Facioscapulohumeral disease

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Chapter 7

General discussion

This study describes facioscapulohumeral disease (FSHD) based on a survey of the relevant literature and on personal experience with 107 patients. After some historical remarks (Chapter 1), the picture of FSHD, as it emerges from the literature, is described in Chapter 2. The differential diagnosis of FSHD is dealt with in Chapter 3. The length of this chapter is not so much caused by a long list of diseases as by the attempt to clear some of the confusion that has arisen after the introduction of the term facioscapulohumeral syndrome (FSHS). Originally, that term served only to summarize the clinical condition of patients in whom facial and shoulder girdle weakness and atrophy were the main features of the disorder (Van Wijngaarden and Bethlem, 1973). Described as such, and disregarding other clinical features, the clinical course, and the pattern of inheritance, it turned out to be a rather non-specific syndrome. Later, this term was used to discuss the differential diagnosis of FSHD (Carroll, 1979). So it became customary to name several diseases in the differential diagnosis of FSHD that are not considered in daily practice, in which all clinical data, including the personal and the family history, are taken into account. Actually, the differential diagnosis of FSHD is rather limited and even more restricted if autosomal dominant inheritance has been established. In that case, only mitochondrial myopathies (Hudgson et al., 1972; Bradley at el., 1978) and spinal muscular atrophies (SMA) should be considered. In the latter, the muscle involvement spreads in an ascending order in contrast to FSHD. Autosomal dominant SMA with a descending course and otherwise resembling FSHD, has not been documented satisfactorily. The differential diagnosis becomes more extensive if the family cannot be examined and if heredity is not obvious. Autosomal recessive conditions resembling FSHD in

all aspects, have not been demonstrated convincingly. Sporadic cases have been described: how many of these patients are de novo mutations of FSHD is not known.

The discussion on the differential diagnosis serves also to support all other arguments that the patients described in Chapter 4 suffer from the same disorder. The results of the physical examination and of the family studies in these patients will be discussed in more detail below.

Chapter 5 describes the laboratory data in our patients. Serum creatine kinase (CK) activity was within normal limits in 34% of the cases. The elevation of the CK activity rarely exceeded four times the upper limit of normal. Similar observations have been reported in the literature. Both with age and duration of the disease a statistically significant decline of CK levels was observed.

Possible linkage between the locus for FSHD and the loci for 35 genetic markers was studied, using blood and saliva of 62 patients and 59 non-affected family members, including 17 non-affected parents from ten kindreds (kindreds A - I). Statistical analysis, using the LIPED program (Ott, 1974), revealed no scores suggestive of linkage. The highest positive lod-score obtained was 1.428 for GM at θ 0.20.

Neurogenic features on electromyography (EMG) are reported in patients with FSHD (McComas, 1977). We observed a large amplitude (1000 microvolts or more) of single motor unit action potentials in some muscles of three patients (10%), while other muscles in these patients revealed a myopathic pattern. Only myopathic patterns were recorded in 74% of the patients. One patient (3%) had neurogenic features on EMG, but also a diabetic polyneuropathy in addition to FSHD. In four patients (13%) EMG was normal.

Muscle biopsies yielded similar results. Small angulated fibres, considered to suggest denervation, were present in six (20%) biopsies. Six biopsies (20%) revealed no abnormalities. Eighteen biopsies (60%) showed myopathic features and other, less well explained changes such as groups of moth-eaten fibres.

As there is ample documentation that myopathic features both

on EMG (Emery, 1981) and on muscle biopsy (Drachman et al., 1967) may be found in cases with neurogenic muscular atrophy, and as the reverse is rarely mentioned (Dastur and Razzak, 1973), there is a distinct tendency in the literature to let the neurogenic features weigh heavier in the discussion on the primary lesion in neuromuscular conditions. This might explain that small angulated fibres in a muscle biopsy have led to the description of autosomal dominant FSH spinal muscular atrophy (Fenichel et al., 1967). We consider the neurogenic features part and parcel of FSHD as they occur only in some members of families with FSHD and not in other members.

The results of physical examination in 107 patients with FSHD and the analysis of the kindreds, as described in chapter 4, testify to the homogeneity of the disorder in these patients. Comparison with results reported in the literature and mentioned in Chapter 2 will be made only when relevant.

Presenting symptoms of shoulder girdle weakness were noted in 82% of our cases, those of facial weakness in 10% and presenting symtoms of foot extensor weakness were reported in 8% of the cases. In no instance the disease presented with symptoms of pelvic girdle weakness. This is in contrast to Chung and Morton's data (1959), collected largely from the literature, in which pelvic girdle onset was reported in 12% of the cases. They suggested that their patient - material was genetically heterogeneous, as they calculated an intraclass correlation of 0.747. It is possible that cases with autosomal dominant neurogenic disorders were included, because most of their patients were studied before the age of modern laboratory tests. Chung and Morton (1959) also reported facial onset in 20% of their cases. It is not very clear which criteria they applied. We considered inability to whistle not specific for facial weakness. At the beginning of our study it was not certain if the symptom of inability to whistle was suffiently sensitive. Seven of our symptomatic patients (10%) remembered events, other than inability to whisle, indicating early facial weakness. Fifty-four of all our 107 patients (51%) never had been able to whistle: all these patients had facial weakness when examined. As the patients

who lost the ability to whistle (12%) could not indicate when this had happened, no specific age at onset of facial weakness could be given. Fourteen patients (13%) had weakness of the orbicularis oris, but could whistle. Becker (1953) and Chung and Morton (1959) did not report foot extensor onset in their cases. Tyler and Stephens (1950) were the first authors who drew attention to early foot extensor weakness in FSHD: this was confirmed by others (Chyatte et al., 1966). Even if FSHD presented itself with complaints of foot extensor weakness, a fair degree of shoulder girdle weakness was observed on physical examination.

Physical examination of 107 patients resulted in a rather circumscribed and uniform picture. We observed facial weakness in 94% of the cases at the time of examination. Becker (1953) reported 81% and Chung and Morton (1959) 83%. In eight of our 107 patients (7%) facial weakness was the sole finding. All other patients (93%) had shoulder girdle weakness. Foot extensor weakness was present in 72 cases (67%) and pelvic girdle weakness in 54 cases (50%). Similar figures are reported by Becker (1953) and Chung and Morton (1959). It should be noted, however, that many of Becker's cases are included in Chung and Morton's material.

Judged by the degree of muscle weakness and based on anamnestic data we found the descending spread of muscle involvement characteristic of FSHD.

We divided the course of the disease in six stages, each stage characterized by the emergence of easily recognizable symptoms. These symptoms in themselves reflect degrees of disability. This simple system proved to be a valuable tool in evaluating the course of a patient's disease. Facial weakness appeared within the first two stages in our material, but it could not be used to record progression, as many patients were unaware of it.

After involvement of the scapular fixators (the rhomboidei, the lower trapezius and the anterior serratus) and of the pectoralis major and latissimus dorsi (stage 1), the foot and toe extensors (the anterior tibial, the peroneus longus and brevis,

the extensor hallucis and extensor digitorum muscles), the abdominal muscles, the other periscapular muscles and the upper arm muscles become involved (stage 2). The onset of pelvic girdle weakness characterizes the beginning of stage 3. In this stage, the onset of weakness of the lower arm muscles might be observed. The onset of stage 4 is marked by the loss of the ability to climb stairs. In stage 4 there is a further progression of the disease, leading to general involvement of most muscles, with notable exception of the extraocular, the pharyngeal, the lingual and masticatory muscles. A patient dependent on a wheelchair, when outdoors, is considered to be in stage 5; when walking inside the house, such patients lean heavily on chairs and tables. In stage 6 a patient is totally dependent on a wheelchair and on nursing care.

We found a distinct asymmetry of muscle involvement in which the right shoulder or arm was significantly more frequently more severely involved than the left. This was not related to the body side; a similar asymmetry was observed in the legs but the more severe involvement occurred in equal frequencies on each side. A statistically significant positive correlation of upper limb involvement was observed with handedness.

As a rule, the tendon reflexes were lower and finally absent with increasing muscle involvement, but there was no constant relation with muscle weakness or atrophy and no constant order of disappearance of reflexes.

Muscle contractures are said to be rare in FSHD (Walton and Gardner-Medwin, 1981). Our experience confirms this general statement, but an exception has to be made for ankle contractures, which occurred in ten of our patients (10%). In three patients they brought about the first complaints.

Pseudohypertrophy of calf muscles was observed in two unrelated male patients (2%), and was absent in other members of their families. A thoracolumbar scoliosis was present in 32% of the cases, and an increased thoracic kyphosis in 11%. The scoliosis was severe in one patient only; in all other patients the scoliosis was very mild. Cardiac symptoms were rare and cardiac disease appeared to be un related to the neuromuscular

disorder.

A high percentage of the cases (32%) was abortive, defined as affected but asymptomatic. Tyler and Stephens (1950) reported 41%. The decline of percentages of abortive cases with age was statistically not significant in our material. As it is plausible that a few of the young asymptomatic patients eventually will become symptomatic, a similarly small amount of sibs might become detectably affected though asymptomatic with advancing age, but the majority of the asymptomatic patients appear to remain so during their lives.

The mean age of onset of the disease, calculated from the reported age of onset of first symptoms, was 17.0 years in the symptomatic patients (15.8 years in males and 19.0 years in females). Regression analysis of the segregation data of the cohort ages in 84 symptomatic and asymptomatic patients and in 80 of their healthy sibs resulted in a mean age at onset of -9 years, assuming that the relation between age at onset and percentage of affected cases is represented by an S-shaped curve. This odd figure is caused by the fact that already in the second decade all expected cases could be diagnosed. Both the cumulative percentages of symptomatic patients, and the regression analysis might be used to calculate genetic risks at different ages.

We observed no patients with infantile onset of FSHD as reported by Brooke (1977), i.e. facial involvement within the first two years of life, followed by a rapid progression of facial and limb muscle weakness, leading to dependence on a wheelchair by the end of the first decade. However, there were several patients in our material who developed symptoms before the age of seven, which was reported to be the earliest age to detect muscle weakness in gene carriers (Tyler and Stephens, 1950; Becker, 1953). Our observations are in agreement with those of Landouzy and Dejerine (1885), who reported onset before the age of five. The above-mentioned regression analysis, resulting in a mean age at onset of -9 years, and anamnestic data on a few patients suggested that an infantile onset is within the possibilities of the disorder represented by our patients. In our opinion, the onset of the disease may be observed from the first

to the last year in life.

In the majority of cases the course of the disease was reported to be relentlessly progressive, Occasionally, long periods of arrest were noted, but their occurrence was rare. The rate of progression was quite variable. The average duration of spread from the shoulder girdle to the foot extensors was 8.8 years and from the foot extensors to the pelvic girdle muscles 9.8 years (Table 4.22.). The stages of the disease, as described above, reflect disability as well. As could be expected, disability increases with age and duration of the disease. Although a fair percentage of asymptomatic cases was found in the seventh decade (30%), at least 20% of the patients in this decade will be unable to climb stairs. Total loss of the ability to walk is rare and occurred in 6% of all cases. Death of patients belonging to the kindreds under study apparently had not been related to the disease. No significant influence of the disease on the age at death could be detected.

Analysis of the segregation data in the extensively studied sibships suggested complete penetrance. Personal experiences in the examination of the families testified to the possible biases in the examiner and, at the same time, suggested that the penetrance is more likely to be almost complete (98-99%). The possibility of an almost complete penetrance is supported by the regression analysis on the cohort ages of the segregation data in the extensively studied sibships. In this analysis 97.5% of the heterozygotes have come to expression at the age of 57, but the standard errors were rather large.

Becker (1953) reported women to be less severely affected than men, and Chung and Morton (1959) reported a significant difference between the age of onset in males (16.8 years) and in females (13.7 years). We found no significant differences between the sexes on the items of age of onset, number of asymptomatic cases, and severity of the disease. A significant difference was found on the numbers of probands only (fifteen males, four females). The reason for this finding is unclear.

Grounds to suggest heterogeneity could not be found in our material. Also the intraclass correlation for the age of onset,

comparing sibships with individuals, gave no arguments for heterogeneity. This intraclass correlation (0.24875) suggested that environmental factors could play a role in the onset of the disease. Also, the significant asymmetry of shoulder girdle and arm involvement (described above) might be caused by environmental factors.

Fitness, judged by the number of offspring of children of an affected parent, appeared normal in patients with FSHD, compared to their healthy sibs. Genealogical investigations, going back an average of 180 years, suggested that none of the families were related. If mutations are the main factor in the emergence of new kindreds with FSHD and if fitness had been normal in the past, one would have expected to encounter more large kindreds. They were not found and this inconsistency is not well explained. The prevalence of FSHD in the province of North-Holland in the Netherlands was estimated to be at lease 1 in 46.000. From the data available it appears that less than 45% of the kindreds have been found.