Facioscapulohumeral disease

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Chapter 2

Facioscapulohumeral disease: review of the literature

2.1. Introduction

Chung and Morton (1959) classified a large number of patients with hereditary neuromuscular disorders according to the pattern of inheritance. They found that the patients with pedigrees suggesting autosomal dominant inheritance fitted the clinical picture of FSHD, as outlined by Walton and Nattrass (1954). Patients with pedigrees suggesting other patterns of inheritance demonstrated only a slight overlap of clinical findings with FSHD. Chung and Morton (1959) concluded that nearly all cases of FSHD could be diagnosed on clinical criteria only. Statistical comparison of anamnestic and clinical data revealed a high degree of resemblance of cases within one family, while a significant difference was found when families were compared among each other. This was interpreted as possibly due to multiple alleles or alternative loci determining FSHD, although the possibility could not be excluded that the apparent similarities of sibs were the result of systematic biases in reporting the onset of the disease. Chung and Morton (1959) could not separate the group of patients with autosomal dominant inheritance into more homogeneous subcategories of the basis of the available evidence. The evidence consisted of personal cases collected in the State of Wisconsin and of cases selected from the literature, including the reports of Sjövall (1936) from Sweden, Levison (1951) from Denmark, Stevenson (1953; 1955) from Northern Ireland, Becker (1953) from Baden, Germany, Lamy and Grouchy (1954) from France, and Walton (1955) from Durham and Northumberland, England. These studies still from much of the basis of our knowledge of the clinical picture of FSHD. Only few other family studies of FSHD were reported since 1950. (Tyler and Stephens, 1950; Boyes, 1950; Walton, 1956; Kazakov et al., 1974).

Many authors though, have written on neuromuscular disorders and commented on FSHD from personal experiences.

2.2. Presenting symptoms

Facial weakness will often go unnoticed: in over 60% of Walton's cases (1955) neither the patients nor their families were aware of it. Inability to whistle or to close the eyes completely when asleep, are often considered a mild quirk of nature. Chung and Morton (1959) reported facial onset of FSHD in 20% of their cases. It is unclear whether they accepted inability to whistle as a symptom indicating facial weakness. Several authors like Brooke (1977), suggested a higher frequency of facial onset by pointing out that many patients with FSHD never had been able to whistle. The frequency of this symptom in an unselected population is unknown nor is it clear how often this symptom is due to facial muscle weakness. If facial onset is present, it is a strong argument for the diagnosis FSHD, since it was not noticed in any other type of muscular dystrophy as described by Chung and Morton (1959).

The most frequently encountered presenting symptoms are those of shoulder girdle weakness Chung and Morton (1959) reported shoulder girdle onset in 77% of their cases. Difficulties at gymnastics while climbing a rope or using the trapeze or the bars, excessive fatigue when writing on a blackboard, difficulties in placing objects on a shelf or working above shoulder level, and drooping of the shoulders are the complaints most often heard. Combing hair or shaving will require special tricks like resting the arms on a table. Several articles mention pain in the shoulder girdle in relation to the development or a exacerbation of the disease (Dubowitz and Brooke, 1973; Bradley, 1979). The significance of this symptom is not known. It may be related to the extensive inflammatory infiltrates occasionally found in the muscle biopsies of patients with FSHD (Munsat et al., 1972). Quite often it may take a fair degree of shoulder girdle weakness before complaints arise. Judging the onset of the

disease by symptoms is likely to result in a much higher age of onset than if the onset could be estimated from the first detectable signs. If peroneal weaknes is present early in the course, occasionally this may lead to the first symptoms, such as tripping over small obstacles, or difficulty running.

Chung and Morton (1959) reported pelvic girdle onset in 12% of their cases, but Becker (1953) never noted symptoms suggesting pelvic girdle onset. He stressed the descending order of muscle involvement in FSHD. This descending course was also reported by Tyler and Stephens (1950).

2.3. Presenting signs

Knowledge of the presenting signs in FSHD is important for the discussion of the differential diagnosis (see chapter 3): FSHD may start either in the facial muscles or in the shoulder girdle muscles, as was demonstrated in the first family described by Landouzy and Dejerine (1885). The exact number of cases with facial onset probably will never be known, since facial weakness frequently remains unnoticed. One finds facial weakness as the only sign of the disease when abortive cases are discovered during a family examination or when anxious parents, who are familiar with the disease, bring a child to the doctor. The most common presenting signs are facioscapular weakness and atrophy (Tyler and Stephens, 1950). Probably next in frequency is shoulder girdle weakness, although accurate numbers are not known. Humeral i.e. upper arm weakness will develop later in the course of the disease and is never reported to be the presenting sign in FSHD. In those cases where peroneal weakness gives rise to the presenting symptoms, on clinical examination shoulder girdle weakness is also found. Therefore (facio)scapuloperoneal weakness may be the presenting syndrome in FSHD, and the disorders described as scapuloperoneal syndromes, should be included in the differential diagnosis of FSHD. Pelvic girdle weakness being the sole and presenting sign of FSHD has not been reported.

2.4. Precipitating factors

Trauma, especially to the shoulder girdle, has been implicated by physicians (Boyes et al., 1950) and by patients (Becker, 1953) to precipitate the disease. Becker (1953) noticed this phenomenon to be more frequent in his group of sporadic cases of FSHD and thought this the result of a need of explanation when visible heredity was lacking. Boyes et al.(1950) also considered unusual physical strain as a possible provoking mechanism in individuals who are "genetically susceptible" to the disease. This could explain the asymmetric onset of the disease in the right arm of a waitress who was under his care. Becker (1953) who discussed the problem of physical strain at length, was very sceptical about this mechanism and did not accept this explanation in hereditary cases.

Other factors which, especially in the older literature, were considered to play a role were infectious diseases. Becker (1953) had found no infectious diseases in relation to the onset of symptoms in his autosomal dominant cases but cited Robinson (1925) who had observed that typhoid fever in one case and influenza in tho other cases had aggravated the muscle weakness. Becker (1953) concluded that the evidence was too flimsy to accept a causal relation. Tyler and Stephens (1950) noted that intercurrent illnesses had little effect on the rate of progression but that immobilisation, paricularly by body casts, resulted in rapid progression of the muscular atrophy. The latter observation has been confirmed by many authors. At present no one believes in a particular precipitating factor in the onset of FSHD.

2.5. The facial muscles

In the majority of cases, facial weakness is present early in the course of the disease, but facial weakness is not obliga-

tory to the diagnosis FSHD. Becker (1953) found the facial muscles to be spared in 18.7% of his cases of autosomal dominant FSHD, and Chung and Morton (1959) in 16.8% of their collected cases. This implies that in families with FSHD quite a few members will start with shoulder girdle weakness while facial weakness may develop later or not at all. Tyler and Stephens (1950) found the zygomaticus and orbicularis oris muscles the first to be affected, although the early detection of weakness in these muscles may be related to their particular function. Weakness of the zygomaticus muscles results in an inability to raise the corners of the mouth and, when the patient smiles, his mouth moves in a horizontal direction producing a grin more than a smile, thereby depriving the smile of its emotional quality ("rire en travers" or transverse smile). When the orbicularis oris is weak, pursing of the lips, whistling, and retaining air under pressure becomes impossible. When viewed from the side, the lips have a pouting appearance due to loss of the normal upward curvature of the lower lip. In many cases the lips appear to be thickened (Becker, 1953). In severe cases the upper lips lose all their mobility and appear to be elongated forming the so-called "bouche de tapir". Brooke (1977) drew attention to the small dimples that sometimes are present on both sides of the corners of the mouth. They deepen when the patient smiles or tries to show his teeth.

The orbicularis oculi muscles generally seem to be less affected than the muscles of the lower part of the face. In the beginning the eyelashes cannot be buried completely on forceful closure of the eyes. If the weakness progresses, a small rim of the sclera becomes visible on an attempt to close the eyes, because the extraocular muscles are never involved in this disease and a normal Bell's phenomenon can occur. In these cases usually blinking is slowed and incomplete. At this stage other facial muscles may become involved as well, resulting in an unlined forehead and a smooth and expressionless face, that originated the term "facies myopathica" or myopathic face (Landouzy and Dejerine, 1885). A frequent finding is the occurrence of an asymmetric involvement of the facial muscles some-

times resulting in an awkward expression. The literature offers no explanation for the asymmetric facial weakness. Data on the frequency of asymmetric involvement are not available. There are also no data on the degree of facial weakness. Probably this is partly due to the fact that there is no proper grading system for weakness of the facial muscless. Although the degree of facial involvement is quite variable, severe weakness without involvement of the shoulder girdle muscles has never been reported. The early and servere involvement of the facial muscles as described in the first family of Landouzy an Dejerine (1885) has led several authors like Erb, Levison, and Becker to remark explicitly that they never had observed this phenomenon. On clinical and post-mortem examination the muscles innervated by the trigeminal, the glossopharyngeal, the vagal and the hypoglossal nerve were never found to be affected. Bradley (1979) reported weakness of the masseter and tongue muscles in a small percentage of his cases, but his numbers are sometimes misleading since he included the family with a FSH syndrome previously reported by Hudgson et al. (1972) in his series. This family had a mitochondrial myopathy (see section 3.5.), and the clinical findings were definitely distinct from the ones in FSHD as were the histopathological and biochemical examinations. Therefore, Bradley's figures are not quite representative for FSHD.

A progressive ptosis and extraocular weakness are no part of FSHD. The patient reported by Winkler and Van Der Weijde (1889) as FSHD with progressive ophthalmoplegia was probably suffering from another disease. These same authors suggested a defect in the motor end plate in this case, a rather modern view at that time.

2.6. The upper extremities, shoulder girdle and neck muscles

It is convenient to describe the weakness and atrophy in FSHD in sections on the upper extremities, the trunk and the lower extremities respectively, as this is the general course of spread of the disease. It is impossible to describe the spread

from one muscle to another, since there is no constant sequence. This descending course and the autosomal dominant inheritance are the main features of FSHD (Becker, 1953).

Grading of muscle weakness by manual testing has only been done by a few authors (Bradley, 1979). The reasons for this are obvious. The axial muscles are difficult to grade if one uses a system like the M.R.C. scale. If the scapula loses its fixation, proper testing of shoulder girdle muscles becomes extremely difficult. The causes of the change of position of the scapula have not been properly described. It is not clear if this is the result of a lack of strength of certain muscles or relatively too much strength of other muscles or both. If the scapula cannot be fixed, with a certain manoeuvre one might not be testing the same muscles as in the case of an unaffected person. One could overcome this problem by testing only certain skills and abilities as suggested by Brooke (1977), but then one tests functions and not individual muscles. Manual muscle testing may only be more or less accurate and reproducible in testing extremity muscles. Mechanical testing of muscles in FSHD has never been reported. Apart from facial muscle weakness, one of the earliest findings in FSHD is the gradual loss of fixation of the scapula. The muscles involved are the rhomboids, the lower part of the trapezius and the serratus anterior muscles. This will result in several visible changes. The scapulae rotate slightly laterally, and move upward, laterally and anteriorly over the thorax. If the rhomboid and serratus weakness progresses, scapulae alatae appear. The change of position of the scapulae contributes to the development of drooping of the shoulders. The clavicles lose their normal upward slope, assuming a horizontal position, rotate anteriorly for reasons poorly explained and ultimately sometimes they may even slope downwards. Another early finding in FSHD is the involvement of the latissimus dorsi and the sternocostal part of the pectoralis muscles (Tyler and Stephens, 1950; Chyatte et al., 1966). Wasting of the latter will result in a flattened outline of the anterior thoracic wall, with a change of the direction of the axillary crease, running more horizontally instead of vertically, and pointing at the sternoclavicular joint. In more

advanced cases wasting of the anterior neck muscles and the pectoralis muscles result in a distinct prominence of the clavicles at the base of the neck (Brooke, 1977). When the patient is seen from the front a small, typical, but unexplained lump may sometimes be seen in the contour of the trapezius on its slope to the acromion. Atrophy of the supraspinatus and infrasinatus may be visible and, due to the localisation of these muscles, quite striking. Landouzy and Dejerine (1885) found these muscles to be spared but most subsequent authors noted weakness and wasting of these muscles, the frequency of which amounted to 90% of Bradley's cases (1979). If the scapula has lost its fixation, the deltoid muscle cannot be properly tested, but if the scapula is held to the thorax by the examiner's hand, the deltoid muscle is often observed to be minimally affected. The sparing of the deltoid muscle which Chyatte et al. (1966) thought characteristic of FSHD, occasionally, and falsely, induces the unwary physician to pose the diagnosis of hypertrophy, particularly so when the surrounding muscles are conspicuously atrophic. Others found incomplete sparing of the deltoid muscles (Tyler and Stephens, 1950; Bradley, 1979) and noted proximal atrophy with distal sparing or atrophy of only the posterior muscle bellies. Another feature on inspection may be the internal rotation of the arms so that the backs of the hands are presented when one sees the patient from the front. This may be due to the changed position of the scapula but it is not clear if relatively strong internal rotators play a role as well. Chyatte et al. (1966) pointed out specifically that the teres major and subscapularis muscles, just like the deltoid muscles, are spared in FSHD. This has not been confirmed by others. The teres major and subscapularis muscles were often not specifically mentioned (Tyler and Stephens, 1950; Bradley, 1979). The time between the onset of shoulder girdle weakness and the onset of upper arm weakness may be quite variable. The atrophy in the upper arms may become quite severe sometimes even early in the course of the disease resulting in so-called "Popeye" arms, because of the relative sparing of the lower arm muscles.

The visible signs as described so far all reflect a certain

degree of involvement. Early detection of shoulder girdle weakness is difficult. There appears to be a great variety of shoulder build. In many slender people the scapula may be prominent and many healthy women have horizontal clavicles. Sloping of the shoulders becomes more prominent with age and also the distance between the medial margins of the scapulae varies greatly, depending, among others, upon thoracic build. Testing of individual muscles, as described for instance by Kendall et al. (1971), is often very helpful but is not quite reliable for testing the shoulder fixators in FSHD since these tests depend upon a good function of other shoulder girdle muscles. The shoulder girdle emerges from this picture as a complex structure in which no muscle ever acts on its own. A large number of variables are involved in any position and movement of the scapula, and this is the reason why there is still debate about normal scapular function, let alone the function in pathological states. Therefore, many clinicians rely on functional tests like the ability to slowly elevate the arm to a vertical position, and the ability to hold the arm horizontally against pressure. A slowly lowering of the raised arms is a sensitive test for minimal serratus anterior weakness (Brooke, 1977) demonstrating a light degree of scapula alata in this manoeuvre. If the scapula fixation becomes weaker, the arms cannot be raised completely but are swung up to catch an object that is above shoulder height. If the hands are clasped together, the arms can be raised more easily, a phenomenon repeatedly described, but never properly explained. When scapular fixation and especially the serratus function worsens, elevation of the arm above shoulder level becomes impossible. At attempts at abduction of the arms, the scapulae ride upwards over the back and their upper borders rise high up into the normal location of the trapezius muscles. This phenomenon is said to be typical of FSHD (Brooke, 1977), but an explanation was never offered. A factor that could be important in the genesis of this sign is the fact that the deltoid muscle in FSHD remains strong for a long time, producing a maximum rise of the completely unfixed scapula. The extremity muscles are more accessible for manual testing of individual muscles which will be

so-called prime movers in certain defined circumstances. Tyler and Stephens (1950) noted the brachioradialis muscles to be affected in a very early stage, even before the involvement of the biceps and triceps muscles, a finding not confirmed by others. Although affected later, the biceps and triceps muscles atrophy rather faster, resulting in a remarkable thin upper arm amid relatively spared deltoid and lower arm muscles. In general the forearm muscles retain their strength for a long time. Only in severe cases weakness of the wrist extensors may develop, occasionally leading to a wristdrop. The wrist and finger flexors will maintain good strength much longer. The instrinsic muscles of the hand will only be affected in severe cases (Becker, 1953). Bradley (1979) noticed involvement of these muscles in more than 50% of his cases with more than 20 years duration of the disease. Chyatte et al. (1966) found that the extensors of the neck were always spared but Bradley (1979) observed that these muscles were affected as well in several cases. He even noticed weakness of the neck flexors in as much as 75% of his patients. This contrasts sharply with the experiences of Van Wijngaarden and Bethlem (1973), who found the neck flexors rarely involved in FSHD. They even used this as a criterion for the diagnosis. The sternocleidomastoid muscles may become weak quite early in the course of the disease (Tyler and Stephens, 1950), but they are almost never absent contrary to their early and severe involvement in myotonic dystrophy.

2.7. The truncal muscles

Little has been written about the truncal muscles in FSHD. Tyler and Stephens (1950) noted that the abdominal muscles were involved only after the disease had spread to the foot extensors and glutaeal muscles. Others, on the other hand, (Wintzen, 1979) found the abdominal muscles often affected rather early in the course of the disease resulting in a protruding abdomen. Weakness of the abdominal muscles adds to the pelvic tilt and the increased lumbar lordosis. Weakness of the glutaeus maximus muscles may

play a role as well. Also part of the increased lordosis may be a compensatory mechanism to retain balance while standing or walking.

In more severely affected patients the increased lumbar lordosis can result in an almost horizontal sacrum, and the line of weight bearing from shoulders to feet passes posteriorly to the sacrum. In this form, the increased lumbar lordosis was already described by Landouzy and Dejerine and demonstrated in their case "Leon M." (1885). Duchenne (1868) had suggested that the lumbar hyperlordosis in FSHD was caused by normally functioning erector trunci muscles unopposed in their action by the abdominal muscles. It is not clear if ligamentous or other factors also play a role in producing this extreme lordosis in FSHD, since this has never been studied. Carroll (1979) stated that this lordosis becomes more marked when a patient is bound to a wheelchair, whereas patients with other types of hereditary myopathies tend to become more scoliotic when they are in a wheelchair, but he fails to explain why or to document how often this phenomenon, typical for FSHD, does occur. A thoracic kyphosis is rarely found in FSHD and a scoliosis, if present, is usually very mild, probably because the major symptoms of the disease usually develop after the spinal growth is completed.

2.8. The lower extremities and the pelvic girdle muscles

Weakness of the anterior tibial muscles was mentioned in the earliest descriptions of FSHD (Landouzy and Dejerine, 1885; 1886) and it was the sole finding in the legs in many cases reported by Boyes et al. (1950) but it was not recognised as an early sign until the publication of the extensive family of Tyler and Stephens (1950). Chyatte et al. (1966) and Vignos et al. (1967) found early weakness of the anterior tibial muscles unique and typical for their group of FSHD patients. Seitz (1957) and Erbslöh (1958) paid special attention to this sign and confirmed Tyler's and Stephen's experience, but at the same time Becker (1953), Walton and Nattrass (1954), Chung and Morton (1959) and

Walton and Gardner-Medwin (1974) still found the pelvic girdle and the proximal muscles of the legs the main sites of involvement in the lower part of the body. Kazakov et al. (1974) studied 55 personal cases and 145 cases from literature and found that the disease could spread in two different ways to the lower part of the body. The first type, which they called "the gradually descending variety", spread initially to the pelvic girdle muscles and then gradually to the upper and lower leg muscles. The second type, which they called "the descending type with a jump", first spread to the lower legs, especially the anterior tibial muscles and from there on to the upper legs and pelvic girdle muscles. The second type was said to be more common. These authors stated that within each family only one type occurred and they argued that this homology or clinical similarity within families indicated that FSHD was genetically heterogeneous and consisted of at least two diseases. Carroll (1979) stated that these findings could not be confirmed, but did not mention on what grounds. Walton and Gardner-Medwin (1981) argued that the patients of Kazakov et al.(1974) were not studied up to modern standards and might very well have included cases with neurogenic atrophy. Weakness of the peroneal muscles will develop somewhat later than the anterior tibial weakness, and by the time this is found, weakness of the gluteal, quadriceps and hamstrings muscles will be clinically present as well. In the majority of cases the calf muscles remain unaffected for a long time: they become involved in the latest stages of the disease only (Tyler and Stephens, 1950). The extensor digitorum brevis muscles remain unaffected for a long period and are sometimes found to be hypertrophied (Brooke, 1977) as a compensatory mechanism for an early foot drop. This finding can be helpful in distinguishing FSHD from neurogenic atrophy. The other intrinsic foot muscles were reported unaffected by Tyler and Stephens (1950). These muscles are only involved in cases with diseases of long duration (Bradley, 1979). Weakness of the foot extensors interferes with walking, resulting in a steppage gait and inability to run. Patients tend easily to trip over small objects, falling forward on their knees. If pelvic girdle weakness develops, a waddling

gait will be visible and gradually rising from a chair or climbing stairs becomes more and more difficult.

The waddling steppage gait with the impressive lumbar lordosis, the drooping shoulders and the myopathic face are very characteristic for FSHD. Finally, walking and standing becomes impossible and the patient becomes wheelchair-bound.

2.9. Pseudohypertrophy of muscles

Pseudohypertrophy is not a hallmark of FSHD (Walton and Gardner-Medwin, 1981). Landouzy and Dejerine (1885; 1886) observed pseudohypertrophy in the supraspinatus and infraspinatus muscles of several cases and considered this to be typical of FSHD. Further observations could not confirm this. Becker (1953) observed one case with pseudohypertrophy of the deltoid muscles but most authors mention a seeming hypertrophy as the deltoid muscle remains intact for a long time amid rather atrophic muscles: the same can be said of the calf muscles. Pseudohypertrophy of the glutaei muscles was occasionally observed by Becker (1953) but is was not mentioned by others. True hypertrophy was described in the extensor digitorum brevis muscle by Brooke (1977) as a compensatory mechanism for an early foot drop. This has not been reported before. Histological studies on these muscles were not undertaken.

2.10. Reflexes

The stretch reflexes diminish rather early in the course of the disease and may eventually disappear. This is a common, but ill-explained finding in myopathic disorders. There are no specific studies on the stretch reflexes in FSHD. Pathological reflexes do not occur in FSHD. Sensory and cerebellar functions are invariably intact.

2.11. Contractures

Contractures are said to be very rare in FSHD (Walton and Nattrass, 1954). Exact numbers and sites are not reported. Occasionally ankle contractures are found. If contractures are a prominent sign in a patient, other diagnoses must be considered, as will be discussed in the next chapter.

2.12. Asymmetry of muscle involvement

An important feature of FSHD is a distinct asymmetry of muscle involvement (Carroll, 1979). This can be present in the facial as well as in the shoulder girdle muscles, and in the extremities.

Mingazzini (1912) and Becker (1953) mentioned a case of unilateral involvement. Becker (1953) noted that the right side was more involved than the left one in 30% of his cases, the left side more than the right one in 15%, while in 55% of his cases both sides were more or less equally affected. He was careful not to draw any conclusions from these figures, since the criteria on which asymmetry was decided were rather crude. These criteria were an asymmetric configuration of the shoulder, an asymmetric strength on arm abduction and an asymmetric onset of muscles weakness. If he also included asymmetry of facial or pelvic girdle muscles, very few symmetric cases remained. Becker considered this asymmetry to be a strong argument for environmental influences on the expression of the gene. He did not mention the possibility of a relation with right or left handedness.

2.13. Skeletal deformities

Skeletal deformities are rare in FSHD. Tyler and Stephens (1950) noted a pectus excavatum in most of their severely disabled patients. This was also present in one unaffected individual. These findings have not been confirmed by others. A mild

scoliosis is often found in the more advanced cases but numbers about its frequency are lacking. Occasionally a kyphoscoliosis has been reported. The increased lumbar lordosis may be a result of muscle weakness itself, and a mechanism compensating for a pelvic tilt in order to maintain balance. The increased lordosis is present in most cases where the disease has spread beyond the shoulder region but again, precise figures are not available. The autopsy case described by Landouzy and Lortat Jacob (1909) had a pectus excavatum, severe muscle contractures, and an increased lumbar lordosis attributed to skeletal changes, but an autosomal dominant pattern of inheritance was not apparent in the family of this patient. Foot deformities are no part of FSHD.

2.14. The cardiac muscles in FSHD

Cardiac involvement in FSHD is considered to be rare. There are only few and no recent reports on this subject. The older literature is hampered by an absent or an inadequate classification of the hereditary myopathies. Most studies report only a few cases of FSHD (Rubin and Buchberg, 1952; Weisenfeld and Messinger, 1952). Schott et al. (1955) studied three patients with FSHD and emphasized the absence of electrocardiographic abnormalities. Manning and Cropp (1958) reported ten patients with "adult type muscular dystrophy". Five of them had left axis deviation which was attributed to rheumatoid heart disease in one case and to coronary sclerotic heart disease in another patient. In the remaining three patients, left axis deviation may have reflected cardiomyopathy. The classification of the myopathy in these cases has been disputed (Perloff et al., 1966; 1971). Gailani et al. (1958) reported on a thyroidectomized FSHD patient with a first degree A-V block, a QRS prolongation and a right branch block, who had a slightly reduced cardiac output. The case discussed by Lisan et al. (1959) had P and T wave abnormalities, a radiological cardiomegaly and congestive heart failure at the age of 32. In this case the diagnosis of FSHD is doubtful because of the early and severe involvement of the triceps surae muscle.

Kilburn et al. (1959) made no distinction between the "limb girdle type" and the "FSH type" of muscular dystrophy. Only two of this eight patients had facial weakness and predominantly shoulder girdle weakness as well. Both had thoracic muscle weakness and pulmonary restrictive defects. One of them had a normal ECG and the other had an incomplete right bundle branch block. The four patients reported by Welsh et al. (1963) had no history of cardiac complaints. They all had normal blood pressure and an normal chest X-ray. One female patient had a heart rate of 52 and a six-year old boy a tachycardia of 102. In another patient a left ventricular conduction delay and a left ventricular hypertrophy "were suggested but not all criteria were present to establish a definite diagnosis". Otherwise the ECG's in these patients were normal. Perloff et al. (1966) studied three patients with FSHD. One of them, a 36-year old woman, had both atrial and third heart sounds and an abnormal brachial arterial response to the Valsalva manoeuvre that could be "compatible with occult cardiac failure". Another patient had a slightly elevated wedge pressure. There were no other findings in these patients suggesting cardiomyopathy. There are three reports of persistent atrial paralysis (PAP) associated with FSHD (Bloomfield et al., 1965; Caponetto et al., 1968; Balwin et al., 1973). All three patients were men. Autosomal dominant inheritance could not be demonstrated and photographs of the patients suggested abduction contractures of the shoulder joints. These patients most likely suffered from what has been described as X-linked recessive scapuloperoneal syndrome with cardiomyopathy, in which the extreme rare condition of PAP is know to develop with age. This syndrome will be discussed in the next chapter. Autopsy reports on FSHD patients are rare. Landouzy and Dejerine (1885) could not detect any cardiac abnormality on macroscopical examination. In the case described by Landouzy and Lortat Jacob (1909) the condition of the heart was not discussed. The case reported by Justin-Besanscon et al. (1964) demonstrated tuberculous lesions in the pericard but the myocard was found to be normal. In summary, no specific cardiac complaints and no specific abnormalities concerning cardiac function are known to occur in FSHD.

2.15. Concomitant diseases

Few authors studied the association of FSHD with other diseases. Tyler and Stephens (1950) mentioned thyreotoxicosis in nine of their patients but thought the association fortuitous. Becker (1953) noticed a goitre in nine of the 94 cases under study. The same author found mental retardation to be present in five patients with FSHD. This association has never been confirmed. There were also two cases (a father and a son) with Huntington's chorea in Becker's series; mitral valve disease was present in three patients, and myocarditis and hypertension each in another patient, but these findings could not be related to the muscle disease. Tyler and Stephens (1950) noted hypertension in six patients of which two had suffered a myocardial infarction. Rheumatic fever was also frequently present in their patients but they found no statistically significant difference between the incidence of rheumatic manifestations in FSHD patients and in unaffected persons.

2.16. Abortive cases

Davidenkow (1930) was the first who drew attention to the frequent occurrence of mildly affected cases in FSHD. He stressed the fact that often neither these patients nor their families were aware that they had the disease. Tyler and Stephens (1950) noted absence of symptoms in 24 out of 58 patients (48%). Thirteen patients were 20 years or older of whom four had "minimal involvement" defined as "just detectable on examination". Walton and Nattrass (1954) were very impressed by these mildly affected cases and introduced the term "abortive". They reported five stationary or abortive cases out of 15 studied (33%). Kazakov et al. (1974) reported 22 (11%) asymptomatic cases among 200 cases of FSHD most of which were taken from the literature. The lack of definition of abortive cases makes it difficult

to study the frequency of this phenomenon in the literature. It should be noted that neither Becker (1953) nor Chung and Morton (1959) mentioned abortive cases in their material. The best definition of abortive cases appears to be "without symptoms but found affected on clinical examination". This definition also includes young persons in whom the disease has just started and who will develop complaints later. A definition of abortive cases such as "without symptoms and beyond the mean age of first complaints" probably would be more correct but is unpractical because the mean age of onset of FSHD is not quite established. In this study the first definition will be used. The clinical picture of abortive cases might then include facial weakness and/or slight shoulder girdle weakness with atrophy. On clinical examination in a rare case, minimal foot extensor weakness might be present as well. Although several authors (Davidenkow, 1930) suggest that FSHD runs a milder course in women, there are no data that would indicate that there are more female than male abortive cases.

2.17 The infantile form

If Duchenne's famous case Henri Juliard (1862) suffered from FSHD -which is likely because of the clinical picture and the pattern of heredity in his family- he represented the earliest report of congenital facial weakness in FSHD. This patient was seen by Duchenne at the age of 13 because of shoulder girdle weakness, noticed one year earlier. He was, like his mother reportedly born with facial weakness. When his mother was examined at the age of 30 the disease had not spread beyond the facial muscles. Her mother and her brother both had shoulder girdle weakness and atrophy as well. The first patient of Landouzy and Dejerine (1885) developed facial weakness at the age of three and shoulder girdle weakness when 15 years old: his sister had suffered from facial weakness since the age of four.

Hanson and Rowland (1971) described similar patients. Three unrelated cases were diagnosed as Möbius' syndrome because of

facial weakness found to be present in the first years of life. All these cases passed the motor milestones at normal ages and developed severe muscle weakness in the first years of the second decade. EMG and muscle biopsy supported the diagnosis FSH myopathy. The first patient had a mother with facial weakness and two brothers who were minimally affected. The second patient had a sister with facial weakness but other family members could not be examined. In the third patient, the father and one sibling were not available for examination; the mother and three siblings were unaffected. Autosomal dominant inheritance has not been ruled out and could very well be present in these cases.

Brooke (1977) was the first to describe infantile FSHD as a special form of this disease. He suggested a specific clinical course and mode of inheritance in this presentation of FSHD, but he omitted to give precise numbers and data. It is unclear how many patients he studied, but he reported that facial weakness is noted in the first two years of life in all cases, leading to an early facial paralysis. Weakness of the shoulder girdle and pelvic girdle muscles develop early, and the progression is so fast that according to him, most children are dependent on a wheel chair by the end of the first decade. The expressionless face limits the emotional, non-verbal communication and isolates the child, making it (in Brooke's experience) more depressed than children with other comparable diseases. The most interesting aspect of Brooke's description is the way this infantile form is transmitted. In all cases except one, Brooke observed in one of the parents slight facial weakness as the only sign of the disease. There was no comment on the exception nor on other members of the families of these patients. Brooke suggested a modifying gene to be present in the non - affected parent of these patients, but in view of the limited data such conclusions appear to be rather premature. At present there is no basis to assume that infantile FSHD is a distinct form of FSHD.

2.18 The late onset adult form

In his monograph on neuromuscular disorders, Brooke (1977) described another extreme of the clinical spectrum of FSHD as the late onset adult form of FSHD. This clinical variety involves patients with a lifelong mild facial weakness having a rapid progression at some stage in their life, commonly in middle age, leading to severe shoulder and pelvic girdle weakness within a couple of years. Muscle biopsy may reveal inflammatory changes, but, according to Brooke, they differ from polymyositis. These patients seem not to respond to corticosteroid treatment. The lifelong presence of facial weakness was suspected upon heteroanamnestic information and induced Brooke to consider this presentation a variant of FSHD. In an earlier publication he suggested that these cases were sporadic ones (Dubowitz and Brooke, 1973). In 1977 he did not comment upon the pattern of inheritance in these cases. Also lacking are data regarding family members. Thus the description of this variant is incomplete and vague, as Brooke himself did admit.

2.19. Age of onset

The onset of FSHD has never been observed objectively. The reported age of onset is therefore based on anamnestic data. Such an approach leaves out the abortive cases because they are without complaints. It is also known from family studies that patients with a considerable amount of facial and shoulder girdle weakness and atrophy, may nevertheless be without complaints. Therefore, the true age of onset of the disease may be several years earlier than is indicated by the complaints of patients. Another problem around the age of onset lies in the involvement of the facial muscles. Most patients are not aware of their facial weakness, nor do they appreciate the meaning of signs, like inability to whistle, or inability to close their eyes completely. Occasionally someone else -a doctor, a mother or an attentive family member- has pointed this out to them. In those

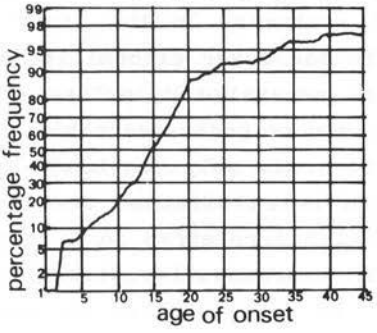
cases the onset of the disease is likely to be reported much earlier. Many people with FSHD will tell that they were never able to whistle. This could indicate facial weakness but, on the other hand, they may never have tried to whistle for various reasons, so this symptom is of little help as it has not been properly studied. The reported age of onset reflects more upon the age of awareness of the disease in patients than upon a true beginning of the disease.

The diagnosis of FSHD may be difficult in the early stages of the disease. Facial weakness may go unnoticed even for a trained physician (Walton, 1955). Atrophy and weakness of the scapular fixators may be difficult to diagnose early in the course of the disease, particularly when the patient is young. Tyler and Stephens (1950) and Becker (1953) all claimed that they were unable to diagnose the disease with certainty below the age of seven. On the other hand, facial weakness was found at the age of three in the proband of Landouzy and Dejerine's first description (1885). Hanson and Rowland (1971) reported patients with congenital facial weakness, later developing FSHD. Also Brooke's (1977) cases, reported as the infantile presentation of FSHD, had facial weakness in the first years of life.

Tyler and Stephens (1950) observed in one large pedigree with 58 living patients that the symptoms or signs recognizable by the patient or his family usually developed between the ages of seven and 20 years, the most common age of onset being between 13 and 15 years. Only five persons (9%) were older than 20 years when they first noticed symptoms. Becker (1953) examined 11 families with autosomal dominant (facio)scapulohumeral muscular dystrophy. The age of onset was thought to be between seven and 27 years, with a peak around 15-16 years. There were only four persons (5%) with an onset later than 27 years (29, 31, 39 and 49 respectively). By the age of 21, 85% of all his cases had been diagnosed as such. Walton and Nattrass (1954) found two cases among 15 with the onset at seven and nine years respectively, ten with the onset in the second decade and three with the onset at 22, 26 and 27 years respectively. It was concluded that the age of onset could "vary from infancy untill late in adult life".

Chung and Morton (1959) presented the ages of onset in a diagram (Fig. 2.1.). It shows that 87% of all patients can be diagnosed at the age of 20 and 93% at the age of 30 years. The diagram is also used to estimate the risk for individuals in families with FSHD to become affected under the assumption that all gene carriers will develop detectable signs of the disease at a certain time in their lives. The probability that a child of a patient will carry the abnormal gene is 0.5 in autosomal dominant diseases, and the risk of such a child, that is unaffected at age z, to develop the disease does not exceed the ratio 100 - G(z) : 200 - G(z) in which G(z) is the percentage of gene carriers clinically affected at that age. This risk is probably even lower, because G(z) in this study was based on recollection data and the disease can be diagnosed on clinical examination years before the onset of first symptoms. In addition Chung and Morton noted a significant higher mean age at onset for males (16.8 years) than for females (13.7 years); they suggested that puberty might be a factor in precipitating the onset of the disease. Becker (1953) found that the age of onset, based on anamnestic data, in ten sporadic cases of FSHD ranged from 15 to 32 years, with an average of 22 years. This figure differed from the average age of onset in the group with proven autosomal dominant inheritance. This difference could reflect genetic heterogeneity but could also be the result of the unexpected playing an important role in the late recognition of symptoms.

figure 2.1 Cumulative distribution of age of onset among 95 patients with FSHD (adopted from Chung and Morton,1959)



2.20 The mode of inheritance

An autosomal dominant pattern of inheritance was found by most authors who reported on FSHD (Landouzy and Dejerine, 1885; 1886; Pearson, 1933; Boyes et al., 1950; Tyler and Stephens, 1950; Becker, 1953; Walton and Nattrass, 1954; Walton, 1956; Chung and Morton, 1959; Kazakov et al., 1974). Myopathies with an autosomal recessive mode of inheritance and presenting themselves with shoulder girdle muscle weakness have been described, but are uncommon (Walton and Gardner-Medwin, 1981). In general, these cases are included in the limb- girdle group of muscular dystrophy. A small percentage of these cases appear to develop facial weakness in the course of their disease. Yet, an autosomal recessive myopathy identical to FSHD has been poorly documented. Brown (1951) reported on in-patients but did not study their families. Therefore her report cannot be accepted as an argument for the existence of a recessive form of FSHD. Stevenson (1953) studied nine families with shoulder girdle and facial muscle weakness in Northern Ireland. In one family a father and a daughter were affected: in the other families the patients only occurred in single sibships. Stevenson did not describe clearly which of the supposedly unaffected persons were examined. In some families the parents were not examined and in others it is evident that he could have studied only one of them. Stevenson's conclusion that FSHD is inherited in an autosomal recessive way is unwarranted on the basis of the data presented. Moser et al. (1966) described four patients in two families suggestive of autosomal recessive inheritance. Only one patient had shoulder girdle onset with facial weakness. In the other three patients the disease had started in the lower extremities. All in all, it appears that an autosomal recessive myopathy, clinically identical to FSHD, has never been properly described.

Apparent sex limitation was only mentioned by Walton (1955) who studied a family with seven affected females in two generations. The same author (1981) referred to a report of a family with an autosomal dominant neuromuscular disorder affecting five

women in two generations (Hertrich 1957). The disorder always had started in the shoulder girdle muscles. Only one patient had a questionable facial weakness. Muscle biopsies were not performed. As long as chance factors cannot be excluded, such families are no proof of sex-limited inheritance.

Sporadic cases of a facioscapulohumeral myopathy constitute another problem. A careful examination of the parents and their families is such cases is always warranted, particularly if genetic advice is sought, while one should have to be sure that non-paternity is excluded. But even when the offspring of such a patient is not affected, a new mutation to FSHD cannot be excluded. Becker (1953) suggested that the 11 sporadic cases of his group of descending shoulder girdle myopathy were different from his autosomal dominant group because of a later age at onset. But is not quite clear whether all these cases were sporadic ones, because in several instances the families could not be examined properly, while in other cases there was a history suggestive of more affected persons in the family, and in one case (family 15) the mother of the proband had a paresis of the orbicularis oris muscle. Walton and Nattrass (1954) included sporadic cases in their limb-girdle group, which was shown to be heterogeneous (Chung and Morton, 1959) and in which sporadic cases with autosomal recessive inheritance could be distinguished. Moser et al. (1966) reported three sporadic cases with facioscapulohumeral myopathy of which two had facial onset of the disease; one of these two patients had no children and her parents and only brother were dead: the parents and the two children of the other patient were examined and found to be healthy.

The literature clearly suggests, that the approach of the clinician who tries to attach modes of inheritance to sets of signs leads to more discussion and confusion than that of the geneticist , who describes the signs at a given mode of inheritance. The geneticist's approach avoids an a priori discussion on semantic problems, such as the meaning of the term facioscapulohumeral, and has the advantage that the patterns of inheritance are well defined. As this approach is felt to be more fruitful,

we should like to define FSHD as an autosomal dominant neuromuscular disorder. Moreover it can be concluded that autosomal recessive disorders closly resembling FSHD have not been properly documented; sporadic cases, resembling FSHD, have been described and might be mutants or phenocopies.

2.21. The penetrance

The penetrance of FSHD was always thought to be complete but this was based on the findings in relatively small pedigrees. Only some authors studied large kindreds. Tyler and Stephens (1950) found the ratio of affected versus non-affected sibs in their large kindred close to 1 : 1 (the actual numbers were 130 versus 143). No correction for the probands could have been made, because they were not indicated in this study. Several patients had died, and only 58 living patients had been examined. Still the authors considered these results to be compatible with complete penetrance. Becker (1953) made corrections for the probands and found that in sibships with at least one affected person, 41% of the sibs were affected and that 46% of the sibs of an affected parent were affected themselves. These figures did not differ significantly from the expected 50% and therefore the penetrance was thought to be complete. Similar numbers were reported by Kazakov et al. (1979) who studied 55 personal cases and 145 histories taken from the literature. They found 49% of the children to be affected if one of the parents had FSHD. These authors stated that FSHD occasionally skipped a generation but they did not document this observation. If their statement is based on published reports only, such as the first family of Landouzy and Dejerine (1885), it is of little value because the skipped generation in this family was never examined.

2.22 Sex influence

Since the recognition of muscle disorders, clinicians have been intrigued by the differences between the sexes. This was largely caused by the presence of the X-linked myopathies. But even when these were separated from the other myopathies, the question remained if the X-chromosome or the hormonal or other biochemical differences between males and females had any influence on the onset or the expression of the hereditary muscle diseases. Several authors have discussed this matter when reporting on FSHD. Becker (1953) found more females than males affected but the numbers did not differ significantly from the expected 1 : 1 ratio. Walton (1955) reported on 17 females and five males in four families but considered the information too limited to draw firm conclusions. Most authors agree that men are as frequently affected as women.

Chung and Morton (1959) reported a statistically significant difference in the mean age of onset in males and females. The authors suggested that the onset of puberty might play a role. However these findings have never been confirmed by others.

Several authors like Davidenkow (1930) had the impression that FSHD runs a milder course in females, but only Becker (1953) came with evidence from his own material. Using pelvic girdle involvement as a criterion for the severity of the disease, he found that 80% of the males and 23% of the females in his study were severely affected. The difference in frequency is statistically significant. But, again, nobody so far has confirmed these observations. Bradley (1979) -using his own index of severity- found women to be slightly more severely affected than men, but his material does not consist purely of FSHD.

2.23. Linkage studies

Linkage or association with a known trait or disease has never been observed in FSHD. Tyler and Stephens (1950) did not find linkage of FSHD with the loci of the ABO, MN and RH blood

groups in their large kindred. Chung and Morton (1959) analysed Walton's (1955) limited data on the bloodgroups ABO, RH, MN, P, FY, and JK in more detail but, again, no suggestion for linkage was found.

2.24 Prevalence and incidence

The prevalence of a disease is defined as the frequency of affected individuals in a population at a given time. The prevalence of FSHD reported by different authors is quite variable, suggesting large regional differences, even if one assumes that not all affected persons are ascertained in the regions with the reported low prevalence. Morton and Chung (1959) reported the prevalence of FSHD being 1 per 435.000 in Wisconsin, after correction had been made for an estimated ascertainment probability, and 1 per 179.000 when based on pooled data from several surveys. Becker (1953) reported a prevalence of 1 per 17.000 in South-Baden (Germany), calculated from familial and non-familial cases. If the 11 sporadic cases were excluded, the prevalence of FSHD amounted to 1 per 20.000 approximately. Walton and Nattrass (1954) reported 22 affected persons in a population of approximately 2 million (1 per 91.000). Moser et al. (1966) found two patients with FSHD among the 910.000 inhabitants of the Kanton Bern in Switzerland, i.e.. 1 per 455.000. Prot (1971) reported the prevalence of FSHD in the region of Warsaw (Poland) to be 1 per 250.000 individuals.

There are several definitions of incidence. The incidence might be defined as the frequency of new occurrences of a disease among individuals of a specific population within a certain period of time, or as the frequency of individuals born in a certain population who will become affected. If the latter definition is used, the incidence is always higher than the prevalence because it may take some years for a defective gene to come to expression, and such a gene may lead to an early death. Morton and Chung (1959) made a correction for the ascertainment probability and found the incidence of FSHD in Wisconsin to be 1 per

263.000 individuals born, and for their combined sources as mentioned in section 2.1., 1 per 109.000.

2.25 Fitness

Fitness is defined as the ability to transmit one's genes to the next generation and have them survive in that generation to be passed on to the next. Becker (1953) reported a normal fitness in patients with FSHD, based on the ratio of children of affected and non-affected sibs. Morton and Chung (1959) stressed the biased ascertainment of more fertile persons, and the possible difference in fertility between non-affected sibs and the general population. Using methods which reduce these biases, they estimated the relative fitness coefficient for patients with FSHD to be about 0.741. (Morton et al., 1963). Emery and Walton (1967) reported a normal fitness if affected sibs were compared with unaffected sibs, but Prot (1971) reported a relative fitness coefficient of 0.80 for her patients with FSHD, when compared with healthy sibs.

2.26 Mutation rate

Becker and Lenz (1955, 1956), using the direct method, estimated the mutation rate of FSHD to be $4.7. \times 10^{-6}$ per gene per generation. Assuming a relative fitness coefficient of 0.89 they arrived at a mutation rate of 5.0×10^{-6} by an indirect method. Morton and Chung (1959) found a mutation rate of 5.0×10^{-7} by an indirect estimate and Prot (1971) reported a mutation rate of 3.0×10^{-7} per gene per generation. These large differences are related to the reported regional differences in the prevalence of FSHD, and apart from the problems of complete ascertainment of this rare and relatively mild disease, many sources of error such as illegitimacy, low expressivity, and possibly incomplete penetrance are involved in establishing the correct number of mutations in a population.

2.27 Clinical course and disabilty

There are no longitudinal studies of FSHD. The clinical course of FSHD has been judged from anamnestic data, and is thought to be slowly progressive in most cases, covering many decades (Tyler and Stephens, 1950). Most authors agree that long periods of arrest are not uncommon (Walton and Nattrass, 1954), but occasionally a rapid progression is noted (Brooke, 1977). The time lapse between involvement of the upper part and lower part of the body varies greatly from patient to patient. Exact figures are rarely given. Walton and Nattrass (1954) mentioned a duration of 20-30 years before the disease had spread to the pelvic girdle muscles. In a later text, Walton and Gardner-Medwin (1981) stated that some cases may run a rapid course, while in others long periods of apparent arrest may be noted. In some instances the pelvic girdle muscles will never be involved. Becker (1953) found that if the pelvic girdle becomes affected, this will happen in 38% of the cases within five years and in 62% within 15 years after the onset of the disease.

Kazakov et al. (1974) studied the way the disease could spread to involve the lower part of the body (see 2.8.). "The descending type with a jump" and "the gradually descending type" never occurred within one family and those two types were thought to suggest genetic heterogeneity of FSHD.

Becker (1953) studied the severity of the disease and suggested that the sex and physique had an influence on the course and severity of the disease. He found that women were significantly less severely affected than men, using pelvic girdle weakness as the criterion for severe involvement (see 2.22). When the disease was studied in relation to the physical build, he found that in general the onset of the disease was later and the disease ran a milder course in the pycnic type, while the leptosome type was affected earlier and more severely. The group of the athletic types and the group of the aspecific types had an onset and a course of the disease somewhere in between the two other groups. There were 76% leptosome types and 24% pycnic and pycno-athletic types in the severely affected

group with pelvic girdle weakness, while there were 71% pycnic and pycno-athletic types and 29% leptosome types in the group of mildly and moderately affected persons.

Other factors that might influence the course of the disease are rarely mentioned. Infectious deseases and traumata are believed to have no influence (Tyler and Stephens, 1950; Becker, 1953). Immobilisation for a long time may aggravate muscle weakness. Boyes et al. (1950) suggested that physical strain could aggravate the disease, but Becker (1953) rejected such explanations.

The degree of disability in FSHD at a certain age is dependent on the clinical course of the disease and is therefore extremely variable. There is no current grading of the disability in FSHD in use, nor is there a generally accepted agreement on the grading of the severity of this disease. Pelvic girdle involvement occurred in 56% of Becker's cases (1953), in 45% of Walton's cases (1955), in 59% of Chung and Morton's cases (1959) and in 60% of the cases described by Ricker and Mertens (1968). Their figures included all age groups. Sometimes inability to walk is considered an indication of severe disability. This was noted to occur in three out of 51 men (6%) and in six out of 72 (8%) women in Becker's material. Ricker and Mertens (1968) observed this in two out of 30 patients (7%), and then only in later life. It can be concluded from this limited information that the frequency of serious disease and disability appears higher at older age. Tyler and Stephens (1950) made similar general statements, and most authors agree with their conclusion that FSHD is a relatively benign disease, even if reports about the infantile form of FSHD (Brooke, 1977) are taken into account.

2.28 Therapy

The best way to preserve muscle strength is through normal daily physical activity. Vignos and Watkins (1966) suggested that an active excercise program, particularly in the early stages of FSHD, could increase muscle strength. The degree of improvement

in strength was correlated with the initial strength of the exercised muscles. Prevention of obesity is of great importance since excessive weight gain has adverse effects on the ability to maintain independent ambulation (Vignos, 1979). Contractures should be treated with stretching. There is no information about the results of Achilles' tendon elongation operation in FSHD, probably because such contractures do not occur frequently in this disease. Experiences with patients with Duchenne type of muscular dystrophy suggest that such operations are contraindicated in the ambulatory phase because the contractures recur rapidly; the postoperative immobilisation might result in disuse atrophy, and the mechanism to maintain extension of the knee might become disturbed, resulting in loss of ambulation (Spencer, 1967).

Operations to improve the function of the arm by stabilisation of the shoulder have been designed specifically for FSHD. In many cases abduction and anteflexion of the arms are impaired quite early in the course of the disease because of a severe paresis of the scapular fixators. In patients with relatively strong deltoid muscles, manual fixation of the scapula will show a remarkable improvement of these functions. In these patients surgical fixation of the scapula might be warranted. The optimal position of fixation appears to be at 20 degrees external rotation. Two techniques have been proposed recently: thoracoscapular bony fusion (Bunch, 1973; Copeland and Howard, 1978) and thoracoscapular immobilisation by fastening the scapula to several underlying ribs with fascia (Ketenjian, 1978). With the former technique the patient will be in a shoulder spica for several weeks, while the latter technique has the advantage that early shoulder motion is allowed postoperatively with the arm supported in a sling. All authors claimed excellent results with their techniques.

2.29 Life expectancy and causes of death

As cardiac and respiratory functions are usually spared, the

life expectancy of patients with FSHD does not differ significantly from the average in the general population. (Chung and Morton, 1959; Prot, 1971). The cause of death does not appear to be related to the myopathy (Becker, 1953) but extensive and systematical studies with regard to this problem are lacking. Walton and Gardner-Medwin (1981) remarked that death through respiratory failure may occur but happens rarely.

2.30 Biochemical studies

The number of biochemical studies specifically on FSHD is rather small. A mild creatinuria is often present with FSHD: being a rather non-specific finding in patients with neuromuscular disorders, it has little importance.

Hurwitz et al. (1967) reported a family in which FSHD and aminoaciduria inherited independently as autosomal dominant disorders. There was an increased excretion of lysine, cystine, ornithine and arginine as a result of a renal tubular defect. An increase of urinary excretion of several aminoacids has been reported in other myopathies but these findings were inconsistent and appeared to be non-specific (Pennington, 1981). An increase of creatine kinase (CK) activity in the serum was found to be the most sensitive biochemical characteristic of neuromuscular disorder. The greatest increase of serum CK activity is found in the rapidly evolving myopathies while smaller elevations or even normal values are found in slowly progressive myopathies like FSHD and denervating disorders. Several other intramuscular enzymes including aldolase, SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamic pyruvic transaminase) and LD (lactic dehydrogenase) are elevated in chronic muslce disease but to a smaller extent than CK. Munsat et al. (1972) found an elevation of the serum LD activity in 20% of his patients with FSHD. The serum aldolase activity was elevated in 15% and the SGOT and the SGPT activities were both elevated in 5% of his cases.

Fowler and Pearson (1964) found the serum CK activity only occasionally raised. Munsat et al. (1972) reported an elevation

in 50% of his cases with FSHD but these values were never higher than four times the upper limit of normal. The same range of CK activity was found by Hughes (1971) in 13 out of 19 cases (68%) with FSHD. Bradley (1979) reported the serum CK levels to be above normal in most cases, but his material included patients with a mitochondrial myopathy resembling FSHD. Hughes (1971) observed CK levels to have a tendency to be raised in subjects up to the age of 45-50 years and to have a gradual drop to normal in older age. There was apparently no correlation between the level of CK activity and the severity of the disease. Munsat et al. (1972) found no correlation between the levels of CK activity and the age of the patients or the duration of the disease. Bradley (1979) was the only author who reported a relation between the level of the CK activity and the rate of progression of the disease. Hughes' (1971) hopes that the serum CK activity would serve to distinguish FSHD and neurogenic atrophy came to nothing since similar elevations of CK activity were observed in spinal muscular atrophy, motor neuron disease and other denervating disorders (Munsat et al., 1973), in the same percentage of cases (Williams et al., 1970; Welch et al., 1972) as in FSHD. Therefore the determination of the serum CK activity is of little help to the differential diagnosis of FSHD (Munsat et al., 1973). Walton and Gardner-Medwin (1981) stated the serum enzyme levels are not raised in preclinical cases.

Many studies have been carried out on the serum CK isoenzymes in muscle diseases, but few included FSHD patients. Jockers-Wretou (1976) found the serum CK-MB fraction in one patient to be 7% of the total serum CK activity which was 54 U/l (normal values up to 50 U/l). Elevation of the CK-MB fraction, which should not exceed 6% (Klapdor et al., 1977), is frequently observed in muscular dystrophies, and is felt to reflect skeletal muscle disease rather than cardiac muscle disease (Silverman et al., 1976). Zweig et al. (1980) observed an increased serum CK-MM and CK-BB fraction activity in one patient with FSHD, which they attributed to "leakage of degenerating and regenerating muscle fibres".

Ibrahim et al. (1981) studied serum enzymes and the serum LD

isoenzymes in seven male patients with FSHD. All patients had a mild elevation of the serum CK, aldolase, SGOT and LD activities: also the average serum activity of the fifth LD isoenzyme fraction was significantly raised in these patients.

Elevated serum pyruvate kinase (PK) levels were found in seven out of ten patients with FSHD, all of whom had normal serum CK levels (Alberts and Samaha, 1974). These ten patients showed an average 12-fold elevation of serum PK activity when compared to their controls. Seay et al. (1978) could not confirm these observations: three of their seven patients with FSHD had an elevated serum CK activity and five of them had an elevated serum PK activity. But Zats et al. (1978) found an increased serum PK activity in 18 out of 20 patients with FSHD while only nine had an elevated serum CK activity. Only one patient had normal activities of both enzymes. These authors suggested that the determination of the serum PK activity might be a more sensitive test than the determination of the serum CK activity in some neuromuscular disorders and particularly in FSHD.

Hische and Van Der Helm (1979) studied the serum myoglobin concentrations in 230 patients with neuromuscular diseases of which eight patients had FSHD. In six of these eight patients both CK and myoglobin levels were raised, in one patient both were normal, and in one patient the serum CK activity only was raised. It appeared that the estimation of the serum myoglobin concentration was not a more sensitive test than the determination of the serum CK activity for the detection of patients with FSHD.

Ionasescu et al. (1972) reported on ribosomal protein synthesis in muscle extracts of patients with FSHD. In a previous in vitro study they had found an abnormally large synthesis of collagen by muscle polyribosomes in contact with soluble enzymes derived from the same muscles of patients with Duchenne type of muscular dystrophy. This could not be demonstrated in FSHD but they did find an increased incorporation of labelled aminoacids in the muscle polyribosomes in four patients who were in an early stage of the disease, whereas three patients in advanced stages of the disease showed a lowered, and in one case a normal, incor-

poration of these aminoacids. These findings suggested an increased protein synthesis in muscles in the early stages of FSHD and the authors speculated that this could be the synthesis of a contractile (but possibly inactive) protein, and that the increased protein synthesis thus reflected a failing attempt at regeneration (Ionasescu et al., 1975). This abnormality appeared controlled by an undetermined factor belonging to the soluble (non-ribosomal) fraction of muscle homogenates. (Ionasescu and Zellweger, 1979).

2.31. Electromyography

At present it is impossible to differentiate the clinical varieties of muscular dystrophy from each other by electrodiagnostic methods. The principal value of electromyography (EMG) is to differentiate the myopathies from the neurogenic atrophies with which they may be confused. The EMG abnormalities in the myopathies are explained in general by the loss of individual muscle fibres within a motor unit while the total number of motor units that can be activated remain unchanged. In needle EMG a polyphasic motor unit action potential is observed as a result of non-synchronous firing of remaining muscle fibres. On an average the action potentials of myopathic muscles are of shorter duration than those of healthy muscles. This is explained by the lowered muscle fibre density in the motor units reducing the early and late components of the action potential at first (Buchthal et al., 1960). The voltage of the motor unit action potentials is usually normal or slightly diminished. On maximal effort, a full interference pattern of normal or slightly reduced amplitude is obtained in most instances. In severely affected muscles the disproportion between the degree of weakness and the reduction in the interference pattern provides an argument for a myopathic disorder. Automatic frequency analysis of the interference pattern may reveal a shift to the higher frequencies in the myopathies, but this is of limited diagnostic value as a substantial shift of frequencies is usually accompanied by a

recognisable excess of polyphasic motor unit action potentials.

Most authors use the term "myopathic EMG" when an interference pattern of motor unit potentials of brief duration and small amplitude with an excess (> 12%) of polyphasic potentials is found (Buchthal and Kamieniecka, 1982). Engel (1975) criticized this term since, theoretically, brief small abundant polyphasic potentials (BSAPP) can be present as well in neurogenic disorders. Introduction of new terms like BSAPP-pattern are equally unsatisfactory (Daube, 1978) because the value of the term lies solely in the meaning it carries to the reader, and it does not absolve the electromyographist to describe in detail all the findings of his examination.

Spontaneous activity has been described in cases of muscular dystrophy (Buchthal and Rosenfalck, 1963) and consists of brief discharges of repetitive activity following insertion or movement of the needle electrode and of fibrillation potentials. This spontaneous activity is rather uncommon in muscular dystrophy but it is frequently found in polymyositis. In polymyositis positive sharp waves may be present as well. Munsat et al. (1972) found them in patients with FSHD who had rather extensive cellular infiltrations, histologically resembling polymyositis.

Fasciculations have never been found in FSHD. Motor nerve conduction is said to be normal in FSHD when measured by conventional methods, but Bethlem et al. (1973) reported slowing of the peroneal nerve conduction velocity in two of their seven cases.

Hausmanova-Petrusewicz and Jedrzedowska (1972) demonstrated enlargement of the motor unit territories, large potentials and pseudomyotonic discharges in some of their patients with muscular dystrophy, features normally indicative of neurogenic disorders. In many instances of FSHD, on routine EMG examination McComas (1977) found in some muscles "myopathic" and in other muscles "neuropathic" features in the same patient: or in some members of a family "myopathic" and in other members of the same family "neuropathic" characteristics: but, unfortunately, these findings are not specified.

Sica and McComas (1971) advanced arguments for a neurogenic factor in FSHD. Using a method described earlier, (McComas et al.

1971) they found a reduced number of functioning motor units in the extensor digitorum brevis muscle in three out of four patients with FSHD. The size of the motor unit was normal in all four cases. Isometric twitch studies showed decreased twitch tension in two cases, a prolonged contraction time in four cases and a prolonged relaxation time in three cases. These findings were thought to be compatible with chronic partially denervated muscles. Maximal impulse conduction velocities and terminal latencies in the peroneal nerves were normal. In the discussion of their results, Sica and McComas (1971) treated patients with FSHD and patients with a limb-girdle myopathy as one group, which led them to premature conclusions about FSHD, since their actual studies on those four patients showed only minor abnormalities, often only in a couple of patients. The technique, methods and interpretations have been severely criticized by Panayiotopoulos et al. (1974; 1976) who were unable to reproduce the findings in 50 patients including three patients with FSHD after appropriate modification of the technique (Panayiotopoulos and Scarpalezos, 1977).

Ballantyne and Hansen (1974) used a computerized method to estimate the quantity of motor units and found this within normal range in the extensor digitorum brevis muscles in three cases of FSHD. The number of motor units was reduced only in cases of myotonic dystrophy. The authors thought that Sica and McComas (1971) had arrived at low numbers of motor units because their method failed in diseases where quantitative alteration in the configuration of the motor unit potentials occurred. A computer method was also used for analysis of evoked motor unit potentials (Ballantyne and Hansen, 1975). These potentials were recorded from surface electrodes over the extensor digitorum brevis muscles and evoked by stimulation of the deep peroneal nerve at the ankle. The latencies and duration of the motor unit potentials were significantly increased in cases with FSHD as compared to controls, which is in contrast to the findings of conventional needle electromyography. The fastest motor conduction velocities were significantly reduced and the shortest distal motor latencies were significantly prolonged in patients

with FSHD. These findings seemed to support the hypothesis of a neurogenic factor in FSHD, but Jennekens et al. (1972) demonstrated with muscle biopsies that, from the second decade onwards and increasing with age, neurogenic features such as type grouping and group atrophy were observed in the extensor digitorum brevis muscles of individuals who had not suffered from neuromuscular disorders. These findings were explained as the result of a slow proces of denervation and reinnervation, occurring as part of the normal ageing processes. This study suggested that the extensor digitorum brevis muscle is not quite suitable for EMG studies such as the ones mentioned above.

2.32. Muscle biopsy studies

Muscle biopsy in FSHD occasionally shows no abnormalities; in classical, slowly progressive cases the changes can be minimal. All histological findings traditionally attributed to myopathies can be found in FSHD. Histochemical studies of the muscle biopsies have contributed a great deal to our knowledge of muscle diseases but these studies included only few cases of FSHD (Brooke and Engel, 1966: five patients; Dubowitz and Brooke, 1973: 11 patients; Bethlem et al., 1973: seven patients; Buchthal and Kamieniecka, 1982: 21 patients). Therefore the histopathology in FSHD is not as clearly established as in the Duchenne type of muscular dystrophy (Munsat, 1972). The reason could be that FSHD is a rare disease and that many patients are not interested in extensive studies once the diagnosis is made in a family member and once they know the relatively good prognosis.

First, the organisation of the muscle fibres (i.e. changes in size and distribution) and secondly, the structural changes will be discussed.

Organisation

A very constant finding on histological examination is an increased variation in fibre size with rounding of the fibres. Dubowitz and Brooke (1973) frequently observed an increase of the

mean fibre diameter of all fibre types. Abnormal hypertrophy factors were more often found than abnormal atrophy factors. The same authors noted small angulated fibres scattered between large fibres in 70% of their biopsies. "They were frequently not the heavily stained angulated fibres seen in denervation, but merely normally staining very minute fibres". Buchthal and Kamieniecka (1982) did not observe small angulated fibres in 21 biopsies of patients with FSHD. The significance of small angulated fibres in FSHD is uncertain. A neurogenic lesion cannot be ruled out although most authors (Buchthal and Kamieniecka, 1982) appear to accept only dark angular fibres that stain intensely with the NADH-tetrazolium reductase stain, as a definite proof of denervation in FSHD. Groups of atrophic fibres were not observed by Brooke and Engel (1966) nor by Dubowitz and Brooke (1973) who specifically stated that "this would serve to differentiate from classical denervation". Bethlem (1970) did not mention angulated fibres in relation with FSHD, but later (1977) he stated that small groups of small angular fibres are sometimes present. Hausmanowa-Petrusewicz and Jedrzedowska (1971), and Dastur and Razzak (1973) also reported small groups of atrophic fibres in cases of muscular dystrophy but it was not clear if cases of FSHD were included. If fibre type predominance is present, type 2 predominance is more frequently observed than type 1 predominance. This helps to differentiate FSHD from other myopathies which have a tendency to type 1 predominance (Dubowitz and Brooke, 1973). Engel and Kossman (1963) reported a case of FSHD with selective involvement of type 1fibres.

Structural changes

Hyaline fibres and necrotic fibres with phagocytosis are frequently, but not abundantly, present. They are apparently more prominent in the rapidly progressive cases. Basophilic fibres with vesicular nuclei and prominent nucleoli can be found which are regarded to represent regeneration. Internally located nuclei are present in some biopsies but this is never a prominent feature. Increase of fat and endomysical fibrosis, which can be found in an early phase of the Duchenne type of muscular

dystrophy, is only rarely present in FSHD and never to a great extent (Ionasescu et al., 1972; Dubowitz and Brooke, 1973).

A rather distinct inflammatory reaction is a remarkable and not unusual finding in FSHD (Brooke and Engel, 1966; Munsat et al., 1972; Dubowitz and Brooke, 1973; Bethlem, 1977). This reaction may be so prominent that it resembles polymyositis. Munsat et al. (1972) reported four rather severe cases of FSHD: two showed a clearly autosomal dominant pattern of inheritance in their families, and in the two other cases the family data were inadequate. The perivascular and interstitial inflammatory responses found on histopathological examination were so extensive that they were treated with corticosteroids. Three patients showed a clinical improvement but later reports (Munsat and Bradley, 1977) attest that this improvement was transient and deterioration ensued as in other cases with FSHD. Lowering of serum CK activity was observed during corticosteroid treatment but the authors stressed that this did not imply therapeutic benefit. Munsat et al. (1972) suggested that the imflammatory reactions they observed were only a stage in the development of FSHD.

Papapetropoulos and Bradley (1974) observed inflammatory infiltrations in six patients with different types of muscular dystrophy (three cases of FSHD, three sporadic cases of other types). They suggested that this was an immunological reaction secondary to the underlying muscle degeneration, leading to muscle damage in its own right. A similar explanation was given by Jennekens et al. (1975) for the inflammatory responses they found in the muscle biopsies of five members of their two families with autosomal dominant neurogenic atrophy in a scapuloperoneal distribution, accompanied by a cardiomyopathy at a more advanced age. These two families are rather exceptional indeed as they do not fit properly in any known category. They will be discussed later.

Target fibres and targetoid fibres have never been described in FSHD. Moth-eaten fibres seem to be present in more than half of the cases (Dubowitz and Brooke, 1973). These small fibres are predominantly type 1 fibres, in which the intermyofibrillar net-

work that normally has a very regular pattern, assumes a whorling appearance with areas that do not stain with oxidative enzyme reactions. These fibres appear to be identical to the lobulated fibres described by Bethlem et al. (1973). The authors found that bundles of myofibrils ran an aberrant course in these fibres and that accumulations of normal mitochondria and glycogen were found in between these bundles. The significance of these moth-eaten fibres is unclear as they were observed in other myopathies, in spinal muscular atrophies (Bethlem et al., 1973) and in diseases like Parkinson's disease and polymyalgia rheumatica (Dubowitz and Brooke, 1973). Yet their frequency in FSHD is remarkable: Bethlem et al. (1973) observed moth-eaten fibres in 13 out of 300 biopsies. Seven out of 11 patients with FSHD showed moth-eaten fibres.

Ringed fibres are occasionally discovered in FSHD: their presence suggest a myopathy although they are observed in diseases such as spinal muscular atrophy and rheumatoid arthritis (Dubowitz and Brooke, 1973) and also in normal muscles (Behtlem and Van Wijngaarden, 1963).

Ultrastructural abnormalities characteristic of FHSD have not been reported (Mair and Tomé, 1972; Price and Van De Velde, 1981).

2.33. Summary

FSHD shares with other autosomal dominant disorders such as, for example, Huntington's chorea or myotopnic dystrophy, a confusing history of descriptions of the diseases. After the first report many observations were made, each emphasizing a peculair aspect of the variable clinical picture. This often led to suggestions that different diseases were hidden under one clinical presentation. But autosomal dominant disorders tend to favour the "lumpers" above the "splitters" and, at present, a variable clinical picture appears to be a feature of autosomal dominant disorders. The same applies to FSHD. Still there are some characteristic findings in FSHD:

- The main features of the disease are early weakness and atrophy of the shoulder girdle muscles, in many instances preceded by facial weakness, although, apparently, facial weakness is absent in approximately 20% of the cases.
- There is an early spread of the disease to the muscles of the upper arms and to the foot elevators. The further extension to other muscles is variable.
- Pelvic girdle involvement is usually a late stage in the course of the disease.
- Asymmetry of muscle involvement is very common.
- Pseudohypertrophy of muscles is extremely rare.
- Contractures and skeletal deformities are not common, but exact figures are lacking.
- Cardiac involvement has never been properly described.
- Abortive cases with minimal or mild muscle involvement and without complaints related to muscle weakness are quite common.
- The mode of inheritance is autosomal dominant. Autosomal recessive myopathies, clinically identical to FSHD, have never been sufficiently documented. Sporadic cases with a myopathy identical to FSHD have been described. As long as it cannot be proven or disproven that they are mutants of FSHD, their classification remains an open question.
- The penetrance of the abnormal gene appears to be complete.
- Men and women appear equally frequently affected. There are no solid grounds to assume that either sex is more severely affected than the other.
- Serum CK activitity is mildly elevated in approximately 50% of all cases but is rarely more than four times the upper limit of normal.
- FSHD runs a benign course, leading to a severe disability in only a small percentage of cases. Only a few persons become wheelchair-bound, and if so, mostly at an older age.
- The patients' ages at death do not differ significantly from the average.

Apart from these characteristic findings, there are several aspects of FSHD that lack the quality of constancy.

- The sequence in which individual muscles become affected is quite variable.
- The rate of progression of the disease differs from case to case: in some instances the disease is steadily progressive, in others long periods of arrest are noted. Occasionally a rapid progression within years is observed.
- The age of onset may vary from the first year of life till late in middle life. There are no good grounds to assume that the infantile form of FSHD constitutes a separate entity.
- The prevalence of FSHD in different parts of the world is quite variable, ranging from 1 in 20.000 to 1 in 455.000 individuals in a population.
- EMG mostly shows abnormalities thought to be compatible with myopathic disorders i.e. an interference pattern with brief, small and polyphasic action potentials. Occasionally recordings suggesting a neurogenic lesion have been reported.
- Muscle biopsies often demonstrate mild changes, that are compatible with primary muscle disease. Sometimes inflammatory reactions of an impressive degree are found. In a number of cases small angulated fibres are seen, suggesting a neurogenic factor in FSHD.

Finally three negative remarks are pertinent to the definition of the present state of knowledge of FSHD.

- Factors precipitating the onset of the disease are not known, although physical exertion has been implied to play a role in the development of asymmetric muscle involvement.
- Association or linkage with a specific disease or genetic marker has never been reported.
- The pathogenesis and the cause of this disease are not known.