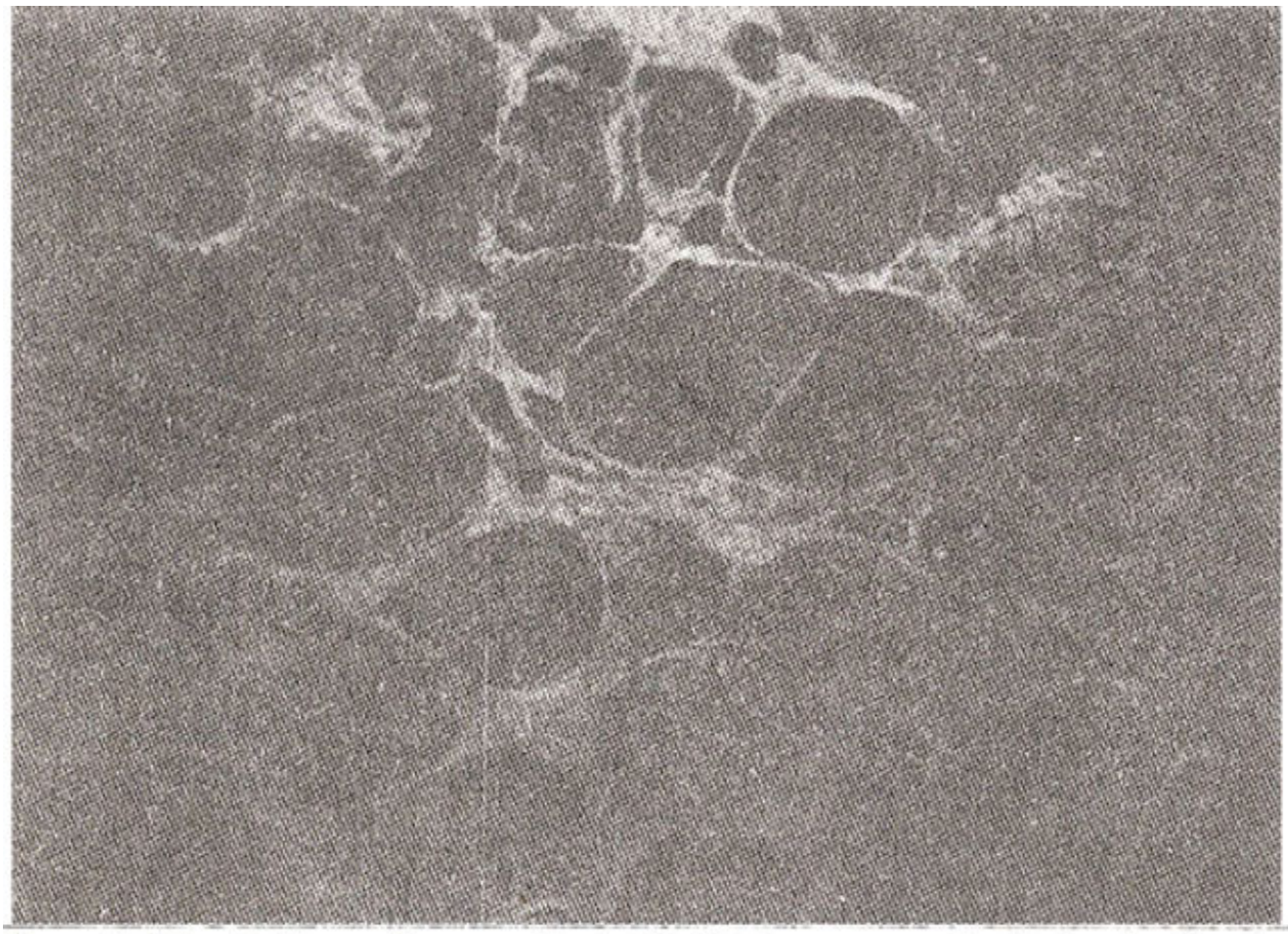

Figure 2. Muscle biopsy from a patient with Duchenne muscular dystrophy showing variation in size, necrosis and regeneration of muscle fibres (H/E stain).

But accurate diagnosis may be difficult without dystrophin analysis when patient is a female child who presents with identical clinical features and has raised serum CK. This study reports pmbable "symptomatic carriers", though in some girls where an X- linked history is lacking, other diagnoses such as limb girdle or autosomal recessive-Duchenne-like muscular dystrophy cannot be ruled out.

Patients and Methods

Two hundred and thirty-two patients were referred to neurophysiology laboratory of Children Hospital, PIMS for evaluation of their neuromuscular status between May, 1992 and August, 1995. On the basis of clinical presentation, raised serum CK and myopathic EMG or both, twelve female patients were diagnosed as "symptomatic carriers" of DMD. An "inclusion and exclusion criteria" (Table I)

Table I. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Progressive motor disability	Features suggesting diagnosis of:
Raised serum CK	- Dermatomyositis
Myopathic EMG	- Polymyositis
	- Peripheral neuropathy
	Reduced foetal movements
	Sucking, swallowing difficulties during infancy
	Congenital deformities e.g., arthogryposis, dislocated hip
	Normal serum CK
	Normal or neurogenic EMG

was used comprising of clinical and laboratory data. Only those patients who presented with delayed motor development or progressive motor disability, raised serum CK or myopathic EMG were included. History of DMD in male family members was considered a reliable evidence in support of the diagnosis. Positive Gower's sign, calf hypertrophy and weakness of pmximal more than distal muscles were additional features.

Patients were examined and serum CK was done in 10, EMG in 9 and muscle biopsy in 5 patients. One girl also had chromosomal analysis. Serum CK levels were also determined infive mothers. As none of the patients had cardiac findings or obvious cognitive difficulties, ECG, chest X-ray and "developmental assessment" were not done.

Results

Clinical features, family history is shown in Table II.

Table II. Clinical and laboratory data.

No.	Age (Y)	Clinical features	CK	EMG	Biopsy	Family history
1	8	Weakness, lordoticgait +Gower	4226	myo	ND	18 y M, now bed ridden
2	4	Delayed development, never walked properly, now bed ridden	5390	myo	dyst	none
3	10	Frequent falls +Gower	1803	myo	normal	none
4	17	Tiptoe walking +Gower, calf hypertrophy, now bed ridden	ND	myo	ND	8y M, waddling, tiptoe walking +Gower, CK5572, mother CK116
5	8	Tiptoe walking, gets tired easily +Gower	370	ND	ND	11y M, waddling, calf-hypertrophy +Gower, CK 3480, mother CK230 (upto 180)
6	8	Frequent falls +Gower, calf hypertrophy	7243	myo	dyst	12y M bed ridden mother CK72
7	9	Late walking +Gower, waddling, 46XX, calf hypertrophy	13000	myo	dyst	Two M sibs died during infancy
8	11	Delayed walking, waddling gait calf-hypertrophy	ND	myo	ND	8y M, frequent falls, +Gower, calf hypertrophy, CK7480
9	10	Waddling gait, now bed ridden	2800	myo	ND	3 mon M, CK3656 biopsy dystrophy 10y, aunt died
10	1	Motor delay, sits briefly	3060	myo	dyst	mother CK 180 (upto 165)
11	8	Late, tiptoe walking +Gower	3693	ND	ND	6yM, waddling, calf hypertrophy, +Gower CK 6708
12	4	Late, tiptoe walking	3710	ND	ND	5y M, waddling, calf hypertrophy, +Gower CK 8165, mother CK 223 (Upto 180)

Age(Y) = age in years, ND = not done, myo = myopathic, dyst = dystrophy, M = male sibbling, patients No.11 and 12 are sisters.

Age at the time ofpresentationvariedbetween one to 17 years. Seven (58%) patients were between the age of 8 and 10 years, 3(25%) less than5 and2 (17%) more than 10 years. Mean age was eight years. All patients presented with either history of delayed development or progressive motor disability or both. Gower's sign was positive in 7(58%) and enlargement of calf muscles was seen in 4 (33%) patients (Figure 3).

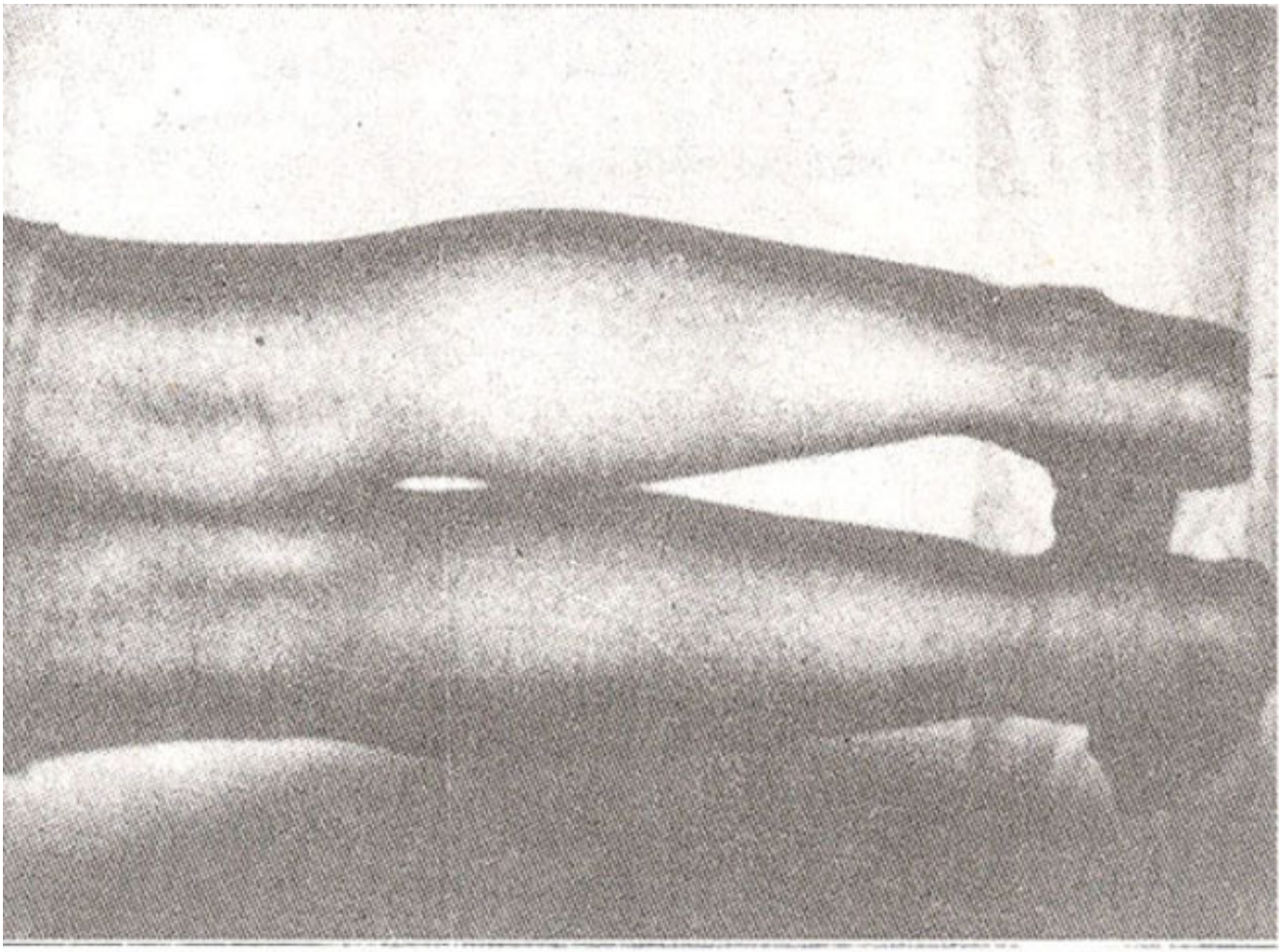

Figure 3. Patient No. 6 with calf hypertrophy. Her Serum CK was 7243.

In 9 patients (90%) serum CK was raised more than ten times above the upper normal limit and in one was slightly raised. EMG was myopathic in 9(100%) patients, 4(80%) musciebiopsies were consistent with the diagnosis of muscular dystrophy while results of one biopsy were reported normal. Chromosomal analysis performed on one patient was normal 46XX. Eight (66%) girls had clear history of one or more affected brothers. Two patients (no.11 and 12) are natural sisters with two affected brothers and in one patient (no.7), 2 brothers died of unknown cause during infancy. In 3 patients (No.2,3 and 10), there was no family history. Three mothers of 4 patients (including 11 and 12) have slightly raised whereas two mothers have nonnal serum CK levels.

Discussion

Twelve girls were diagnosed as symptomatic (manifesting) carriers. Although Duchenne muscular dystrophy is much more common in boys but girls have been described as having the disease in mild form. One of the Gower's female patients was apparently a "manifesting carrier"[18,19] With characteristic phenotypical features, majority of our patients especially those who have a clear history of one or more affected males in the family, most probably are manifesting carriers. This canbe explained onthe basis of Lyon's hypothesis which suggests that in the affected girls most of the muscle cells-X-chromosomes, inherited from mother are active and lead to the manifestations of the disease[20,21]. Those females can also have DMD who have a translocation of the short arm of the X-chromosome with one of the other chromosomes. Boyd et al[22] reviewed 20 girls with X- autosome

translocation with breakpoints at Xp[21] associated with Duchenne or Becker muscular dystrophy. Turner syndrome with an XO pattern is another rare situation which may co-exist with DMD in a girl, since the abnormal X is not suppressed by the missing normal chmmosome. In our patient who had chromosomal analysis, results were normal 46XX. Some other X-linked recessive disorders can also manifest in females with normal karyotype by inactivation of paternal X-chromosome or lyonization, as in cases of female patients of haemophilia[23] or vasopressin-resistant diabetes insipidus[24]. Moser and Emery[2], reported a large series of manifesting carriers with age varying from 4 to 79 years.
While others[25] reported seven patients who presented during second and third decades of life with slowly progressive weakness. All had raised serum CK, myopathic EMGs and myopathic muscle biopsy. Sewry et al[26] described three manifesting carriers aged 3,5 and 12 years and a presumptive carrier, 24 years old motherof 5 years old child. All had mosaic pattern on immunohistochemical staining. In our series patients are generally young and severely affected. The clinical course, rapidity of progression and severity of clinical manifestations can be similar both in boys and girls with DMD[27]. Two of our patients (No. 11,12) are sisters though not twins, with two affected brothers and a carrier mother with raised serum CK. There are several reports of monozygotic twin girls where one of the twin is a manifesting carrier and the other twin is normal heterozygous for DMD[28-30]. In one of the twins the mother was a non- manifesting carrier[28]. In four of our patients[2,3,7,10]. there was no family history, though phenotype was identical to DMD. Yainamoto eta! reported a two years symptomatic carrier of DMD confirmed by dystrophin studies an! there was no family history. Moser and Emery[2] suggested that manifesting carriers of DMD are as common as limb girdle muscular dystrophy (LGMD), atleast in adults. There is considerable clinical overlap between LOMID and dystrophinopathies. In the past, DMD patients were diagnosed as LGMD. In one series,[7] patients out of 41 and in other 13 patients out of 46 LGMI) were rediagnosed alter dystrophin studies as dystrophinopathies including DMD, BMD and manifesting carriers[32,33]. In LGMD onset is usually late and CK is either normal or slightly raised. This diagnosis was not considered in our patients. However, in two patients[9,10], other diagnoses such as autosomal- recessive Duchenne-like muscular dystrophy and congenital muscular dystrophy (CMD) were considered. Autosomal recessive Duchenne-like muscular dystrophy has been reported from Africa[34], Middle East[35] and some other countries[36]. This condition differs slightly from X-linked DMD and has a milder course, affects deltoid muscles more severely, intelligence and ECG are normal and muscle biopsy has a more local pattern of muscle pathology[37]. It affects both boys and girls equally and sytrophin is normal[38] Characteristic features of CMD include fixed deformities such as arthrogryposis, swallowing and respiratory difficulties or mental retardation. None of the rtient in this series had any of these features. Matsuniura et al reported occunence of CMD (Fukuyama type) and DMD in a Japanese family.
In our patients ECGs were not done, however, several investigators have reported ECG abnormalities inupto 90% of cases of DMD[40,41]. Commonly described abnormalities are sinus tachycardia, abnormally tall R waves and shallow S waves in the leads Vi and V2 and deep, narrow (non-infarction) Q waves in the lateral chest leads, short P-R interval, Rsr' pattern in VI and bundle branch block. Emery[42] and Russelet al[43] have shown that amplitude sum (R-S)in lead VI is significantly greater in carriers than controls and RJS ratios in Vi and V2 are abnormal in carriers. There was no co-relation between CK levels and ECG findings[43]. Until recently, serum CK was the most commonly used screening method to detect DMD carriers. Similarly manual muscle testing has been used to detect the female carriers. By standardised manual muscle testing techniques, weak proximal muscles can be demonstrated in most carriers and some degree of proximal muscle weakness has been reported in majority of carriers[44]. With the availability of molecular genetics such as DNA analysis, polymerase chain reaction (PCR) techniques and dystrophin assays either by Western blot or immuno-

histochemical studies, have revolutionized the ability to make accurate diagnosis of DMD/BMD, manifesting and non-manifesting carriers. However, at present these highly sensitive and accurate diagnostic facilities (to my knowledge) are not available in this country. Therefore, we shall have to rely on clinical manifestations, family history and laboratory data such as serum CK, EMG and muscle biopsy. Presence of X-linked inheritence in the family and raised serum CK in mother can be of great help in the diagnosis of Duchenne and Becker muscular dystrophy in females.

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