Symptomatic Carriers of Muscular Dystrophy

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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 siblings. 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. Duchenne 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\(^10\)-\(^14\)\). Dystrophin 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 antidystrophin antibodies” (Figure 1A).
The complete or almost complete absence 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)
on immunohistochemical staining of skeletal muscle membrane\textsuperscript{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\textsuperscript{17} (Figure 2).
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 probable “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)
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 proximal 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 in five 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.
Age at the time of presentation varied between one to 17 years. Seven (58%) patients were between the age of 8 and 10 years, 3 (25%) less than 5 and 2 (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).
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%) muscle biopsies 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 a 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 normal 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 can be explained on the 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 disease20,21. 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 al22 reviewed 20 girls with X-autosome
translocation with breakpoints at Xp\textsuperscript{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 chromosome. 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\textsuperscript{23} or vasopressin-resistant diabetes insipidus\textsuperscript{24}. Moser and Emery\textsuperscript{2}, reported a large series of manifesting carriers with age varying from 4 to 79 years. While others\textsuperscript{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\textsuperscript{26} described three manifesting carriers aged 3.5 and 12 years and a presumptive carrier, 24 years old mother of 5 years old child. All had mosaic pattern on immunohistological 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\textsuperscript{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\textsuperscript{28-30}. In one of the twins the mother was a non-manifesting carrier.\textsuperscript{28} In four of our patients\textsuperscript{2,3,7,10}, there was no family history, though phenotype was identical to DMD. Yainamoto et al reported a two years symptomatic carrier of DMD confirmed by dystrophin studies and there was no family history. Moser and Emery\textsuperscript{2} suggested that manifesting carriers of DMD are as common as limb girdle muscular dystrophy (LGMD), at least in adults. There is considerable clinical overlap between LOMID and dystrophinopathies. In the past, DMD patients were diagnosed as LGMD. In one series,\textsuperscript{7} patients out of 41 and in other 13 patients out of 46 LGMD were rediagnosed after dystrophin studies as dystrophinopathies including DMD, BMD and manifesting carriers\textsuperscript{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\textsuperscript{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\textsuperscript{34}, Middle East\textsuperscript{35} and some other countries\textsuperscript{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\textsuperscript{37}. It affects both boys and girls equally and syntrophin is normal\textsuperscript{38}. Characteristic features of CMD include fixed deformities such as arthrogryposis, swallowing and respiratory difficulties or mental retardation. None of the patients in this series had any of these features. Matsuniura et al reported occurrence of CMD (Fukuyama type) and DMD in a Japanese family. In our patients ECGs were not done, however, several investigators have reported ECG abnormalities in up to 90% of cases of DMD\textsuperscript{40,41}. Commonly described abnormalities are sinus tachycardia, abnormally tall R waves and shallow S waves in the leads V1 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\textsuperscript{42} and Russelet al\textsuperscript{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 correlation between CK levels and ECG findings\textsuperscript{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\textsuperscript{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 inheritance 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.

Acknowledgement

My special thanks are due to Dr. I. Nonaka M.D., Head, Division of Ultrastructural Research, National Institute of Neurosciences, NCNP, Tokyo, Japan, for providing photographs of muscle biopsy with normal dystrophin and mosaic pattern of symptomatic carrier of DMD.

References