Severe Muscular Dystrophy in Girls*

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Discussions about the classification of muscular dystrophy revolve, to a considerable extent, round the question whether clinical similarity or mode of inheritance should form the basis of groupings. It is recognized, however, that the most numerous and clinically homogeneous group of the muscular dystrophies is the sex-linked form characterized by early onset, initial weakness in the pelvi-femoral muscles, and rapid progression. Pseudohypertrophy of muscles is more common in these cases than in other types of muscular dystrophy, and progression is so rapid that few patients are able to walk after the age of 15 years (Stevenson, 1964). However, Becker (1955), Walton (1955), and others have described a milder form in families where progression is much slower but age of onset overlaps with those of cases in the severe group.

Sporadic male cases of autosomal recessive determined limb girdle dystrophy with early onset cannot be distinguished with confidence from the severe sex-linked form until followed up over several years. Moreover some autosomal recessive cases may be as severe as the sex-linked form so that only the familial pattern of the disorder enables a clinico-genetical diagnosis to be made. Cases of this type are reported and quoted by Klopfer and Talley (1958).

In the early literature a few cases of 'Duchenne' type muscular dystrophy in girls were reported. Stevenson (1953) pointed out that most of such cases were much less severe than the sex-linked form in males and that Bell's (1943) classification on a basis of pseudohypertrophy could not be sustained, as this phenomenon was common to a wide range of clinical and genetical types. Walton (1955) reported two sporadic cases in girls in his 'Duchenne' cases, but one subsequently progressed rather slowly and the other (Walton, 1956) proved to be of male nuclear sex and presumptive XO karyotype.

The published reports thus suggest that there are rare cases in girls, otherwise indistinguishable from the severe sex-linked type, where a severe autosomal recessive gene is the determinant; in addition there is the possibility that relative to the few reported families an excess of sporadic cases in girls does occur. Such a girl was encountered in course of another inquiry concerning muscular dystrophy in the Oxford area, and it was decided to make an attempt to find a group of cases for study.

Subjects and Methods

It was realized that severe cases in girls must be very uncommon and that only screening of a very large population would yield a sufficient number of cases. Dr P. Henderson, Principal Medical Officer of the Ministry of Education, kindly provided a list of local authority and voluntary day and residential schools for physically handicapped girls in England. School Medical Officers of local education authorities and Head Teachers or attending Medical Officers at all the schools, were asked to notify all girls with muscular dystrophy who were unable to walk by the age of 16 years. It was felt that such a criterion would include all the really severe cases and that most such girls would be attending special schools. Information was given in respect of 30 of the 32 schools.

In all 18 girls were notified and all were visited. Of these, 4 were found not to have muscular dystrophy and one family did not wish to co-operate. One case proved to be a rather rapidly progressive sporadic case of limb girdle muscular dystrophy with face affected. She was still walking with difficulty at 16 years. Two others were of a milder type without affected face. There were, therefore, available for study 10 severely affected girls in addition to the girl ascertained in the Oxford area.

The clinical and genetical data on these 11 girls are set out in the Table.

All these families were visited and the girls were examined. They presented clinical pictures very similar to those encountered in the severe sex-linked form in boys. All had been investigated by paediatricians and/or neurologists. All had single sex-chromatin bodies in cells from buccal smears.

* Received March 25, 1964.
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TABLE

SUMMARY OF DATA RELATING TO CASES OF RAPIDLY PROGRESSIVE MUSCULAR DYSTROPHY OF EARLY ONSET IN FEMALES ASCERTAINED IN ENGLAND

<table>
<thead>
<tr>
<th>Family</th>
<th>Pedigree Ref.</th>
<th>Affected Born</th>
<th>Age at Onset (yr.)</th>
<th>When Living at Dec. 1, 1962</th>
<th>Pseudo-</th>
<th>Torque Endurance</th>
<th>Obesity</th>
<th>Age at Times of Birth of Affected Girls of</th>
<th>Summary of Sibships</th>
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<td></td>
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<td></td>
<td>A</td>
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<tr>
<td>G 1</td>
<td>III 1 5 12</td>
<td>16</td>
<td>- Deltoid</td>
<td>+</td>
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<td>22</td>
<td>22</td>
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<td>III 1 13 14</td>
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<td>25</td>
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<tr>
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<td>17</td>
<td>+ Deltoid</td>
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<td>30</td>
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<td>-</td>
<td>37</td>
<td>37</td>
<td></td>
<td>No</td>
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* See pedigree in Figure.
† A = Affected.
‡ U = Unaffected.
§ B.S. = Buccal smear.
Note.—Age shown in parentheses indicates the age attained at December 1, 1962, but child is still able to walk.

As will be seen from the Table only one family had a sib affected—the brother in family G 1. This family, where no parental consanguinity was known, appears to correspond in type to those with severe effect recessive dystrophy described by Klopfer and Talley (1958).

In Family G 3, though no sibs of the index girl were affected, three children of the mother’s sister and a cousin of the mother were affected pedigree. The propositus III. 3 always walked with great difficulty and ceased to walk unaided at 13 years. When seen at 15 years, she had gross pseudohypertrophy of the calves, wasting of adductor and pelvic muscles, and less severe dystrophy of the shoulder girdle muscles. Her cousin III. 9, aged 12 when seen, had never walked and shows a very similar clinical picture to his cousin. III. 11 died of leukaemia at 1 year. III. 12 only walked at 2 years and was walking with difficulty when seen at 6 years. III. 14 also was only beginning to walk with difficulty when seen at 2 years. In both III. 12 and III. 14 the clinical picture was similar to that in the other affected relatives. III. 6 appears to have suffered from muscular dystrophy: he last walked at 15 years, and from 9 years of age had been in a wheel-chair much of the time. He died aged 21 from an unknown cause. The history is rather vague, but it is possible that II. 5 was affected.

It is impossible to dogmatize about the mode of inheritance in this family. Consanguinity of any of the relevant matings is strongly denied, and it seems highly improbable that three close relatives should each by chance have married a heterozygote carrier. Clinically the condition is indistinguishable from the severe sex-linked form and no such severe dominant cases have been described, so that perhaps recessive inheritance is the most likely explanation.

The remaining 9 girls were the only cases known in these families and in none were the parents related.

Discussion

The most obvious explanations for these 9 sporadic cases are that they are either the only homozygous offspring of two heterozygote parents or that they represent phenocopies. Two of these
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girls were only children and the remaining 7 had 14 unaffected sibs, 4 brothers and 10 sisters. In this number of sibships of the sizes shown in the Table (ascertained by one affected) we should expect, on a recessive hypothesis, only 9 affected, but we observe 7; so that clearly it could very well be a chance finding that all cases were singletons. If we take all 11 families into consideration the number affected is very close to expectation. It is not suggested that all cases in England of comparable severity to the cases presented were ascertained, and it is difficult to relate those ascertained to a population. The age range of cases when seen was from 9 to 17 years inclusive. There are about 6,000,000 children in this age-group in England, so that the ascertained frequency of the sporadic cases is about 1/650,000. Even if only one-third of cases were ascertained and there was an equal frequency of comparable sporadic boys then the frequency would still only be about 1/100,000. On that basis and assuming the prevailing first-cousin marriage rate in the population to be about 0.5%, we should have expected about 10% of parents to be related, and the lack of consanguinity in these parents is not necessarily an argument against a recessive hypothesis. If these girls were phenocopies we should probably still expect a comparable number of affected sporadic boys. There is no need to postulate the occurrence of phenocopies in boys to fit the pattern of segregation of the severe sex-linked form if we assume equal mutation rates in the X chromosome in males and females (Cheeseman, Kilpatrick, Stevenson, and Smith, 1958); but such a low frequency of sporadic cases would not be detectable in any series of sex-linked muscular dystrophy cases of a size which could be thoroughly ascertained and investigated.

Morton and Chung (1959) submitted their own and other published data on the muscular dystrophies to discriminant function analysis. This appeared to ‘identify’ a limb girdle autosomal recessive group, but in an undue proportion of the sibships only one sib was affected. The authors suggest that these ‘sporadic’ cases represent phenocopies. Unfortunately they do not mention the sex or the severity of such cases. It seems likely that some of the cases here reported represent recessive homozygotes, but for reasons suggested above it is doubtful whether all may be so explained. In addition to G1 and G3 where relatives were affected another family that included very severely affected individuals, and where the parents were first cousins, was recently ascertained in the Oxford area. None of the affected were alive when the family came to notice. In this family a boy and a girl had had very rapidly progressive muscular dystrophy and the hospital notes suggested that they were indistinguishable from the severe sex-linked form. However, no families with such severely affected girls were seen in series reported by Stevenson (1964), Walton (1955), or Blyth and Pugh (1959), which suggests that they are very uncommon.

Summary

An account is given of 11 girls with severe rapidly progressive muscular dystrophy ascertained through the Local Education Authorities in England. All these girls have concordant nuclear and phenotypic sex. In 9 of the families the cases were sporadic. The clinical picture in these girls appears to be indistinguishable from that in the severe form in boys, which constitutes a very high proportion of sex-linked cases.

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