A Spanish family is reported with dystrophinopathy of myalgia and cramps syndrome type. There were five affected males and three females, and also six asymptomatic carriers. Muscle biopsy showed a dystrophic pattern, but immunohistochemistry carried out with three anti-dystrophin antibodies was normal. Dystrophin analysis by western blot revealed a dystrophin of reduced quantity and molecular weight. DNA analysis showed a deletion of the dystrophin gene involving exons 45–52. The natural history of this disorder and the large intrafamilial clinical variability are discussed.

Exercise intolerance associated with myalgia, muscle cramps, or myoglobinuria may be associated with a dystrophinopathy. Gospe et al in 1989 were the first to describe a family with an X linked recessive disorder of childhood onset characterised by muscle cramps, myalgias, and exercise intolerance. On examination patients had pseudohypertrophic calves but no muscle weakness. Analyses revealed raised serum creatine kinase (CK) levels and myoglobinuria. Muscle biopsy showed myopathic changes and the immunohistochemical examination and immunoblot revealed an abnormal dystrophin. Several dystrophin gene deletions have been described as the origin of this syndrome.

Since Gospe’s description of the disorder in an American family, sporadic cases have been reported. Figarella-Branger et al found five males with exercise intolerance and abnormal immunohistochemistry. DNA analysis revealed a deletion in the dystrophin gene in two of these patients, affecting the proximal part of the rod domain in one and the distal part of this domain (exons 45–52) in the other. Ishigaki et al reported a four year old Japanese boy with myalgia and cramps which developed at the age of 28 months; there were persistently raised CK values but normal physical examination and muscle biopsy. DNA analysis revealed a deletion of exons 13–18 in the dystrophin gene. Kleinsteuber et al reported an eight year old boy with this syndrome and deletions of exons 45–51 of the dystrophin gene. Doriguzzi et al described a nine year old boy with exertional myalgia; he had episodes of myoglobinuria and was found to have a deletion of exons 45–48 of the dystrophin gene.

In this paper we report a Spanish family with myalgia and cramps showing deletion of exons 45–52 of the dystrophin gene. The natural history of the disorder can be studied in this large family. The intrafamilial clinical variability is remarkable.

FAMILY STUDY
The Spanish family reported (fig 1) contains no consanguineous relationships. The propositus (II,4) complained of muscular pain and cramps in the extensor muscles of the lower limbs provoked by normal activity and physical exercise from the age of four years. The patient could not run and became easily tired when walking long distances or going upstairs. At the age of 45, the symptoms extended to the muscles of the forearm and hand. He also developed myoglobinuria with fever and after physical exercise. He had never experienced chest pain. Neurological examination revealed only hypertrophic calves. Analysis showed persistently high serum CK levels (2000 to 4000 U/l at rest in different evaluations). At age 50, the patient remains the same and no muscle weakness has developed.

The propositus’s mother, aged 76 (I,2), had suffered from leg cramps during sleep since she was a child. She had hypertrophic calves and her serum CK was 384 U/l (normal <185).

Two brothers, aged 47 (II,5) and 40 (II,7) respectively, complained of similar symptoms and were affected to a variable degree. They first experienced myalgias and cramps in the first decade of life. Neither of them had ever had cardiac symptoms. Patient II,5 had no limitation on physical activity. Patient II,7 had reported some difficulty in going up stairs or standing up from a chair in the past year. Examination revealed hypertrophic calves and mild bilateral paresis in both quadriceps (4/5 strength) with amyotrophy of the distal part. Serum CK was persistently high, between 953 and 1315 U/l. Four years after the first evaluation, muscular strength remains the same.

One sister of 52 (II,3) had complained of leg cramps after physical exercise since she was a child. She also had hypertrophic calves and a serum CK of 327 U/l. Her youngest child of 17 (III,8) had suffered from cramps and myalgias since he was four years old. His symptoms improved in adolescence and he even participated in sport. Examination revealed hypertrophy in the quadriceps muscles and the calves. He had myoglobinuria and CK levels of around 4000 U/l on several determinations. Two years later he is a very good football player and shows diffuse muscular hypertrophy.

One grandson (IV,1) of the propositus’s sister (II,1), aged seven, had had cramps and muscular pain in all four limbs and myoglobinuria since he was three years old.

Other members of the family, who were asymptomatic, also participated in the genetic study (table 1).

Complementary tests
All affected males had raised serum CK at rest on repeated evaluations. Three females (I,2; II,1, and II,3), one of them asymptomatic, had a slightly raised serum CK. The propositus had normal results in the ischaemic exercise lactate and ammonium test. Electromyography and cardiac investigations (ECG and echocardiography) were also normal.

Biceps muscle biopsy was carried out in patients II,3, II,4, and II,7. Haematoxylin and cosin staining showed similar results: a myopathic pattern with variation in fibre size, basophilia, necrosis, ring fibres and clefs, internal nuclei, and fibrosis. Biochemical tests (lipid, glycogen, and mitochondrial metabolism) were all negative. The immunohistochemical

Abbreviations: BMD, Becker muscular dystrophy
procedure was carried out with three antibodies (Novocastra®) against different protein domains—anti-dys1, rod domain; anti-dys2, C terminus; and anti-dys3, N terminus—with normal results. Spectrin immunohistochemical labelling, immunoreactivity for \(\alpha\), \(\beta\), \(\delta\), and \(\gamma\) sarcoglycans, and a laminin test were also carried out, with normal results.

A dystrophin western blot was undertaken on SDS-PAGE, using goat polyclonal anti-rod (30 kDa) or mouse monoclonal anti-C-terminus dystrophin antibodies (Novocastra), as described elsewhere. This was done on the muscle biopsy from patient II. A non-dystrophic muscle was used as a control. The post-blot gel was stained with Coomassie blue to estimate the amount of muscle proteins present in each sample to obtain the relative quantity of dystrophin. We found a band of dystrophin corresponding to the carboxyl domain, of lower molecular weight and lesser intensity (fig 2)

**Genetic analyses**

Molecular analysis was carried out using multiplex polymerase chain reaction (PCR). Genomic DNA was extracted from peripheral blood following the protocol described by Dracopoli et al. We analysed 23 exons and two gene promoters located in the main deletion hot spot of the gene in three different PCRs. Deletions of exons 45–52 were identified in affected male patients.

A study of female carriers was carried out by indirect molecular analysis with microsatellite markers. The entire nuclear family was included in the study and the segregation analysis served to identify female carriers.

**Table 1** Clinical and genetic features in affected family members

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Clinical features</th>
<th>Serum CK (IU)</th>
<th>Biopsy</th>
<th>Dystrophin gene deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I,2</td>
<td>76</td>
<td>F</td>
<td>Cramps, calf hypertrophy</td>
<td>384</td>
<td>–</td>
<td>del 45–52</td>
</tr>
<tr>
<td>II,1</td>
<td>55</td>
<td>F</td>
<td>Calf hypertrophy</td>
<td>314</td>
<td>–</td>
<td>del 45–52</td>
</tr>
<tr>
<td>II,2</td>
<td>54</td>
<td>F</td>
<td>None</td>
<td>120</td>
<td>–</td>
<td>del 45–52</td>
</tr>
<tr>
<td>II,3</td>
<td>52</td>
<td>F</td>
<td>Cramps, calf hypertrophy</td>
<td>1227</td>
<td>Yes</td>
<td>del 45–52</td>
</tr>
<tr>
<td>II,4</td>
<td>49</td>
<td>M</td>
<td>Myalgia, cramps, calf hypertrophy, myoglobinuria</td>
<td>2560</td>
<td>Yes</td>
<td>del 45–52</td>
</tr>
<tr>
<td>II,5</td>
<td>45</td>
<td>M</td>
<td>Myalgia, cramps, calf hypertrophy</td>
<td>1250</td>
<td>–</td>
<td>del 45–52</td>
</tr>
<tr>
<td>II,7</td>
<td>40</td>
<td>M</td>
<td>Myalgia, cramps, weakness, calf hypertrophy, myoglobinuria</td>
<td>953</td>
<td>Yes</td>
<td>del 45–52</td>
</tr>
<tr>
<td>III,1</td>
<td>23</td>
<td>F</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>III,4</td>
<td>18</td>
<td>F</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>III,8</td>
<td>17</td>
<td>M</td>
<td>Myalgia, cramps, calf hypertrophy, myoglobinuria</td>
<td>4000</td>
<td>–</td>
<td>del 45–52</td>
</tr>
<tr>
<td>III,11</td>
<td>20</td>
<td>F</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>del 45–52</td>
</tr>
<tr>
<td>III,12</td>
<td>21</td>
<td>F</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>del 45–52</td>
</tr>
<tr>
<td>III,18</td>
<td>15</td>
<td>F</td>
<td>None</td>
<td>100</td>
<td>–</td>
<td>del 45–52</td>
</tr>
<tr>
<td>IV,1</td>
<td>7</td>
<td>M</td>
<td>Myalgia, cramps, calf hypertrophy, myoglobinuria</td>
<td>3212</td>
<td>–</td>
<td>del 45–52</td>
</tr>
</tbody>
</table>

CK, creatine kinase; F, female; M, male.
The clinical, histopathological, biochemical, and genetic data of the family we describe correspond to a myalgia and cramps syndrome. The natural history of the disease in this family may provide a mildly abnormal dystrophin which explains a normal immunohistochemical reaction in cases with myopathic muscle biopsy and normal dystrophin immunostaining. Immunoblotting can be the key to identifying the abnormal protein.

BMD and myalgia-cramps syndrome seem to represent different phenotypic expressions of the same disease. This confirms the extremely variable presentation and progression of dystrophinopathies. A better understanding of the molecular basis of this syndrome may provide useful strategies to minimise or eliminate the symptoms of dystrophinopathies.

Conclusions

The clinical, histopathological, biochemical, and genetic data of the family we describe correspond to a myalgia and cramps syndrome. The natural history of the disease in this family suggests that there is large intrafamilial clinical variability, with some mildly affected patients and others with more definite symptoms, even to the extent of muscle weakness.
Further cases need to be reported so that the natural history of this supposedly benign dystrophinopathy can be clarified.

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