Facioscapulohumeral Muscular Dystrophy and Occurrence of Heart Arrhythmia

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Key Words
Facioscapulohumeral muscular dystrophy • Heart involvement • Arrhythmia

Abstract
Background: Subjects with facioscapulohumeral muscular dystrophy (FSHD) do not generally suffer from significant cardiac symptoms. Although with heterogeneous results, studies reported to date indicate that heart alterations unrelated to cardiomyopathy are possible in FSHD. Patients and Methods: We describe the findings of a multicenter investigation aimed at detecting cardiac abnormalities in 83 FSHD patients, 44 males and 39 females with a mean age of 47 years. All patients underwent clinical heart examination, 12-lead electrocardiography and 24-hour Holter monitoring; echocardiography was also performed on most patients. Results: Among the 83 patients, 62 with no cardiovascular risk factors were identified. Ten of them manifested clinical or subclinical cardiac involvement: 5 reported symptoms represented mostly by frequent palpitations secondary to supraventricular arrhythmia and another 5 exhibited electrocardiographic signs of short runs of supraventricular paroxysmal tachycardia. In the absence of cardiovascular risk factors, we found symptoms or signs of heart involvement of mainly arrhythmic origin in 10 of our 83 FSHD patients (12%). Conclusions: Considering our data and those available in the literature as a whole, arrhythmic alterations seem to be detected more frequently than expected in FSHD patients.

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Table 1. General clinical data of 83 patients with FSHD

<table>
<thead>
<tr>
<th>Grade</th>
<th>Muscular Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No weakness</td>
</tr>
<tr>
<td>I</td>
<td>Mild in scapulohumeral muscles or in lower limb muscles (± F)</td>
</tr>
<tr>
<td>II</td>
<td>Mild in both upper and lower region muscles (± F)</td>
</tr>
<tr>
<td>III</td>
<td>Moderate in upper or in lower region muscles (± F)</td>
</tr>
<tr>
<td>IV</td>
<td>Moderate in both upper and lower region muscles (± F)</td>
</tr>
<tr>
<td>V</td>
<td>Severe in upper or lower region muscles (± F)</td>
</tr>
<tr>
<td>VI</td>
<td>Severe in both upper and lower region muscles (± F)</td>
</tr>
<tr>
<td>VII</td>
<td>Profound in lower ± severe or profound in upper region muscles (± F)</td>
</tr>
</tbody>
</table>

Upper region muscles (scapular and arm muscles): mainly considers the weakness of arm abduction; it is graded as mild (abduction over 90°), moderate (between 45° and 90°), severe (less than 45°) and profound (loss of abduction).

Lower region muscles (pelvic and lower limb muscles): mainly considers the disturbance in gait; it is graded as mild (patient rises from the floor and walks with distal or proximal weakness), moderate (unable to rise from the floor but able to walk unassisted), severe (walks only with aid) and profound (unable to walk and to stand).

Facial muscles: facial weakness is considered only as present (+ F) or absent (– F).

Table 2. Rating scale of weakness in patients with FSHD

<table>
<thead>
<tr>
<th>Grade</th>
<th>Muscular impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No weakness</td>
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<td>V</td>
<td>Severe in upper or lower region muscles (± F)</td>
</tr>
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<td>VI</td>
<td>Severe in both upper and lower region muscles (± F)</td>
</tr>
<tr>
<td>VII</td>
<td>Profound in lower ± severe or profound in upper region muscles (± F)</td>
</tr>
</tbody>
</table>

not available, older anecdotal reports on patients apparently affected by FSHD described ‘atrial paralysis’ [17, 18]. Subsequently, however, major clinical studies on the issue yielded different, sometimes even controversial, results. While Stevenson et al. [16] reported a remarkable presence of arrhythmia or susceptibility to arrhythmia in a group of 30 FSHD cases in 1990, a few years later de Visser et al. [19] found no alterations in the electrocardiography (ECG) Holter monitoring of 31 patients. More recently, in the study of a larger case series Laforet et al. [15] again confirmed the possible presence of heart arrhythmia in FSHD.

We report the findings of a multicenter study on the frequency of symptomatic or asymptomatic heart abnormalities in a series of 83 patients affected by FSHD.

Patients and Methods

Subjects of the Study
This clinical research was carried out as part of a collaborative study involving 3 Italian neuromuscular centers, located at the universities of Padua, Turin and Verona.

A total of 83 patients were considered. They represented the consecutive series of FSHD patients referred to the 3 neuromuscular centers involved in this clinical research since 1998. The diagnostic definition for the patients followed the clinical criteria established by the European Neuromuscular Centre (ENMC) Consortium as reported by Padberg et al. [10] in 1997. Table 1 presents the main clinical data collected in our series of FSHD patients. There were 44 males and 39 females with a mean age of 47 years (range 14–79). The disease was familial in 55 and sporadic in 28 patients. The onset of the muscular disturbance in our patients was between 5 and 64 years of age (mean 18). The degree of muscular involvement at the time of the cardiologic study was determined for each patient by a 7-grade scale which measured the weakness of the muscles of the upper and lower limbs. As shown in table 2, the scores on this weakness scale range from 0 (no muscular deficit) to 7 (profound weakness). Muscular impairment was mild in 35 of the 83 patients (42%), scoring 0–II on the weakness scale. It was moderate in 36 patients (43%) with scores of III or IV, while it was severe or profound in 12 (15%) with scores between V and VII. All patients showed facial muscle involvement.

DNA Molecular Diagnosis

A molecular study of the DNA-specific rearrangements of the disease was carried out on all FSHD patients considered in our investigation, and the clinical diagnosis was confirmed in all patients by the evidence of a 4q35 EcoRI fragment shorter than 35 kb (mean 19, range 10–27). DNA was extracted from peripheral blood, digested with the restriction enzyme EcoRI, double digested with EcoRI/BlnI and hybridized with probe p13E-11. The DNA fragments were then evaluated by pulsed-field gel electrophoresis. These molecular analyses were performed as reported elsewhere [20].

Cardiac Investigation

The clinical histories of all 83 FSHD patients considered in the study were examined, focusing on possible cardiac symptoms and the presence of cardiovascular pathology risk factors such as diabetes mellitus, hypertension, dyslipidemia, smoking, obesity, dysthyroidism, familial sudden death and age. Subsequently, each patient was evaluated for signs of heart abnormalities by a clinical cardiac examination. Standard 12-lead ECG and 24-hour ECG Holter monitoring were then performed on all patients. FSHD patients with symptoms or signs of heart involvement also underwent echocardiography, which was additionally carried out in 43 other cases with no cardiovascular risk factors.
Results

Twenty patients presented heart pathology risk factors such as diabetes mellitus, hypertension, dyslipidemia, smoking, obesity, dysthyroidism, familial sudden death and age over 60. These were not included among our subjects with heart abnormalities. Moreover, a 22-year-old FSHD patient with Wolff-Parkinson-White syndrome was excluded, considering her congenital cardiac abnormality not linked to FSHD.

Table 3 summarizes the clinical data and results of the 12-lead ECG, the ECG Holter monitoring and the echocardiography for the 10 FSHD patients with symptoms or signs of cardiac involvement, selected from the 62 cases with no cardiovascular risk factors. Overt heart symptoms were evident in 5 cases. In 3 patients (cases 2, 3 and 5), the cardiac symptomatology was represented by arrhythmic disturbances which were characterized by prolonged daytime or nocturnal palpitations. These episodes lasted about 2–3 min (case 3) or 3–5 min (cases 2 and 5) and the patients responded to antiarrhythmic drugs like β-blockers (case 2) or calcium channel blockers (cases 3 and 5). In these 3 cases, the 24-hour ECG monitoring identified sustained paroxysmal supraventricular tachycardia of the reciprocal type, with rates of 120–160 beats/min (table 3). The 59-year-old patient represented as case 1 in Table 3 had experienced recurrent daytime palpitations since the age of 57 (with a duration of 5 min to 3 h), sometimes associated with syncopal episodes. In this patient, the clinical and electrocardiographic examination revealed a paroxysmal form of atrial fibrillation which was treated with sodium channel blocking drugs. Case 5, a 48-year-old man, suffered from episodes of retrosternal chest pain, brought on by exertion. The patient had presented these disturbances since the age of 40. During one such clinical event, the 12-lead ECG recorded an ST segment depression, confirming the diagnosis of angina pectoris; between episodes, the same examination as well as 24-hour ECG Holter monitoring were normal.

Echocardiography was performed on all these symptomatic FSHD patients and was normal for all of them, except for case 1 who presented a mild mitral prolapse.

Table 3. Clinical and molecular data of 10 FSHD patients with heart involvement

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>EcoRI fragment kb</th>
<th>Onset of FSHD years</th>
<th>Weakness grade</th>
<th>Heart symptoms</th>
<th>Onset of heart symptoms years</th>
<th>Standard ECG</th>
<th>Holter ECG</th>
<th>Echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (59)</td>
<td>F</td>
<td>27</td>
<td>6</td>
<td>VII</td>
<td>syncopal episodes, palpitations</td>
<td>56</td>
<td>paroxysmal atrial fibrillation</td>
<td>paroxysmal atrial fibrillation</td>
<td>mild mitral prolapse</td>
</tr>
<tr>
<td>2 (24)</td>
<td>M</td>
<td>15</td>
<td>16</td>
<td>I</td>
<td>episodes of sustained palpitations</td>
<td>20</td>
<td>normal</td>
<td>sustained PSVT</td>
<td>normal</td>
</tr>
<tr>
<td>3 (38)</td>
<td>F</td>
<td>20</td>
<td>14</td>
<td>III</td>
<td>episodes of sustained palpitations</td>
<td>30</td>
<td>normal</td>
<td>sustained PSVT</td>
<td>normal</td>
</tr>
<tr>
<td>4 (48)</td>
<td>M</td>
<td>17</td>
<td>15</td>
<td>VI</td>
<td>chest pain episodes</td>
<td>40</td>
<td>ST segment depression</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>5 (30)</td>
<td>F</td>
<td>23</td>
<td>13</td>
<td>III</td>
<td>episodes of sustained palpitations</td>
<td>25</td>
<td>normal</td>
<td>sustained PSVT, isolated VPCs</td>
<td>normal</td>
</tr>
<tr>
<td>6 (49)</td>
<td>M</td>
<td>30</td>
<td>20</td>
<td>III</td>
<td>no</td>
<td>–</td>
<td>normal</td>
<td>PSVT</td>
<td>normal</td>
</tr>
<tr>
<td>7 (49)</td>
<td>M</td>
<td>17</td>
<td>15</td>
<td>III</td>
<td>no</td>
<td>–</td>
<td>normal</td>
<td>PSVT</td>
<td>normal</td>
</tr>
<tr>
<td>8 (57)</td>
<td>F</td>
<td>17</td>
<td>13</td>
<td>V</td>
<td>no</td>
<td>–</td>
<td>normal</td>
<td>PSVT, isolated VPCs</td>
<td>normal</td>
</tr>
<tr>
<td>9 (54)</td>
<td>M</td>
<td>28</td>
<td>20</td>
<td>III</td>
<td>no</td>
<td>–</td>
<td>normal</td>
<td>PSVT</td>
<td>mild mitral prolapse</td>
</tr>
<tr>
<td>10 (39)</td>
<td>F</td>
<td>21</td>
<td>13</td>
<td>II</td>
<td>no</td>
<td>–</td>
<td>normal</td>
<td>PSVT, ST depression</td>
<td>normal</td>
</tr>
</tbody>
</table>

All these cases are aged under 60 and do not present cardiovascular risk factors. Figures in parentheses indicate age in years. Sustained PSVT = Paroxysmal supraventricular tachycardia with runs of more than 30 beats; PSVT = paroxysmal supraventricular tachycardia with runs of 6–21 beats; VPC = ventricular premature complex.

1 The muscular involvement of each patient is graded according to the weakness scale represented in table 2.

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As illustrated in table 3, ECG Holter monitoring detected asymptomatic signs of heart arrhythmia in 5 subjects with no heart pathology risk factors. In these patients, brief atrial tachycardia episodes (runs of 6–21 beats) were observed on the 24-hour ECG recording at a rate of 120–180 beats/min. Paroxysmal supraventricular tachycardia appeared to be of the reciprocal type in cases 6, 7, and 9 and of the focal type in cases 8 and 10. In case 10, the ambulatory 24-hour ECG detected a tachycardic episode lasting 7 s which was associated with an ST segment depression (0.1 mm). In this patient, the possibility of an ischemic heart disease was ruled out by normal findings on dipyridamole stress ⁹⁹mTc MIBI-SPECT myocardial imaging. As shown in table 3, all 5 FSHD patients with asymptomatic paroxysmal supraventricular tachycardia were also tested with echocardiography. This examination demonstrated a very mild mitral prolapse in case 9, while it gave unequivocal normal results in the other 4.

Echocardiography, performed in another 43 FSHD patients with no cardiovascular risk factors, yielded normal results aside from 7 cases; it detected mild mitral prolapse in 4 and very mild mitral regurgitation in 3.

Altogether, symptoms or signs of heart involvement in the absence of cardiovascular risk factors were found in 10 of our 83 FSHD patients (12%) and were mainly represented by arrhythmic disturbances. The heart abnormalities did not appear to correlate with the size of the 4q35 fragments of our patients. Moreover, the cardiac alterations did not correspond to the degree of muscle involvement measured by the weakness scale.

**Discussion**

As clearly experienced by neurologists dedicated to neuromuscular diseases, symptoms related to heart involvement are not considered to be characteristic of FSHD [1, 2, 8–10]. However, long before major studies were published on heart disturbances and FSHD [15, 16, 19], possible cardiac alterations in patients affected by this degenerative myopathy were discussed in anecdotal cases. Some authors [17, 18] described ‘atrial paralysis’ in a few FSHD subjects. Later, the clinical diagnosis of these patients was considered inconsistent [8, 15, 16] and this specific heart alteration was no more reported in subsequent studies on FSHD. Only in 1990, following the clinical research by Stevenson et al. [16], was consistent evidence on possible heart abnormalities in FSHD produced. These authors focused their extensive investigation on analyzing any possible subclinical cardiac involvement in a series of 30 patients. In 27% of them, they detected an abnormal A-V node or infranodal conduction. Additionally, they found susceptibility to supraventricular flutter or fibrillation by intracardiac atrial stimulation in some patients. Altogether, while confirming the usual absence of overt cardiac symptoms, the study indicated that the disease may present heart arrhythmia.

In 1992, de Visser et al. [19] published a report on clinical conditions of the heart in a large group of patients with different types of muscular dystrophy. In the 31 FSHD cases, which were essentially examined by 24-hour ECG monitoring, they found no symptoms or evidence of subclinical arrhythmic abnormalities [19]. Different results were produced by the clinical research published by Laforet et al. [15] in 1998. Their study identified conduction delay or supraventricular abnormalities in 5 out of the 100 patients considered. In agreement with these data, the findings acquired by our multicenter investigation indicate that FSHD patients may present heart symptoms, albeit infrequently and clearly not related to cardiomyopathy but to arrhythmia. Moreover, our study identified supraventricular paroxysmal tachycardia as the major cause of symptomatic heart involvement in FSHD. Indeed, 3.6% of our patients presented disturbances related to this type of arrhythmia, with a frequency higher than 0.22% which is the prevalence rate ascertained for supraventricular paroxysmal tachycardia in the general population [21]. It is worth observing that in our investigation this heart abnormality was also the main arrhythmic alteration among the subclinical cardiac signs found in FSHD patients. Interestingly, these results from our multicenter study are in conformity with the conclusions of the investigation by Stevenson et al. [16] which indicated susceptibility to supraventricular arrhythmia as a possible feature of FSHD. In contrast to the results of previous reports on FSHD and on other types of muscular dystrophy [8, 15, 16], we did not find bradyarrhythmia in our patients.

Peculiar heart abnormalities in FSHD were reported by Galetta et al. [13] and Kimura et al. [14]. In the first of these reports, the detection of abnormalities of the QRS post-potentials in a group of 24 patients suggested a predisposition to ventricular arrhythmia. In the second, the authors described a family in which 3 subjects presented FSHD in association with a 'long QT syndrome'. Since the main locus of this hereditary arrhythmia maps on chromosome 4q25-7, in close proximity to the FSHD locus on 4q35 [22], the authors speculated on a relationship between the 2 diseases [14]. Notably this assumption...
would concur with the recent pathogenetic hypothesis [6, 7] that relates clinical FSHD manifestations to a position effect of 4q35 deletion on the proximal transcriptional genes.

Overall, the results of our multicenter study suggest that symptoms or signs of heart involvement in FSHD are possible and are mostly arrhythmic in type, although in-frequent and not related to cardiomyopathy. Moreover, they indicate that the major clinical or subclinical rhythm abnormality is represented by supraventricular paroxysmal tachycardia. As recently observed by the ENMC Consortium [8], further studies in larger series of patients will be able to establish the definite occurrence and features of cardiac involvement in FSHD.

References


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