Facioscapulohumeral disease

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Chapter 3

The facioscapulohumeral syndrome: differential diagnosis of facioscapulo-humeral disease

3.1. Introduction

Van Wijngaarden and Bethlem (1973) studied several patients in whom facial and shoulder girdle muscle weakness and atrophy, which was called a facioscapulohumeral syndrome (FSHS), were the main features of their disorder. These patients suffered from different neuromuscular diseases. The authors concluded that such a syndrome is not specific for any disease. Yet the use of the term facioscapulohumeral syndrome (FSHS) became en vogue. Some authors used the adjective FSH in the literal sense, denoting the major sites of muscle involvement. Others (Carroll, 1979) confused the issue and used the term FSHS to discuss the differential diagnosis of FSHD, thereby including several disorders that demonstrate so many particular features in addition to facial, scapular and humeral weakness, that FSHD is rarely considered. These disorders with remote resemblance to FSHD will be mentioned briefly below. In the following sections we will discuss only those disorders that may resemble FSHD clinically. Shoulder girdle weakness is essential. Detectable muscular atrophy is expected if a fair degree of weakness is present. Additional weakness of the facial muscles heightens the resemblance to FSHD, but it is not obligatory. As peroneal weakness may lead to presenting symptoms in FSHD, scapuloperoneal (SP) syndromes should be included in the differential diagnosis of FSHD. FSHD presenting with pelvic girdle weakness has not been reported in the large series of Tyler and Stephens (1950) and Becker (1953). Neuromuscular disorders with pelvic girdle onset will not be considered in the differential diagnosis of FSHD.

Patients with myasthenia gravis may exhibit a FSHS in the course of their disease (Van Wijngaarden and Bethlem, 1973), but

the history and physical examination rarely brings FSHD into the differential diagnostic considerations. The two patients of Van Wijngaarden and Bethlem (1973) had extraocular weakness as well, which excludes FSHD. For similar reasons oculopharyngeal myopathy and all other myopathies with extraocular weakness are excluded from the differential diagnosis of FSHD. Möbius' syndrome shows other cranial nerve palsies besides facial weakness and skeletal deformities in most cases (Henderson, 1939; Hanson and Rowland, 1971). Patients with myotonic dystrophy may exhibit a FSH syndrome. Most of these patients have additional features pointing at the proper diagnosis. Serratrice et al. (1969) reported on a patient with phosphofructokinase deficiency, who had a SP syndrome. He had a history of exercise intolerance, but no history of muscle cramps. His deltoid and sternocleidomastoid muscles were quite atrophic. These findings should suggest another diagnosis than FSHD. The muscle biopsy with biochemical and analysis yielded the proper diagnosis. Patients with systemic carnitine deficiency (Karpati et al., 1975; Carroll et al., 1980) and with muscle carnitine deficiency may exhibit a FSH syndrome. Although the clinical presentation may vary considerably, most patients demonstrate additional symptoms and signs that exclude FSHD.

3.2. Scapuloperoneal muscular dystrophy

The question whether scapuloperoneal muscular dystrophy (SPD) exists represents a semantic problem. If SPD is defined as an autosomal dominantly inheriting primary myopathy with involvement of the shoulder girdle and foot extensor muscles, but without facial weakness in any patient of the family (Rowland, 1977), then SPD has never been properly described as will be demonstrated below. If one accepts, however, that the definition of SPD may include occasional involvement of the facial muscles, it is obvious that there is no clear distinction between FSHD and SPD, since facial weakness is absent in approximately 20% of the affected cases in families with FSHD and foot extensor weakness

frequently is an early finding. It is probable that the seeming distinction between the two conditions could arise when the adjective facioscapulohumeral was taken literally as the main sites of muscle involvement.

The adjective scapuloperoneal (SP) was coined by Davidenkow (1926) to describe a syndrome that apparently occurred in Russia only at that time, but has never been observed since. SP amyotrophy (Davidenkow, 1939) was said to be an autosomal dominant disorder with muscular weakness in a SP distribution and sensory disturbances located distally in the extremities. After a long discussion, and in spite of the absence of post-mortem studies, this syndrome was thought to constitute a separate nosological entity standing between FSHD and peroneal muscular atrophy. Davidenkow's syndrome, as it was called, will be discussed in detail in section 3.6..

Seitz (1957) described a 48-year old Turkish male who developed a slowly progressive shoulder girdle weakness since the age of 30. By the 45th year the foot extensors became involved. Sensory examination was normal. His family was said to be healthy but was not examined. EMG and the muscle biopsy findings were compatible with a myopathy. Seitz reviewed the literature on this syndrome and rejected the - sometimes discrete - sensory disturbances in Davidenkow's cases as criteria for a nosological classification because of the subjective nature of the sensory examination. He concluded that Davidenkow's cases must have been myopathic disorders like his own case, and so the term SP muscular dystrophy was born. His conclusion elicited a chain of confused and confusing reactions. Some of the confusion can be clarified if the chronological sequence of the articles can be abandoned. Therefore, the reports on cases with autosomal dominant inheritance will be discussed first and then those on sporadic cases.

Serratrice et al. (1979) described 14 cases with SP myopathy. Seven patients had an onset of symptoms in the shoulder girdle muscles, seven in the foot extensors. Two of the four sporadic cases and six of the ten hereditary cases had facial involvement. Only in one family the facial muscles were spared in

all cases (a father and a daughter); the other family members were not commented upon. This study lacked family examination anyway. It is the more amazing that they reached the same conclusion as Ricker and Mertens did one year earlier (1968) namely, that a SP syndrome might be a stage in the development of FSHD.

A similar conclusion was drawn by Kazakow et al. (1975) about the famous family K. This family was reported initially by Oransky in 1927. All members had shoulder girdle weakness and the four affected persons that were examined all had foot extensor weakness. Three of them had facial involvement as well. Conventional electro-diagnostic examination favoured a myopathy. The pattern of inheritance was clearly autosomal dominant. Oransky (1927) could not classify this syndrome. He thought it an unusual combination of what he called "the proximal scapulo-humeral or Erb's type" and "the distal or Naville's type of muscular dystrophy". It is not clear whether he was aware of Landouzy and Dejerine's publications. In any case, he did not mention them. This family was also examined by Davidenkow (1939) who found a discrete sensory loss in two cases. Kazakow et al. (1975) reexamined this family and found no sensory abnormalities, normal peripheral nerve conduction velocities, and a myopathic pattern on EMG examination. In his opinion this family suffered from FHSD.

Thomas et al. (1975) reported six patients. In all instances the disease started in the foot extensors. Its myopathic nature was suggested on EMG examination and muscle biopsy. In two cases (mother and daughter), autosomal dominant inheritance was likely. The age of onset was 18 years. Both patients lacked facial weakness or cardiac abnormalities. In two other cases there was a suggestion of heredity based on anamnestic data, while two other cases seemed to be sporadic. The age of onset in those four cases varied from 28 to 57 years. One of them had facial weakness: three of them (40, 48 and 57 years old) had cardiac abnormalities that could have been caused by ischaemia or by cardiomyopathy. Unfortunately, this important distinction could not be made on the available data. As the family data also were inadequate, this

report was not very helpful in the discussion on SPD.

The patients reported by Münzer (1927), Seitz (1957), Hausmanova-Petrusewicz and Zielinska (1962), Lovelace and Menken (1969), and by Steidl and Urbanek (1971) were all considered sporadic cases, but in no instance were the families examined. In the case of Delwaide and Schoenen (1976), two brothers and two nephews were found to be healthy but the parents could not be examined. Accordingly, by lack of adequate family examination, the existence of sporadic SPD is still an open question.

Still it is amazing how much attention is paid to unanswered questions. Brooke (1977) mitigates the fact that a separate section of his book is devoted to SPD by the statement that "in approximately one half of the patients there is also associated facial weakness and in this instance the differential diagnosis (with FSHD) may not only be difficult but irrelevant". The recognition of a SP syndrome "lies only in the fact that other illnesses may mimic SPD". Since one half of the patients have facial weakness it seems that the term FSH syndrome would do equally well. Bethlem (1977) appears rather non-committal about autosomal dominant SP myopathy. He wrote that "some authors consider this myopathy a variant of FSHD". He stated that muscle biopsy may show moth-eaten or lobulated fibres, a fact never reported before and given without reference. Whatever his opinion, this comment demonstrates once more that there is no distinction between FSHD and SPD.

The inference seems fairly well justified that the case for autosomal dominant or sporadic SPD as a clinical entity does not rest on solid evidence in as much as a proper clinical and genetic description has failed to be brought forward.

3.3. Congenital myopathies

There are several congenital neuromuscular disorders that may present with a FSH syndrome. Because congenital or infantile FSHD appears to start with facial diplegia, only Möbius' syndrome seems to be a serious candidate in the differential diagnosis.

Both disorders do not present with hypotonia (Hanson and Rowland, 1971). Möbius' syndrome is characterized by external rectus weakness in most cases, is not progressive, and is sometimes accompanied by skeletal deformities such as clubfeet or extra digits. Congenital or infantile FSHD is a progressive disorder, without extraocular muscle weakness and with a positive family history in most cases.

Patients with congenital myotonic dystrophy display facial diplegia but the generalized hypotonia, the examination of the mother and her family, the laboratory findings, and the clinical course did rule out FSHD in most cases so far (Harper, 1979).

Since Van Wijngaarden en Bethlem (1973) described patients with myotubular myopathy, central core disease, and nemaline myopathy under the heading of FSH syndrome of early onset, these conditions appear regularly on the list of differential diagnosis to FSHD (Carroll, 1979). This is why they will be discussed, although in most patients with these disorders there are ample findings, additional to facial and scapular weakness, to exclude the diagnosis FSHD. The three disorders mentioned above are often included in a larger group of diseases arbitrarily called "congenital myopathies". These congenital myopathies share a particular abnormality on histological, histochemical and ultrastructural examination of muscle biopsies. This group probably represents heterogeneous diseases and the specifity of the various morphological abnormalities is doubted (Brooke, 1977; Bethlem et al., 1978). The pathogenetic mechanisms which produce the lesions are unknown. Attempts have been made to outline some kind of general picture for this group of diseases (Bethlem, 1977) but, apart from hypotonia after birth ("floppy infants") with delayed motor milestones and type 1 fibre predominance in many cases, most other presumed features have too many exceptions. Still, congenital skeletal abnormalities should raise the clinician's suspicion with respect to this group of diseases. Since myotubular myopathy, central core disease, and nemaline myopathy are most consistently mentioned in relation with the FSH syndrome, they will be discussed in more detail.

Most cases of myotubular or centronuclear myopathy presented

as floppy infants. Sometimes the onset of the disease was later in childhood and occasionally in adult life (Goulon et al., 1976). Autosomal dominant (Mc Leod et al., 1972), autosomal recessive and X-linked recessive modes of inheritance were suggested (Van Wijngaarden et al., 1969). Muscular weakness was mainly proximal. Ptosis, extraocular muscle weakness and facial weakness were present in about half the cases (Bethlem, 1977). Extraocular weakness rules out FSHD. In the rare cases when facial and scapular weakness are the main features of the clinical picture, the findings on muscle biopsy will differentiate this disorder from FSHD. These findings include myotube-like fibres, increased amount of internal nuclei, type 1 predominance and, occasionally type 1 atrophy.

Central core disease was first described by Shy and Magee (1956) as a congenital autosomal dominant non-progressive myopathy. Autosomal recessive (Dubowitz and Platts, 1965) and sporadic cases have been reported subsequently (Bethlem and Posthumus Meyjes, 1960; W.K. Engel et al., 1961; Bethlem et al., 1971; Morgan-Hughes et al., 1973). The main clinical features include congenital hypotonia, delayed motor milestones, and a mild non-progressive weakness affecting mainly the proximal muscles, the legs being more involved than the arms. Occasionally, mild weakness of the fae and neck is present leading to the designation FSH syndrome. However, skeletal deformities are not uncommon, giving clues to the proper diagnosis (Telerman-Toppet et al., 1973). In most cases, type 1 fibre predominance is found. The condition is named after the cores that are almost exclusively present in type 1 fibres.

Although central core disease is a non-progressive condition in most cases, Bethlem et al. (1971) described an eight-year old boy with a progressive weakness since his first year of life leading to a severe FSH syndrome with almost complete facial diplegia and protrusion of the lips. In the muscle biopsy, cores were present in approximately 10% of the type 1 fibres. Bethlem et al. (1966) also reported cores in a familial non-progressive myopathy with muscle cramps after exercise. Therefore, he preferred (1977; 1978) to make a distinction between central core

disease and diseases with cores. Since the origin and the significance of the cores are unclear, it is uncertain how many different diseases are included under the heading central core disease.

The term nemaline or rod myopathy denotes a congenital myopathy with rod-like structures in the muscle fibres (Shy et al., 1963). The patients present with generalized hypotonia after birth, delayed motor milestones and muscular weakness of the trunk, the shoulders, and the pelvic girdle. Facial and bulbar weakness is often present leading to difficulties in swallowing and sucking and, occasionally, to respiratory dysfunction. Skeletal abnormalities, such as an elongated face, a high arched palate, prognatism and kyphoscoliosis are present in a considerable number of cases. All these features render a diagnosis of FSHD unlikely. In most instances the disorder is non-progressive. Occasionally a severe course may lead to death from respiratory complications. Many reports concerned sporadic cases, but autosomal dominant and autosomal recessive modes of inheritance have been described (Arts, 1976; Arts et al, 1978).

Of particular interest to the subject under study is a condition that has been described as late onset rod disease (W.K. Engel and Resnick, 1966). In most instances the proximal muscles were more involved that the distal ones, but Brooke (1977) emphasized the clinical presentation as a scapuloperoneal syndrome, with foot drop as an early sign. He did not comment on the facial and bulbar muscles. As the pathogenesis of rods is uncertain and rods have been described in many other non-neuromuscular conditions, the nosological place of late onset rod disease and its relation with nemaline myopathy remains obscure.

In summary, the presentation of the congenital myopathies apparently rarely raises diagnostic suspicion with respect to FSHD, as this has never been reported. In those cases where facial and shoulder girdle weakness are the main clinical findings, additional features often point to the correct diagnosis and the muscle biopsy findings will be decisive.

3.4. Polymyositis

Polymyositis is a non-hereditary myopathy of unknown cause with a non-infective inflammatory reaction found in biopsied muscles. The disorder may run an acute, subacute, or chronic course with a varying degree of severity. The problem of the classification of the inflammatory myopathies and the etiology and pathogenesis of polymyositis and dermatomyositis will not be discussed. Bohan and Peter (1975), in their excellent review on this subject, used four criteria for the diagnosis polymyositis. They included the clinical picture, the serum muscle enzyme activities, the EMG findings, and the muscle pathology. The diagnosis was considered definite if those four criteria were met, probable if three, and possible if two criteria were present.

Clinical picture

As an initial symptom, muscle pain or tenderness is present in 58% of all cases (Barwick and Walton, 1963). Muscle weakness is mostly symmetrical and involves the proximal limb and the girdle muscles in 98% of the cases; the neck flexors and pharyngeal muscles are affected in approximately two-thirds of the patients (Pearson, 1966). In more advanced cases (one third of all), the distal muscles of the extremities are affected but this is rarely the main site of weakness (Walton and Adams, 1958). Involvement of the extraocular muscles is extremely rare. Facial weakness is reported to develop on the course of the disease in 11% of the cases (Barwick and Walton, 1963), but facial weakness is rarely an initial sign. This may be the reason why very few cases of polymyositis have been reported under the heading FSH syndrome. In fact, the interest in polymyositis, with regard to the differential diagnosis of FSHD, was only raised when muscle biopsies of some cases of FSHD demonstrated extensive inflammatory changes (Munsat et al., 1972). A rapid course of weeks or months, dysphagia, early involvement of the neck flexors, and a negative family history, are more compatible with polymyositis than with FSHD. Muscle pains play no decisive role

as they might occur in both conditions. Only in a few subacute or chronic cases one might find no clues pointing to the proper diagnosis (Brooke, 1977).

Serum muscle enzymes

Serum creatine kinase (CK) activity is raised in 64% of the cases at the time of presentation (De Vere and Bradley, 1975) and is the most useful enzyme to test. The degree of elevation does not correlate with the degree of weakness and disability. The raised CK activity is an indication for the activity of the disease although the CK activitity may be within normal limits in patients with a clinical exacerbation of the disease (Brooke, 1977). Since serum CK levels in FSHD are normal or only slightly raised, one might encounter numerous circumstances in which determination of serum CK activity is not helpful for the differential diagnosis.

EMG

EMG examination in polymositis may reveal increased insertional activity and abnormal spontaneous activity such as fibrillations, positive sharp waves and bizarre high-frequency discharges (pseudomyotonic discharges) (Mechler, 1974). The motor unit action potentials are often short, small, and polyphasic. If this complete picture is present, it renders a strong argument for the diagnosis polymyositis. But in those cases where spontaneous activity cannot be found, FSHD appears equally possible.

Muscle biopsy

The muscle biopsy in polymyositis may show atrophy of both fibre types. Perifascicular atrophy in particular suggests dermatomyositis, and is thought to reflect ischaemic changes secondary to vasculitis. An increased number of fibres with internal nuclei is noted, and structural changes such as necrotic fibres with phagocytosis, and basophilic fibres with vesicular nuclei and prominent nucleoli are often found. Vacuolar

degeneration is frequently observed resulting in a practically non-staining fibre in routine stains, such as the haematoxilin and eosin stain and Gomori's trichrome stain. This is thought to be rather characteristic for polymyositis and may be observed in 50% of the biopsies (Dubowitz and Brooke, 1973). Moth-eaten fibres are present in approximately 45% of the cases. An increase in endomysial and, later, perimysial connective tissue is frequently (35%) noted. Approximately 70% of the cases demonstrate some degree of interstitial or perivascular mononuclear infiltrations (Dubowitz and Brooke, 1973). Most authors find the inflammatory infiltration or the perifascicular atrophy requisite to the histopathological diagnosis. DeVere and Bradley, (1975) found the full range of these specific pathological abnormalities in 46% of their cases only. Pearson (1966) reported the muscle biopsy to be without abnormalities in 10-15% of his cases.

The rather extensive inflammatory infiltrations that have been described in patients with FSHD (Munsat et al., 1972) might raise a serious problem for the differential diagnosis. Munsat suggested that these infiltrations occurred mainly in the initial stages of FSHD, but this has never been substantiated. Papapetropoulos and Bradley (1974) extended the discussion to the infiltrations sometimes noted in other forms of hereditary myopathy and suggested that the inflammatory infiltrations could reflect a secondary immunological reaction to the underlying muscle degeneration (Currie, 1970, 1971; Caspary et al., 1971). Treatment with prednisone did not influence the clinical course in these cases (Munsat and Bradley, 1977). Therefore, a positive response to corticosteroids is suggested by some authors as another criterion to the diagnosis of polymyositis.

Dubowitz and Brooke (1973) stated that fibre hypertrophy never was present in cases of polymyositis and suggested that this finding, when present, could differentiate FSHD from polymyositis. Munsat et al., (1972) did not comment on fibre hypertrophy in their cases. Schimrigk (1974), who did note fibre hypertrophy in his case, might have used this finding as an argument to arrive at a diagnosis. He reported a 36-year old

woman with a FSH syndrome, probably of longer duration, who complained of a tight, painful feeling in the muscles of her calfs. These muscles were not weak. EMG was not reported. Because a triceps surae biopsy demonstrated widespread inflammatory infiltrations, fibrosis, fibre necrosis, and a varying fibre diameter with hypertrophic fibres, the diagnosis FSHD was not made, even though the family history suggested a hereditary condition.

A similar problem arose in the case described by Bates et al. (1973). This concerned a 62-year old man with a two year history of progressive weakness in the legs, followed by weakness and atrophy of the hands and the shoulder girdle muscles. The patient denied muscle pains and dysphagia. On clinical examination, he also had weakness of the neck flexors. His lower facial muscles were affected, but his family denied any change in facial expression since his childhood. There was no family history of neuromuscular diseases. His relatives were not examined.

Serum CK activity was markedly raised. EMG showed short, small polyphasic motor unit action potentials and fibrillations on the left deltoid muscle. The motor nerve conduction velocities in the left forearm were normal. Biopsy of the right deltoid muscle revealed a marked variation in fibre size, with numerous atrophic but also a few hypertrophic fibres. Some of the atrophic fibres were arranged in small groups, but most of them were randomly distributed. Foci of necrosis, phagocytosis and regeneration were prominent, and there was significant endomysial fibrosis. Several foci of interstitial and perivascular infiltration were noted. The condition in this patient was diagnosed as polymyositis and he was started on prednisone. This resulted in a significant subjective and objective improvement.

This patient, with a possibly lifelong weakness of the lower facial muscles, fits well in the tentative category of FSHD with late onset, as outlined by Brooke (1977). These patients are said to have significant inflammatory changes in their muscle biopsies, but they do not do so well on corticosteroides. Examination of the family might have given the answer.

Although polymyositis, presenting with a FSH syndrome, appears to be a rare occurrence, the 11-year old girl reported by Rothstein et al. (1970; 1971) qualifies for this diagnosis. In a couple of days she developed muscle pains and tenderness with weakness of the facial, shoulder girdle, and upper arm muscles. The raised serum CK activity (eight times the upper limit of normal), the EMG findings, and the muscle biopsy were all compatible with the diagnosis of polymyositis. Hypertrophic fibres were not reported. Examination of the parents and three siblings was normal. On prednisone, 70 mg. daily, only a slight improvement of muscle strength was noted.

The cases reported by Cumming et al. (1977) demonstrated a localized nodular myositis. They subsequently developed a more classical picture of polymyositis, as in the case reported by Heffner and Barron (1981). The liberal use of the term FSH syndrome for cases with dysphagia and dysarthria will never pose a problem of differential diagnosis with respect to FSHD.

In conclusion, one may confidently infer that polymyositis presenting with a FSH syndrome is extremely rare. The clinical course and the laboratory findings lead to the proper diagnosis in most cases. On the other hand, small mononuclear infiltrations are rather non-specific findings in neuromuscular disorders, and can be quite extensive in FSHD. Examination of family members is helpful in many, and is essential in chronic cases. Hypertrophy of fibres in the muscle biopsy might argue against the diagnosis of polymyositis.

3.5. Myopathies with abnormal mitochondria

Myopathies with abnormal mitochondria (or mitochondrial myopathies) constitute a widely variable group of diseases, having in common that the mitochondria in the muscle fibres are abnormal in number, size, shape and/or function. The morphological abnormalities are studied by electron microscopy but abnormal mitochondria can be suspected at light microscopy if so-called "ragged red fibres" are present in the modified

trichrome stain, or if an excessive reaction or an abnormal distribution is found with the oxidative enzyme stains. In many cases there is an intracellular accumulation of lipids. The morphological abnormalities of the mitochondria appear non-specific as they are found in many other and unrelated neuromuscular disorders as well. Moreover, abnormal mitochondria may also be present in disorders that involve other organ systems besides muscles, like Kearns-Shy syndrome or ophthalmoplegia plus (Kearns and Sayre, 1958; Shy et al., 1967; Drachman, 1968), Alpers syndrome or progressive infantile poliodystrophy (Shapira et al., 1975) and others (Bradley et al., 1978).

Most cases of the mitochondrial myopathies were sporadic, but all modes of inheritance have been described. Variations in ages of onset have been reported and all kinds of clinical presentation have been observed, including the FSH syndrome. In many instances additional features were present, like salt craving, excessive fatigability, growth retardation, nerve deafness, lactic acidosis, loosely coupled stated of oxidative phosphorylation or hypermetabolism of non-thyroid origin. Many of these findings are believed to be secondary phenomena. More needs to be known about the function and pathology of mitochondria before a useful attempt at classification can be made. Awaiting this knowledge, we will mention some of the reports of cases that presented as FSH syndromes.

In 1967 Van Wijngaarden et al. described a 15-year old boy with a progressive limb-girdle syndrome, who was found to have a subsarcolemmal accumulation of pathological mitochondria. Biochemical analysis demonstrated a loosely coupled state of oxidative phosphorylation. This patient subsequently developed facial and extraocular weakness. Van Wijngaarden and Bethlem (1973) included this patient in their discussion of the FSH syndrome. As extraocular weakness is no part of FSHD, this diagnosis will not be considered in such cases.

D'Agostino et al. (1968) described two sisters with diffuse progressive muscular weakness and growth retardation who were found to have enlarged and abundant muscle mitochondria. The second patient had "a rather expressionless face", suggesting

mild bilateral facial weakness.

The 13-year old patient described by Spiro et al. (1970) had a congenital non-progressive myopathy, with weakness of the proximal limb muscles, and slight weakness of the facial and sternocleidomastoid muscles. A remarkable feature was his craving for salt. There was no history of periodic paralysis. Stains for lipids and oxidative enzyme activity were uniformly increased and did not permit fibre type differentiation. The mitochondria were morphological normal but their numbers were increased. Studied in vitro they showed loose coupling of oxidative phosphorylation.

The family described by Hudgson et al. (1972) was quite remarkable in that the clinical features of the myopathy in this family were very similar to FSHD. The disorder inherited in an autosomal dominant way affecting males and females, but apparently was transmitted only from mothers to children. The penetrance of the condition was high. The expression was quite variable. Four patients with a normal physical examination had an elevation of the serum CK activity. One of them was found to have the same pathological and biochemical abnormalities in a muscle biopsy as his clinically affected relatives. Therefore, these four patients were considered to be affected subclinically. Seven members of this family were found to be affected on physical examination. The ages at onset varied from six to 50 years. At the time of examination the duration of the disease ranged from six to 19 years. In two cases weakness was noted initially in the shoulder girdle, and in the pelvic girdle in four cases. In the proband's case, the mode of onset could not be decided. Six patients had both pelvic and shoulder girdle weakness, and one patient had only slight weakness of the hipflexors. Four patients had facial muscle weakness. In addition, the proband demonstrated slight wasting of the tongue with dysarthria and wasting of the temporal and masseter muscles. There was another patient who had dysarthria but no facial weakness. Five out of six patients, with upper limb involvement, had sternocleidomastoid muscle weakness and two of them also had weakness of the anterior neck muscles, a feature Van Wijngaarden en Bethlem (1973) thought to be less compatible with FSHD. Also the other features, such as onset in

the pelvic girdle muscles, involvement of the temporal, masseter and lingual muscles and dysarthria, strongly suggest a diagnosis other than FSHD.

The serum CK activity was elevated in five clinically affected patients ranging from 69 to 426 IU/L (normal up to 60 IU/L). Taurine excretion in the urine was elevated in three clinically affected and in one subclinically affected patient. Taurinuria was also found in the two cases described by D'Agostino et al. (1968), and mentioned earlier in this section. Although muscle is the main source of taurine, and taurine excretion rises in acute muscle damage, the relation between the taurinuria and this myopathy remained obscure.

EMG was performed in four cases, showing a myopathic pattern in all muscles examined. In one of these cases spontaneous fibrillations and positive sharp waves were found in the extensor digitorum brevis muscle. The motor nerve conduction velocities were all normal.

Muscle biopsies were performed in two affected patients and in one man who only had an elevated serum CK activity. The pathological changes were the same in all biopsies, although less pronounced in the asymptomatic patient. The biopsies demonstrated a considerable amount of necrotic fibres, a moderate degree of fibrosis and infiltration of the fascicles with fat cells. A number of large capillaries were present in the areas of regeneration. Throughout the biopsy, many fibres demonstrated an excessive amount of lipid and an increased oxidative enzyme activity. Both fibre types were involved.

Ultrastructural studies revealed many giant mitochondria, often with concentric cristae and small electron-dense inclusions, and sometimes with paracristalline inclusions. Some small fibres showed abundant and bizarre mitochondria with morphological peculiarities like myelin figures and autophagic vacuoles. Many more normal looking fibres contained an excess of small lipid droplets or large areas of glycogen granules. A remarkable finding was the large number of capillaries in the affected fibres. A liver biopsy obtained from the propositus showed no structural abnormalities of the mitochondria.

Biochemical studies of isolated muscle mitochondria revealed a loosely coupled state of oxidative phosphorylation (Worsfold et al., 1973). In addition, there was a greatly increased amount of muscle lipid, mainly triglycerides.

Bradley et al. reported later (1978) on one female patient of this family who had died due to a viral pneumonia and cerebral venous thrombosis, during which she developed gross lactic acidaemia. Post-mortem examination showed that the mitochondrial morphological abnormality was restricted to the skeletal muscle. Another male of this family, who also had the mitochondrial myopathy, developed a cerebellar syndrome. His mother, who had been affected and had died since Hudgson's et al. (1972) report, had suffered from a transient cerebellar syndrome for several years, of which only a slight dysarthria had remained at the time of examination. In addition, the skeletal muscle carnitine level had been investigated in the proband and was found to be normal.

The pathological and biochemical abnormalities render the condition in this family distinct from FSHD. Especially when the family is taken as a whole, the clinical picture is different as well, although in a more subtle way.

One may conclude that mitochondrial myopathies may occasionally present as a FSH syndrome. Careful clinical examination will make FSHD less likely. Additional laboratory investigations will lead to the proper diagnosis.

3.6. Scapuloperoneal muscular atrophy with sensory disturbances (Davidenkow's syndrome)

In 1939 Davidenkow published the data on one sporadic and 26 familial cases of a condition he named scapuloperoneal (SP) amyotrophy. He made 13 personal observations in five families and included in his study the large family previously described by Oransky in 1927. The disorder was said to be autosomal dominantly inherited, and to begin between the age of 17 and 20 years in most cases. In some patients the age at onset was as late as 45 years. Men and women were equally affected. The clinical

expression of the disease was quite variable; abortive cases were not uncommon. The muscle weakness could start in the upper or in the lower extremities, or become manifest in both simultaneously. In fully developed cases the pectoralis, trapezius, rhomboidei and serratus anterior muscles were affected bilaterally, with sparing of the deltoid and levator scapulae muscles. The muscles of the upper arms became involved much later in the course of the disease and weakness of the hands and fingers was only occasionally observed. The facial muscles often participated in the process, although this remained limited to an asymmetric involvement of the orbicularis oris muscle in most cases. In the legs the foot extensor and peroneal muscles usually were affected, while the foot flexors and supinator muscles frequently were weak as well, but to a lesser degree. In the majority of the cases the atrophy did not extend in a proximal direction and the muscles of the pelvic girdle remained intact. Pseudohypertrophy of muscles was not observed. So far, the description of the clinical picture is identical to FSHD.

Fasciculations were present in two patients (the father and his daughter of family "Su"). Pes cavus, although minimal,was frequently found. Sensory disturbances were absent and consisted of hypaesthesia and hypalgesia with a distal distribution in the limbs. Complaints of pain and paraesthesias were rare. The vibration and position senses were intact in most cases. Occasionally, perioral hypaesthesia was found. Electrical examination of the affected muscles demonstrated a partial reaction of degeneration. Muscle biopsies were not performed.

The nosological place of this syndrome has been disputed extensively. In 1927 Davidenkow thought SP amyotrophy to be a variety of Charcot-Marie-Tooth disease or peroneal muscular atrophy (PMA). In a subsequent article (1939), he noted that the pattern of the muscular atrophy resembled the distribution in FSHD but that, on the other hand, he had never observed a SP syndrome in all the families with PMA he knew. This last observation was later confirmed by Ricker et al. (1968) and by Dyck and Lambert (1968). In 1939 the nosological place of SP amyotrophy remained undecided. In 1954, still lacking

pathological studies, Davidenkow wrote: "the so-called scapuloperoneal amyotrophy occupies a place exactly between the neurogenic (peroneal) amyoptrophy and the facioscapulohumeral myopathy". Confirmation of this syndrome by others is still needed. A similar condition has not been reported since. In a few sentences in an earlier report, Eisenlohr (1889) mentioned a family that might have fitted Davidenkow's description, but the details were scanty.

There are a few reports about similar conditions that were apparently not inherited in an autosomal dominant way. The sporadic case reported by Meadows and Marsden (1969) was a 21-year old girl with progressive muscular weakness and atrophy located distally in all extremities since she was eight years of age. Subsequently she developed bilateral infraspinatus weakness. The term SP syndrome is hard to justify in this case, because the shoulder girdle muscles were certainly not one of the main sites of muscle weakness. Sensory abnormalities were absent. EMG revealed neuropathic features, and the motor nerve conduction velocities became progressively slower in the course of the disease. Muscle biopsy did not show specific abnormalities, with the exception of loss of fibres from intramuscular nerve bundles and degenerative changes in some terminal nerve fibres, suggesting denervation. The initial diagnosis, spinal muscular atrophy (SMA), was changed to PMA because of the slowing of the motor nerve conduction velocities. The authors suggested that all Davidenkow's cases probably suffered from PMA, ignoring that their case did not fit at all in Davidenkow's description.

In 1975 Schwartz and Swash described a 27-year old male with progressive weakness and atrophy of the periscapular, triceps, biceps and foot extensor muscles. There was a mild bilateral facial weakness as well, making the clinical picture of a FSH syndrome complete. The neck muscles, the deltoid and the extensor digitorum brevis muscles were virtually uninvolved. All sensory qualities were impaired in a symmetrical glove and stocking distribution. The family was not examined, but was reported to be unaffected. Muscle biopsy and EMG findings were compatible with a neurogenic disorder. The sensory nerve conduction velocities were

slowed, as was the motor nerve conduction velocity in the median nerve. Apart from the hereditary aspect, this case fitted Davidenkow's description quite well.

Toghi et al. (1971) reported two sibs, a 14-year old boy and a 12-year old girl, with progressive weakness and atrophy in a SP distribution with onset at the age of seven, and with sensory disturbances of glove and stocking type. Pes cavus and quinovarus was present bilaterally. EMG and muscle biopsy suggested a neurogenic disorder. The motor nerve conduction velocities of the ulnar and peroneal nerves were within normal limits. Sural nerve biopsy showed demyelination and degeneration of axons. All findings were indicative of a neuropathy. Details of the family were lacking. The authors presumed autosomal recessive inheritance.

The patient described by Spalke et al. (1976) will be mentioned because she was presented as a case of SP amyotrophy, although there were some details that made her case different from Davidenkow's description. The authors reported a 41-year old woman who was noted to have hanging shoulders at the age of 17. When 31 years old she developed, in a couple of weeks, progressive weakness of the right foot and toe extensors, accompanied by paraesthesias in her right leg. Two years later the left shoulder girdle weakened and atrophied in a few months, accompanied by cramp-like pain. This muscle weakness gradually progressed to a symmetrical FSH syndrome with ptosis and "bouche de tapir". At the time of examination the pain in her left arm was still present. There was a stocking and glove distribution of impairment of pain, temperature and touch sensation. The vibration and position senses were normal. Electrocardiography revealed a right bundle branch block. EMG showed a myopathic pattern. The motor nerve conduction velocities were within normal range. Only the sensory nerve conduction velocity of the left median nerve was decreased, and histochemical examination of the deltoid and anterioir tibial muscle revealed myopathic features. The biopsy of the sural nerve showed no histological or ultrastructural abnormalities. The father, grand-father, two paternal aunts, and one paternal cousin were reported to have

problems of gait, suggesting an autosomal dominant mode of inheritance. They were not examined, however. The authors concluded that their case could not be classified. Harding and Thomas (1980) described an interesting family in which the female proband showed all features of Davidenkow's syndrome. Her sister has distal sensory loss and muscle weakness, compatible with Charcot-Marie-Tooth disease (PMA), while a deceased brother had shown generalized weakness of the upper limbs with normal strength in the lower limbs. The diagnosis was supported by EMG examination. The parents of these three sibs were allegedly not affected. Harding and Thomas (1980) suggested that Davidenkow's syndrome might be "a phenotypic manifestation of type I hereditary motor and sensory neuropathy" (PMA), but they were unable to prove the autosomal dominant mode of inheritance.

The discussion on Davidenkow's syndrome, autosomal dominant SP atrophy with sensory disturbances distally on the extremities, can be summarized best by the observation that since the original publications this syndrome has never been described.

The sporadic case described by Schwartz and Swash (1975) and the two possibly autosomal recessive cases reported by Toghi et al. (1971), and the cases of Harding and Thomas (1980) cannot be considered to suffer from the same disorder.

3.7. Spinal muscular atrophies

The spinal muscular atrophies (SMA) have received tremendous interest from neurologists and geneticists in recent years. Wohlfart et al. (1955) and Kugelberg and Welander (1956) separated hereditary proximal SMA from the limb-girdle syndrome. Their description can be summarised as follows:

1. Onset of symptoms from childhood to adolescence.
2. Proximal muscular atrophy.
3. Presence of fasciculations.
4. No bulbar involvement.
5. Slowly progressive clinical course.
6. Neurogenic findings on EMG and muscle biopsy.
7. Autosomal recessive mode of inheritance.

Gradually the syndrome, as outlined above, was expanded. Magee and De Jong (1960) were the first to describe autosomal dominant inheritance. Tsukagoshi et al. (1965) reported adult onset and involvement of the bulbar musculature. Numerous additional reports on SMA have been published. Several attempts at classification have been made (Namba et al., 1970; Emery, 1971; Pearn, 1981), using the criteria of the clinical picture, the age of onset and the mode of inheritance. In some instances SMA is part of a more complex clinical picture (Pearn, 1981). Although autosomal recessive inheritance is present in most cases, no enzyme deficiency has ever been observed with exception of a recent report on a young male with hexoseaminidase A deficiency (Johnson et al., 1982).

The diagnosis of SMA is based on the clinical picture, on the results of EMG, on the examination of muscle biopsies, and sometimes, on the study of muscle innervation as well (Coërs et al., 1973; Coërs and Woolf, 1981). Determination of the serum CK activity plays no significant role in the diagnosis of SMA, as it is more commonly only slightly raised, and does not discriminate SMA from myopathic conditions.

The clinical picture is that of muscular atrophy with fasciculations in the absence of sensory abnormalities. Occasionally extensor plantar responses are found (Bouwsma, 1978). Such findings will never be present in FSHD. Hypertrophy of the calf muscles, foot deformities and muscle contractures are frequently noted in SMA and very rarely in FSHD. Namba et al. (1970) reported cranial nerve involvement (including facial weakness) in 17.8% of his cases with juvenile chronic proximal SMA and in 31% of his cases with adult onset chronic proximal SMA. The fasciculations of the tongue, the bulbar involvement, and the tremor of the hands render a confusion with FSHD unlikely, even on clinical grounds alone.

EMG will show spontaneous activity such as fibrillations or fasciculations, and motor unit action potentials of long duration and high amplitude, with a reduced interference pattern on voluntary contraction (Meadows et al., 1969). Yet, EMG occasionally has been found to be normal or even myopathic, as

defined in chapter 2 (Emery, 1971). A myopathic pattern is not in frequently found in SP-SMA (Kaeser, 1965, Mercelis et al., 1980).

Muscle histology reveals atrophy of groups of fibres (group atrophy). Histochemical studies may show type grouping, a phenomenon explained by collateral reinnervation of affected fibres by normal motor neurons. Particularly in longstanding cases, target fibres may be present. In early stages of neurogenic atrophy, small angular fibres may be seen, scattered between normal looking fibres, but small angular fibres may also be the only abnormality in FSHD. To make the picture even more complicated, myopathic features such as variation in fibre size, rounded fibres, central nuclei, basophilic fibres, and even necrosis and phagocytosis may be found in cases with neurogenic atrophy (Drachman et al., 1967; Gardner-Medwin et al., 1967; Mumenthaler, 1970; Namba et al., 1970; Achari et al., 1974). These changes are explained as a result of partial and defective reinnervation by neighbouring motor neurons. It should be clear that the diagnosis of SMA hinges on the laboratory examinations in many cases, but that the same examinations could lead to faulty conclusions (Mercelis et al., 1980).

The most fruitful classification of the SMA's at present appears to be the one proposed by Emery (1981), which is presented in a slightly modified form in Table 3.1. Although the facial muscles may be involved in a considerable amount of the cases with proximal SMA, and particularly later in the course of the disease, the other clinical features and the laboratory examinations virtually never bring FSHD in the differential diagnostic considerations, even in cases with autosomal dominant inheritance. The same holds true for progressive bulbar paralysis of childhood or Fazio-Londe disease (Gomez, 1979; Bundey, 1981). All 14 reported cases in the literature had facial weakness, but they all had involvement of other cranial nerves as well.

It appears that in the description of SMA the adjectives FSH and SP are used in a literal sense, indicating the main sites of involvement. Since both adjectives may cover a part of FSHD, it is clear that FSH-SMA as well as SP-SMA must be considered in the differential diagnosis. The cases reported in the literature

under these diagnoses will be discussed briefly, in the chronological order as outlined in Table 3.2. Cases with a cardiopathy will be discussed separately in the next section.

Mares et al. (1964) described a father, his son and two daughters all of whom developed a progressive FSH syndrome with facial involvement. The age at onset varied from eight to 20 years. EMG studies performed in all patients showed a reduced interference pattern with action potentials of increased amplitude.

Table 3.1. Classification of the Spinal Muscular Atrophies. (modified after Emery, 1981)

I.	Proximal SMA		
	A Infantile, autosomal recessive		
	B Intermediate, autosomal recessive		
	C Juvenile	1. autosomal dominant	
		2. autosomal recessive	a. Usual form (Kugelberg-Welander)
			b. Ryukyu form
			c. with microcephaly
	D Adult	1. autosomal dominant	
		2. autosomal recessive	
		3. X-linked recessive	
II.	Distal SMA	1. autosomal dominant	
		2. autosomal recessive	
III.	Juvenile progressive bulbar palsy, autosomal recessive		
IV.	Scapuloperoneal SMA		
	A. Juvenile	1. autosomal dominant	
		2. autosomal recessive	
	B. Adult	1. autosomal dominant	
V.	Facioscapulohumeral SMA, autosomal dominant		

Table 3.2. Reports on facioscapulohumeral and scapuloperoneal spinal muscular atrophies without a cardiopathy (only first authors cited)

Facioscapulohumeral Spinal Muscular Atrophy		
1. autosomal dominant:	Mares	1964
	Fenichel	1967
	Ricker	1968
	Furakawa	1976
	Furakawa	1981
2. sporadic cases:	Furakawa	1969
	Patel	1969
	Krüger	1974
Scapuloperoneal Spinal Muscular Atrophy		
A. Juvenile onset		
1. autosomal dominant:	Feigenbaum (cases 1,2,3,6)	1970
	Serratrice (cases 1,2,3)	1976
2. (autosomal) recessive:	Feigenbaum (cases 5,7,8)	1970
	Negri	1973
	Takahashi (case 1)	1974
	Mercelis	1980
3. sporadic cases:	Emery	1968
	Munsat	1968
	Zellweger	1968
	Schuchman	1970
	Feigenbaum (cases 4,9,10)	1970
	André	1972
	Hromada	1973
	Serratrice (cases 7,8)	1976
B. Adult onset		
1. autosomal dominant:	Kaeser	1964/1965/1975
	Tsukagoshi	1969
	Serratrice (cases 4,5)	1976
2. sporadic cases:	Fotopulos	1966
	Takahashi (case 2)	1974
	Serratrice (cases 6,10)	1976

These findings were not specified per patient or per muscle. Muscle biopsies revealed myopathic abnormalities in two cases. The authors did not arrive at a definite conclusion about the primary site of the lesion.

Fenichel et al. (1967) reported on a mother and a daughter who both developed facial weakness at the age of 13, followed by shoulder girdle weakness. The deltoid muscle appeared weaker than the pectoralis muscle. No fasciculations were observed. Only in the daughter the disease had progressed to pelvic girdle muscle involvement. Sensory examination was normal. A first EMG in the daughter was normal, but a repeated study showed increased insertional activity and occasional fasciculations in the deltoid and biceps muscles without other neurogenic features. A similar, though not specified, result was obtained from the mother. Biopsy of the left quadriceps muscle in the daughter revealed a few angulated fibres of both fibre types. The neurogenic basis of the disorder was "identified primarily by the muscle biopsy". Since small angulated fibres are known to occur frequently in FSHD, this basis appears very small indeed.

A similar diagnostic problem is posed by the cases described by Ricker et al. (1968). A father and a son were reported with a progressive FSH syndrome with facial involvement since the age of 23. EMG in the son demonstrated myopathic and neurogenic features. A muscle biopsy showed myopathic features and isolated small angulated fibres, so that the diagnosis neurogenic FSH syndrome appears quite debatable in these cases.

Furakawa and Toyokura (1976) reported on a mother, her daughter and her son, all of whom had developed a FSH syndrome in their second decade of life. The tongue and other bulbar muscles apparently were normal. A previous biopsy of the left deltoid muscle in the mother was reported to show myopathic features. EMG in all three cases revealed fasciculations, and neurogenic and myopathic characteristics. Recently (1981) Furakawa et al. reported briefly on 13 patients out of eight families with FSH-SMA. Autosomal dominant inheritance was said to be present in most cases. Electrocardiographic abnormalities were noted in several patients, but this was not specified. Details on these

patients are eagerly awaited, especially since the diagnosis in the cases mentioned before depends heavily on EMG. As small angulated fibres are quite common in muscle biopsies of patients with FSHD (Dubowitz and Brooke, 1973) and as neurogenic findings on EMG in these patients are not rare (McComas, 1977), it is reasonable to question the existence of autosomal dominant FSH-SMA.

A few reports on sporadic cases with FSH-SMA have been published. In older literature this syndrome bears the eponyms of Vulpian and Bernardt. The deltoid muscles are said to become affected early in these cases, which contrasts with the findings in FSHD.

The first patient described by Furakawa et al. (1969) had facial weakness and progressive shoulder girdle weakness since he was 18 years old. The second patient had shoulder girdle weakness only. Both had fasciculations and neurogenic findings on EMG. Muscle biopsy in the first case showed large groups of small fibres. No other members of the families were affected.

Patel and Swami (1969) reported a teen-age case of SMA with shoulder girdle weakness and equivocal facial weakness, without further elaboration or discussion.

The 61-year old man studied by Krüger and Frank (1974) had facial weakness and a slight ptosis on the right side since the age of 55. The shoulder girdle and upper arm muscles were weak and atrophic. The deltoids were spared. Fasciculations were present in the upper arms. The pelvic girdle and legs were not involved. EMG and muscle biopsy supported the diagnosis neurogenic muscular atrophy. His family was said to be free of neuromuscular diseases, but was not examined.

The cases of SP-SMA with juvenile onset and with adult onset will be discussed separately, in accordance with the general principles of Emery's classification. The question remains if such a division is justified but, so far, all cases belonging to one family had either juvenile or adult onset. Sporadic cases are all those cases in which the mode of inheritance was uncertain.

Feigenbaum's (1970) case 2 was the only one with onset of the disease in the shoulder girdle muscles. In all other cases

the disease started in the peroneal muscles, and ran an ascending course, which is not the usual pattern of FSHD. Another remarkable feature of SP-SMA is the high incidence of foot-deformities such as pes cavus and pes equinovarus. Kaeser (1965, 1975) and Mercelis et al. (1980) emphasized the often conflicting findings on EMG and muscle biopsy regarding the primary site of the lesion, and the possibility of finding neurogenic features in one part of the body and myopathic features in another part on EMG examinations.

Cases with autosomal dominantly inheriting SP-SMA of juvenile onset have been reported by Feigenbaum and Munsat (1970; cases 1,2,3 and 6) and by Serratrice et al. (1976; cases 1,2 and 3).

A recessive mode of inheritance could have been present in three male cases (5,7 and 8) reported by Feigenbaum and Munsat (1970). The diagnosis in these cases was supported both by EMG and muscle biopsy.

The male patient reported by Negri et al. (1979) was mentally retarded. The two living brothers of this patient had distal atrophy of the legs, with fasciculations and neurogenic findings on EMG. Neither the parents nor the three sisters had complaints.

The pedigree of the first case (a male) reported by Takahashi et al. 1974 revealed consanguinity. The authors suggested autosomal recessive inheritance, although no similar cases were reported in the family. The patient had a progressive SP syndrome since the age of 12 without facial involvement. EMG showed myopathic features in the lower legs and neurogenic features in the upper arms. Biopsy of the gastrocnemius revealed myopathic changes, while biopsy of the triceps brachii demonstrated group atrophy.

Mercelis et al. (1980) reported on two brothers with SP-SMA. In the elder patient, EMG had shown a myopathic pattern on several occasions. The muscle biopsy findings in this case were equivocal. His younger brother clearly showed neurogenic features on EMG and muscle biopsy. Both had presented with foot extensor weakness in the first decade. No definite conclusion on the

pattern of heredity could be reached in all these recessive male cases.

Sporadic cases of SP-SMA, both males and females, have been reported by Emery et al. (1968), Munsat (1968), Zellweger and McCormick (1968), Schuchmann (1970), Feigenbaum and Munsat (1970, cases 4,9 and 10), André et al. (1972), Hromada et al. (1973), and Serratrice et al. (1976, cases 7 and 8). Serratrice's case number 9 had sensory disturbances and bilateral extensor plantar responses. This case was rather deviant from all other cases and cannot be considered a SP-SMA.

Autosomal dominant chronic SP-SMA of adult onset was first described by Kaeser (1964, 1965, 1975). Twelve persons (six males, and six females) in five generations were affected. Four patients were examined (1965). The disease started between 30 and 50 years. Weakness and atrophy of all lower leg muscles were the presenting signs. Initially the intrinsic foot muscles, the extensor digitorum brevis and the plantar muscles were all spared. In the first three generations the disease had spread to involve the thigh and pelvic girdle muscles. In 1965 the shoulder girdle muscles were reported not to be affected in these generations. In 1975, however, Kaeser stated that these muscles were slightly affected, although all these patients had died long before 1965. Even the fourth generation was reported in 1965 to be without shoulder girdle involvement. In this generation, one patient had weakness of the palatal and pharyngeal muscles, leading to dysphagia. Autopsy was performed in this case. Shoulder girdle, upper arm and facial weakness occurred only in the fifth generation. One patient in this generation also had dysphagia and extraocular muscle weakness. The distribution of the shoulder girdle weakness was particular in that the sternocleidomastoidei, the upper part of the trapezius, the rhomboidei, the supraspinatus, the infraspinatus and the triceps brachii muscles were severely affected, while the serratus, deltoid and biceps muscles remained relatively spared.

EMG studies revealed somewhat different findings on repeated examinations, one time thought to be more compatible with a chronic neurogenic lesion, the other time with a myopathic

disorder. The motor nerve conduction velocities were normal on repeated occasions. Muscle biopsy in one case revealed myopathic features (1965). Autopsy in another case showed group atrophy in all muscles examined. The anterior horn cells of the spinal cord and the bulbar motor nuclei demonstrated vacuolisation and central chromatolysis. The peripheral nerves were all normal (1964). In 1977 Probst et al. published another autopsy report on a member of this family. The number of anterior horn cells were normal at all levels but the anterior horns showed axonal swellings, accumulation of possibly pathological lipofuscin and large numbers of intra-axonal corpora amylacea. The anterior roots, the peripheral nerves and the intramuscular nerve endings appeared without abonormalities. The muscles showed selective type 2 atrophy, type grouping and accumulation of neutral fat, mainly in the type 1 fibres. All the abnormalities found in Kaeser's family suggested anterior horn cell disease, yet they are distinct from those to be found in chronic proximal SMA (Kugelberg and Welander, 1956) in which the number of anterior horn cells is reduced considerably.

The three sibs, presented by Tsukagoshi et al. (1969) pose a problem as to the correct diagnosis. One patient had "disturbances of superficial sensations in the distal parts of the four limbs". Demyelination was present in a sural nerve biopsy in this case. EMG and muscle biopsy in the other patients were compatible with a neurogenic lesion. A sural nerve biopsy in one of these patients was normal. As the father was "probably affected", autosomal dominant inheritance was suggested. In spite of the conflicting findings, the authors considered their cases to suffer from SMA. Harding and Thomas (1980) however, considered these cases to be examples of Davidenkow's syndrome.

Cases 4 and 5 reported by Serratrice et al. (1970) were also autosomal dominant cases with adult onset of SMA, and first symptoms in the legs. Details on these patients were not offered.

The first sporadic case with adult onset SP-SMA was reported by Fotopulos and Schulz (1966). This 55-year old woman complained of weakness in both legs since she was 44. Her condition had progressed to a SP syndrome, with weakness of the neck flexors

and the sternocleidomastoidei muscles as well. Fasciculations of the thigh muscles were observed on one occasion. Sensory examination was normal. The family history was negative for neuromuscular disorders. EMG showed a neurogenic pattern in the legs and a myopathic pattern in the shoulder girdle muscles. Biopsy of the calf muscles demonstrated myopathic features and group atrophy. The authors thought their case an intermediate between a myopathic and a neurogenic condition and unclassifiable in the current taxonomic schemes. Others, like Kaeser (1975), had no hesitation in grouping this case under the neurogenic conditions.

The second case, reported by Takahasi et al. (1974), had a SP syndrome with a slowly ascending course. EMG of the arms showed myopathic findings, and EMG of the legs both myopathic and neurogenic features. Biopsy of the quadriceps muscle revealed both myopathic characteristics and a few groups of small fibres.

The cases 6 and 10, reported by Serratrice et al. (1976), were apparently sporadic. In the first case the disorder had started in the legs; in the second case shoulder girdle onset was suggested. Details on these cases were not offered.

One must conclude that the existence of autosomal dominant FSH-SMA has not been firmly established. The cases reported as such are not (yet) proven to be non-FSHD. Sporadic cases with SMA in a FSH distribution have been reported, but are apparently rare. SP-SMA is a well established entity. The ascending course which is almost invariably present, the lack of facial weakness in the majority of cases and the high frequency of foot deformities are relative arguments against the diagnosis FSHD. Bulbar weakness excludes FSHD. EMG and muscle biopsy may yield both myopathic and neurogenic features, making the proper diagnosis difficult in a considerable number of cases. These findings have been explained as the result of dying back of terminal axonal twigs (Jennekens, 1975).

3.8. Facioscapulohumeral and scapuloperoneal syndromes with cardiomyopathy

FSH syndromes with cardiomyopathy can be divided in:

A. X-linked recessive myopathic conditions with muscle contractures, in which the cardiomyopathy presents as a progressive impulse generation and conduction defect, leading to persistent atrial paralysis (PAP), with ventricular hypertrophy in the elderly patients.

B. Autosomal dominant myopathic conditions with muscle contractures, cardiac impulse conduction defects, and cardiomegaly.

C. Neurogenic conditions with impulse conduction defects and cardiac enlargement.

A. Clinical medicine is long since familiar with observations that atrial paralysis may occur as a terminal condition in myocardial infarction and in hyperkalemia. It also can occur as a transient phenomenon in severe sinus arrythmias, in anoxia, drug intoxication and in open heart surgery. A prolonged and persistent atrial paralysis (PAP) was described for the first time in 1965 in a patient with a FSH syndrome (Bloomfield and Sinclair-Smith). Since then PAP has been described in sporadic and familial cardiac disorders, with or without myocardial amyloid deposits (Allenworth et al., 1969; Nagle et al., 1972). PAP, in association with a myopathy, was reported in three sporadic cases (Bloomfield and Sinclair-Smith, 1965; Caponetto et al., 1968; Baldwin et al., 1973). They were all studied by cardiologists who paid extensive attention to the cardiac abnormalities but, regrettably, poorly informed the readers about the neuromuscular condition. Because PAP is very rare, and all three cases were men with a FSH myopathy, it is very likely that these patients were suffering from the same condition described later as X-linked recessive scapuloperoneal myopathy with cardiomyopathy. Moreover, photographs of these three patients suggested that they all had abduction contractures of the shoulders and flexion contractures of the elbows. Every

author offered a slightly different name for the same syndrome: X-linked SP syndrome (Thomas et al., 1972), X-linked scapulo-humero-distal muscular dystrophy (Rotthauwe et al., 1972), X-chromosomaler benigner Muskeldystrophie mit Frühkontrakturen (Camman et al., 1974), X-linked humeroperoneal neuromuscular disease (Waters et al., 1975). It is debatable if the family, described by Emery and Dreifuss (1966) under the name "benign X-linked muscular dystrophy", should be included. This family differed from the others by presenting with a limb-girdle syndrome instead of a SP syndrome, and by the absence of a flexion limitation of the neck. Since calf hypertrophy was absent and PAP was suggested in two cases, this family is usually included in the description of the X-linked SP syndrome with cardiomyopathy (Rowland and Layzer, 1979). Rowland et al. (1974) even suggested the name "Emery-Dreifuss muscular dystrophy" while describing an extensively studied sporadic case.

The disorder usually manifests itself between the age of two and ten years, affecting males only. The reported pedigrees are compatible with X-linked recessive inheritance. In the family reported by Thomas et al. (1972), the disorder was linked with deutan colour blindness. The initial signs were flexion contractures of the elbows, accompanied (or followed within a few years) by ankle contractures. Upper arm weakness and atrophy was an early finding in all families, except in the one of Emery and Dreifuss. In this family pelvic-femoral weakness appeared early, progressing to a limb-girdle syndrome. In the other families the upper arm and peroneal weakness was conspicuous, while the periscapular muscles were less affected. Several patients with mild facial weakness were present in all families. Accordingly, it is quite understandable that the sporadic cases were described as a FSH syndrome. Lack of muscle hypertrophy and early muscle contractures were other features that distinguished this syndrome from benign X-linked recessive muscular dystrophy (Becker type). Elbow and ankle contractures were early signs. Limitation of flexion of the neck and bending of the back were present in all families, except in the one reported by Emery and Dreifuss (1966). Abduction contractures of the shoulders were mentioned or

were suggested from photographs in all families. Pes cavus was frequently encountered. EMG revealed a myopathic pattern in most patients. In one patient of Thomas' family and in several patients of the two families examined by Waters et al. large motor unit action potentials of long duration were found. Motor and sensory nerve conduction studies, when made, were normal in all cases. Muscle biopsies revealed myopathic changes. Rotthauwe et al. (1972) found type 1 predominance in his two biopsies. Waters et al. (1975) found type 2 predominance and type 1 atrophy. Because of the EMG and biopsy findings, these authors remained undecided on the primary lesion in their patients. Post-mortem studies, carried out on one patient of Thomas' family, confirmed the myopathic nature of the disorder. The peripheral nerves were found to be normal. The spinal cord, unfortunately, was not examined. Histological examination of the heart in this case showed "extensive fibrous replacement of the myocardium".

The cardiological examination in these families remained mostly limited to physical examination and an electrocardiogram (ECG). Only the report of Waters et al. (1975) on two families furnished quite extensive data. The cardiac abnormalities started later in life than the myopathy, and consisted of a progressive slowing of the pulse generation and conduction, leading to a progressive bradycardia. Complaints of dizziness or syncope were rare. Most patients were aware of the progressive slowing of their pulse. ECG was made of all 15 affected patients. No ECG was normal. P-wave abnormalities with a first degree atrio-ventricular (A-V) block were present in four patients, atrial flutter in one, atrial fibrillation in two, a complete A-V block in one, atrial fibrillation with complete A-V block in three, and PAP with a slow junctional pacemaker in four patients. Emery and Dreifuss (1966) and Rotthauwe et al. (1972) reported similar findings although several ECG's were normal. In the other families (Thomas et al., 1972; Camman et al., 1974), ECG's were registered in a limited number of cases. They revealed conduction defects but no PAP.

Five of Water's patients underwent echocardiography and cardiac catheterisation. Two patients with normal ventricular

rates had a normal ventricular function. Three patients, with chronic bradycardia secondary to PAP, had a marked increase in the left ventricular end-diastolic volume and left ventricular mass. These patients had demonstrated cardiomegaly on physical examination. The authors suggested that these findings indicated a compensatory physiologic response to the profound bradycardia of long duration, and not intrinsic ventricular myocardial disease.

Thomas et al. (1972) did not comment specifically on the condition of the atria in their autopsy report. Therefore, the selected degeneration and the fibrosis of the atrial myocardium, suggested as an explanation for PAP (Waters et al. 1975), still need pathological documentation. It is important to secure the diagnosis PAP during life by as many criteria as possible. They are:

1. Absence of P-waves on regular, oesophageal and intracardiac ECG's.
2. Supraventricular type of QRS.
3. Absence of A-waves on jugular venous pulse on right atrial pressure tracings.
4. Inability to stimulate the atria electrically.
5. Immobility of the atria on echocardiography, fluoroscopy and cineangiography.

The necessity of cardiac catheterisation is debated. However, the inability to stimulate the atria is conclusive. It may be hard to make the diagnosis on an ECG alone.

Most patients die suddenly at an early age. Rotthauwe et al. (1972) reported sudden death between 37 and 59 years of age. Waters et al. (1975) recommended "on-demand" ventricular pacemaker insertion in patients who have ventricular rates below 50 beats per minute.

B. The father and his three children reported by Chakrabarti and Pearce (1981) suffered from a neuromuscular disorder with progressive contractures of the neck and limb muscles. All four patients had a SP syndrome with normal facial muscles. Histological examination of a muscle biopsy in one child and a

normal spinal cord on post-mortem examination of another child suggested the myopathic nature of the condition. The mode of inheritance appeared to be autosomal dominant with late onset in the father, but early onset (before the age of three) in his children, which makes this condition distinct from the X-linked recessive myopathy described above. The cardiac abnormalities were present in the father and in two of the children, and included atrial fibrillation, left bundle branch block, absence of P waves with a nodal escape rhythm and complete heart block, leading to cardiomegaly and heart failure. On the basis of this information, the disorder in this family appears to be an independent entity.

C. The patients reported by Mawatari et al. (1973), Takahashi et al. (1974) and Jennekens et al. (1975) constitute a different group of diseases. Mawatari et al. (1973) examined three male patients with a scapulo(humero)peroneal syndrome. The age at onset varied between seven and ten years. Two brothers had a restriction of neck flexion, ankle contractures and complete A-V block with bradycardia on EKG examination. The other patient (a maternal cousin) had ankle contractures and an incomplete right bundle branch block, with left axis deviation on his ECG. Two other maternal cousins had peroneal weakness, with atrophy and ankle contractures. They were not examined cardiologically. Two of the mothers of these patients had a first degree A-V block, as did the patients' maternal grandmother. The most likely mode of inheritance appeared X-linked recessive with slight expression in the carriers, but autosomal dominant inheritance with variable expression could not be ruled out. EMG and muscle biopsy were compatible with a neurogenic condition. The motor nerve conduction velocities were normal.

The last two patients (two brothers) presented by Takahashi et al. (1974), under the title "Scapuloperoneal dystrophy associated with neurogenic changes", appeared to be the same as the ones reported by Takahashi et al. in 1971. These patients developed progressive muscular atrophy when 11 and 12 years old. No other members were said to be affected, but they were not

examined. Since every mode of inheritance was possible, this was not discussed. Contractures were not present in these patients. Bulbar muscular weakness with facial involvement appeared between the 40th and 50th years. Syncopal episodes and palpitations were reported after the patients had passed the 35th year. Both patients had a complete A-V block with high T-waves and bradycardia on their ECG's. Chest X-rays showed cardiac hypertrophy. EMG and muscle biopsy demonstrated both myopathic and neurogenic features. One of these patients sustained a cerebral infarction. He died four years later. Post-mortem examination showed the anterior horn cells of the spinal cord to contain a large number of lipofuscin granules, but the number of cells seemed normal at all levels. In the brainstem the facial and hypoglossal nuclei were well preserved, except for a few atrophic cells. The tongue demonstrated abundant myopathic changes without neurogenic features. The heart revealed many atrophic fibres of variable size, located mainly in the subendocardial and subpericardial tissue. The authors considered a decision as to the primary site of the lesion impossible. They regarded the myopathic changes too extensive to be explained as secondary phenomena. The spinal cord was normal and a peripheral nerve lesion seemed unlikely, because of the normal sensory examination. Unfortunately, no nerve conduction studies were undertaken, no nerve biopsy was done, and the nerves were not examined at autopsy. A peripheral nerve lesion, therefore, cannot be ruled out. Nonetheless, the authors suggested that dying back of terminal axonal twigs might explain the phenomena encountered.

Jennekens et al. (1975) suggested a similar mechanism to be present in two families (26 patients) with an autosomal dominant "scapulo-ilio-peroneal syndrome with cardiopathy". Among the 16 examined patients, the age of onset varied between 17 and 42 years. The bulbar muscles and the neck flexors were affected in approximately a third of all patients. Occasionally facial weakness was noted. Contractures were absent. ECG changes developed gradually from nonspecific findings to abnormalities of pulse-formation and conduction. PAP was not encountered, Radiological examination demonstrated cardiac hypertrophy and

left hemidiaphragm elevation in many cases. EMG showed neurogenic and myopathic characteristics. Although most muscle biopsies demonstrated group atrophy, the myopathic features were quite extensive with a remarkable interstitial and perivascular inflammatory reaction in four out of eight biopsies. Immunological tests were normal and did not support the thesis that the inflammatory reaction could be considered a secondary immunological response to the underlying muscle degeneration (Papapetropoulos and Bradley 1974). Genetic studies using 19 genetic markers failed to demonstrate linkage.

The findings on clinical and laboratory examination made the families of Mawatari et al., Takahashi et al., and Jennekens et al. not quite comparable. Also, the mode of inheritance was different in all families as far as this could be ascertained. Possibly all these reports deal with different diseases.

In summary, X-linked recessive SP myopathy with cardiomyopathy appears an independent, well defined, and quite consistent entity. The mode of inheritance, and clinical features, such as muscle contractures and a progressive cardiac conduction defect leading to the rare syndrome of persistent atrial paralysis, make this syndrome distinct from FSHD. Although the adjective FSH would fit this syndrome equally well, it appears appropriate and in accordance with the literature to continue to call this syndrome X-linked recessive SP myopathy with cardiomyopathy. A similar disorder without documented PAP but with an autosomal dominant mode of inheritance has been reported.

Other FSH syndromes with cardiomyopathy have been described. Bulbar and facial weakness were present only occasionally. All modes of inheritance have been suggested. Neurogenic abnormalities were present in all cases, but in several reports the myopathic features were so extensive that the authors could not reach a conclusion about the primary lesion. The findings were similar to those found in cases described as chronic adult SP-SMA.

3.9. Summary

Sporadic cases with FSH myopathy have been repeatedly documented (Walton and Gardner-Medwin, 1981). Autosomal dominant SP myopathy without involvement of the facial muscles has never been reported, autosomal dominant SP myopathy with facial weakness is indistinct from FSHD (Kazakow et al., 1975). The families of the sporadic cases with SP myopathy are not examined exhaustively, or not at all. Even without this information, it appears that there are no good grounds to consider SP myopathy a separate and independent entity.

Many disorders are reported to resemble FSHD at some stages of their courses. Yet all these disorders reveal additional, though sometimes minimal signs pointing at their proper diagnosis. The examination of families renders important clues to the diagnosis. Autosomal dominant inheritance is suggestive for FSHD. In cases where the family cannot be examined, one has to rely heavily on laboratory studies such as EMG and muscle biopsy and, occasionally, on biochemical studies. But even in autosomal dominant cases, additional studies may be necessary to rule out neurogenic conditions and rare disorders such as mitochondrial myopathies.

Polymyositis presenting with a FSH-syndrome is rare. The correct diagnosis is important because it could involve therapeutic measures like corticosteroids. The diagnosis might be difficult to make as occasionally extensive inflammatory reactions are present in muscle biopsies of patients with FSHD (Munsat et al., 1972). Mitochondrial abnormalities will be suspected on histochemical studies of muscle biopsies, although the clinical picture may have suggested already that FSHD is a less likely diagnosis (Hudgson et al., 1972). The existence of autosomal dominant FSH-SMA has not been established beyond doubt. The small angulated fibres and the neurogenic features on EMG in these cases are reported in FSHD as well. None of the patients had group atrophy or target fibres in their muscle biopsies. Sporadic cases of FSH SMA have been recognised since the end of the nineteenth century. This disorder necessitates laboratory

studies in sporadic cases. SP-SMA appears to be a well established disorder. The clinical course is an ascending one. Laboratory studies may sometimes reveal myopathic features in some muscles and neurogenic features in other muscles. Fasciculations and foot deformities, if present, are relative arguments against FSHD. Autosomal dominant SP amyotrophy with sensory disturbance (Davidenkow's syndrome 1927; 1929; 1930; 1939) has never been observed since the original descriptions. Sporadic and possibly autosomal recessive disorders resembling Davidenkow's syndrome have been reported. The sensory abnormalities exclude FSHD. X-linked SP syndrome with cardiomyopathy differ from FSHD by their mode of inheritance, the cardiac conduction disorders, and by the clinical picture of muscular atrophy with rather extensive muscle contractures. Both myopathic and neurogenic conditions have been reported, but also conditions in which the primary lesion could not be decided upon. This syndrome might turn out to be heterogeneous. Also a similar disorder with autosomal dominant inheritance has been reported recently (Chakrabarti and Pearce, 1981). More important to the differential diagnosis of FSHD are the two families reported by Jennekens et al. (1975) with autosomal dominant neurogenic muscular atrophy and progressive cardiac pulse formation and conduction defects. Most muscle biopsies showed group atrophy, but myopathic changes and inflammatory reactions were extensive on occasions that confusion with FSHD seems quite possible, if the results of muscle biopsies only are taken into account. Only a few of these patients had facial weakness.

Thus it appears that there is a fairly limited differential diagnosis of FSHD. Facial and shoulder girdle weakness, being the most conspicuous findings on clinical examination, are in themselves rather unspecific. The term FSH syndrome serves no other purpose than to summarize the physical examination of a patient.