Eur Arch Psychiatr Neurol Sci (1988) 237:230–236

European Archives of Psychiatry and Neurological Sciences

Autosomal Dominant Emery-Dreifuss Syndrome: Evidence of a Neurogenic Variant of the Disease*

Th. N. Witt[1], C. G. Garner[1], D. Pongratz[2], and X. Baur[3]

[1]Neurologische Klinik, Klinikum Großhadern, Marchioninistrasse 15, D-8000 München 70, Federal Republic of Germany
[2]Friedrich Baur Stiftung, Medizinische Klinik Innenstadt, D-8000 München, Federal Republic of Germany
[3]Medizinische Klinik I, Klinikum Großhadern der Universität München, D-8000 München, Federal Republic of Germany

Summary. The first German family with autosomal dominant Emery-Dreifuss syndrome (EDS) is described, with electrophysiologic and myopathologic results providing evidence of a primary neurogenic disease. According to classification of the scapulo peroneal syndrome without cardiomyopathy, we conclude that there are two variants of EDS: one myopathic, the other neurogenic in origin. Therefore, the term Emery-Dreifuss muscular dystrophy should be avoided. Instead, each case of EDS should be classified as myopathic or neurogenic with X chromosome recessive or autosomal dominant inheritance.

Key words: Emery-Dreifuss syndrome – Autosomal dominant inheritance – Single-fiber EMG – Fiber type-I atrophy – Spinal muscular atrophy

Introduction

Dreifuss and Hogan (1961) and Emery and Dreifuss (1966) first described a particular X-linked muscular disorder with early contractures and cardiomyopathy. Most further cases reported showed predominant atrophy of the scapulo humero peroneal muscles. Despite contradictory myopathic and neuropathic findings obtained by electromyography (EMG) and muscle histology, Rowland et al. (1979) proposed the term Emery-Dreifuss muscular dystrophy (Emery-Dreifuss disease) to define the unique clinical features and the X-linked recessive inheritance.

Chakrabarti and Pearce (1981) first noted a similar syndrome with autosomal dominant inheritance, and nine cases within four families with that transmission have been examined and described in detail to date. On the basis of conventional EMG and muscle histology most of these cases were classified as myopathic origin.

We report the results of an electrodiagnostic and myopathologic study on three members of the first German family with autosomal dominant Emery-Dreifuss syndrome (EDS).

Materials and Methods

The pedigree of the investigated family with EDS, showing autosomal dominant inheritance, is listed in Fig. 1.

Case 1 and 2 are brothers, case 3 is the son of case one. The father of cases 1 and 2, his sister and brother and one son of this brother died in middle age of sudden heart death. This son had a pacemaker implanted 6 months before his death because

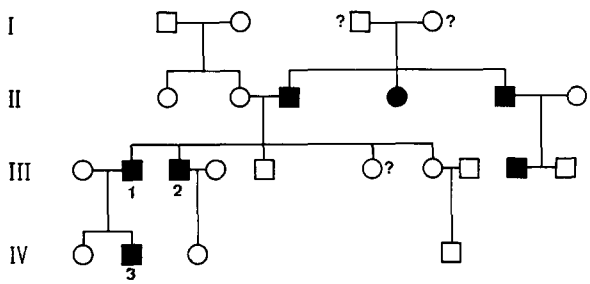

Fig. 1. Pedigree of the investigated family with Emery-Dreifuss syndrome (EDS). Symbols: *Circle* = female, *square* = male, *light symbols* = normal members, *dark symbols* = patients with EDS, *?* = EDS possible, *1–3* = investigated patients

Offprint requests to: Th. N. Witt

* The results of this study were presented in part at the 8th international congress of electromyography and related neurophysiology, Sorrento, Italy 1987

Table 1. Clinical data of three patients with EDS

	Case 1	Case 2	Case 3[a]
Age	47	43	17
Sex	Male	Male	Male
Age of onset (decade)	First	Third	Second
Distribution of weakness	Humeroperoneal***	Humeroperoneal**	No weakness
Contractures	Elbows, ankles, neck****	Elbows, ankles**	Elbows***
Creatine kinase (normal < 80 U/l)	Elevated (80–295 U/l)	Normal (39 U/l)	Elevated (312 U/l)
Cardiology	AV-block III 1983 pace-maker 9/86 heart transplant	AV-block III 1986 pace-maker	Normal

* Very mild
** Mild
*** Moderate
**** Severe
[a] Son of case 1

of an AV-block III. Because of a progressive therapy-resistant myocardiac insufficiency case 1 received a heart transplant in September 1986. The clinical findings of the three cases are summarized in Table 1. For further details see Baur et al. (1987).

Conventional EMG, including motor unit potential analysis, single fiber EMG and turns/s versus amplitude/turn analysis in at least 10 recording sites according to the method described by Stalberg et al. (1983) was done in the m. biceps brachii in all three cases, and additionally in the m. tibialis anterior in cases 1 and 2. The motor and sensory nerve conduction velocity (NCV) of the median nerve, the motor NCV of the peroneal nerve, and the visual (VEP) and somatosensory evoked potentials (SEP) of the median and tibial nerves were measured in all cases. The EMG and NCV studies were performed using a Medelec Mystro device, the VEP and SEP with a Nihon Kohden Neuropac 8. A muscle specimen was taken from the m. biceps brachii in cases 1 and 2. Standard histologic stains and histochemical preparations were used on deep frozen material. Histometric analysis with regard to fiber type distribution and calculation of atrophy and hypertrophy factors were performed (Brooke and Engel 1969 a and b; Brenni et al. 1981; Dubowitz 1985).

Results

Electrodiagnostic Results

Motor and sensory NCV of the median nerve, motor NCV of the peroneal nerve, SEPs of median and tibial nerves, and VEPs were within normal ranges in all three cases.

Concentric Needle EMG. The results of the concentric needle EMG-recorded motor unit potentials in the m. biceps brachii (cases 1 to 3) and the m. tibialis anterior (cases 1 and 2) are given in Table 2.

With low effort innervation the activity pattern had a low amplitude and relative full appearance, suggesting early recruitment of motor unit potentials, whereas with increasing effort there was a lack of further recruitment, showing mostly reduced interference patterns at maximum effort with increased amplitudes.

Table 2. Results of concentric needle EMG

	Case 1		Case 2		Case 3
	Biceps brachii	Tibialis anterior	Biceps brachii	Tibialis anterior	Biceps brachii
Spontaneous activity	Fibrillation potentials (+), complex repetition discharges (+)	–	–	–	–
Motor unit potential analysis:					
Mean duration	8.9 ms	6.3 ms	8.1 ms	10.3 ms	6.4 ms
Range	3.6–19.6 ms	4.3–11.5 ms	3.4–15.4 ms	5.5–16.9 ms	2.8–13.4 ms
Polyphasic potentials	55%	65%	60%	60%	35%
Interference	Reduced	Full	Reduced	Full	Reduced
Pattern	High amplitude	Low amplitude	High amplitude		

– Missing
(+) Occasionally

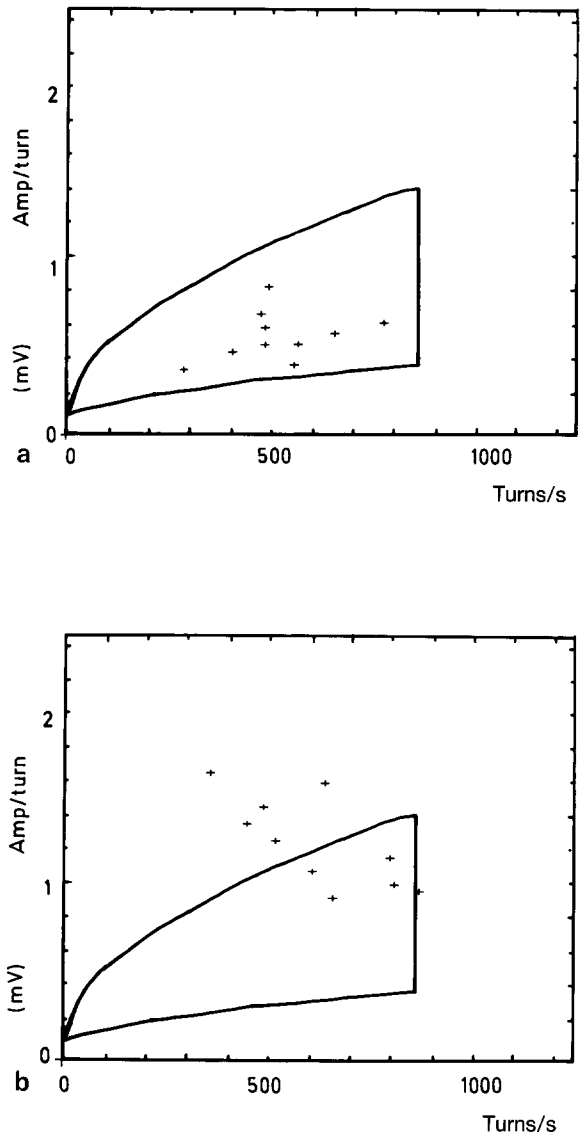

Fig. 2a and b. Amplitude/turn versus turns/s analysis in case 1 (m. biceps brachii). **a** Medium effort; normal values. **b** Maximum effort; increase in amplitude/turn in 5 of 10 recording sites, suggesting a neuropathic lesion

Automatic Analysis of the EMG Interference Pattern. Turns/s versus amplitude/turn were analyzed at 10 different recording sites of the m. biceps brachii in all cases and in m. tibialis anterior in cases 1 and 2 with medium and high voluntary effort. Abnormal high amplitudes/turn are seen in neurogenic diseases, abnormal low amplitudes/turn and an increased ratio of turns/s are typical findings for a myopathic lesion.

With medium effort, normal values were seen in all tests. An increase in amplitude/turn above the normal range occurred during high voluntary effort in all examined muscles. An increase of turns/s with normal amplitude was seen rarely. In none of the 60 registration sites within the investigated muscles

Table 3. Results of single-fiber EMG

	Case 1	Case 2	Case 3
Biceps brachii			
MCD	71 µs	68 µs	78 µs
Blocking	+	(+)	+
Fiber density	2.3	2.8	2.8
Tibialis anterior:			
MCD	36 µs	45 µs	Not done
Blocking	–	+	Not done
Fiber density	2.3	2.8	Not done

– Missing
(+) Rarely
+ Frequent
MCD, mean consecutive difference

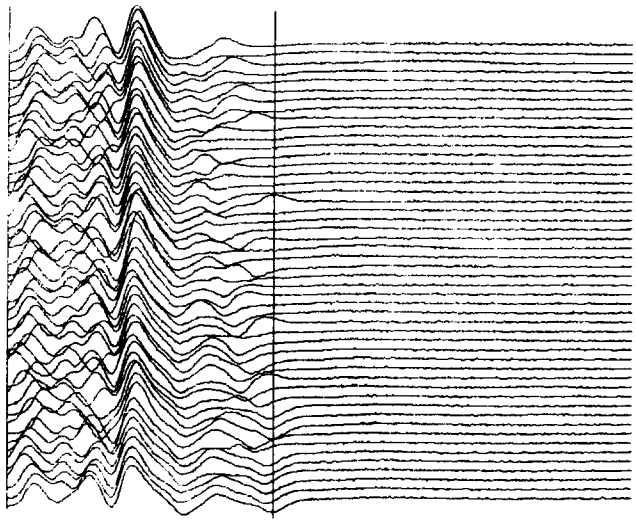

Fig. 3. Example of a single-fiber electromyography (EMG) recording in m. tibialis anterior of case 2. Markedly increased jitter of at least 4 different fibers, frequent blocking and high fiber density, as typically seen in chronic denervation

Table 4. Myopathologic and histometric results of muscle biopsy in case 1 (left m. biceps brachii) and case 2 (right m. biceps brachii)

	Case 1	Case 2
Fiber size variation	+	+
Type-I atrophy	++	++
Type-II hypertrophy	+	+
Group atrophy	(+)	+
Fiber type grouping	–	+
Increased internal nuclei	(+)	–
Necrotic fibers	–	–
Connective tissue proliferation	(+)	–
Target fibers	(+)	(+)

– Missing
(+) Mild
+ Moderate
++ Severe

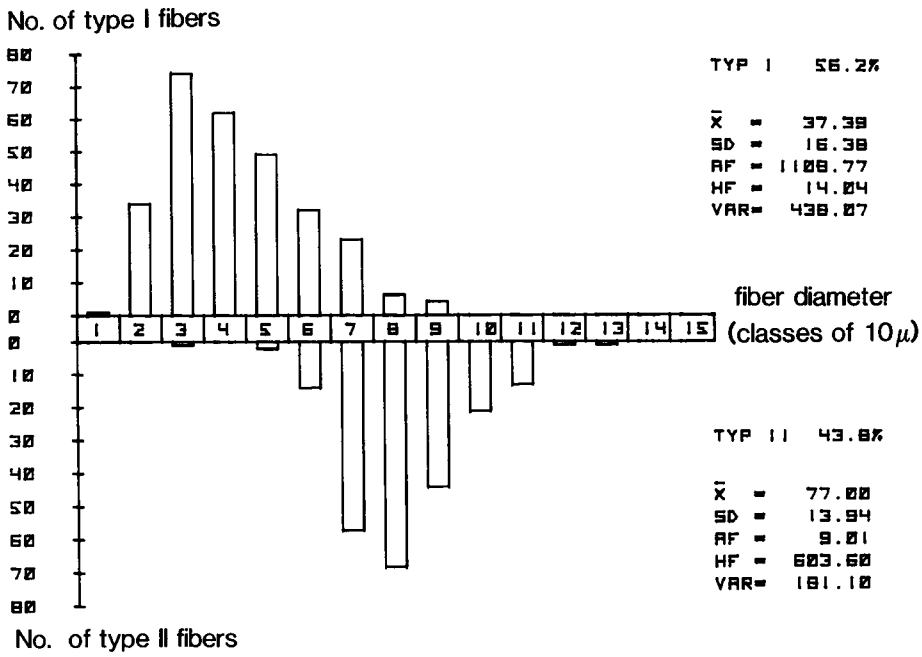

Fig. 4. Histogram of fiber type distribution in case 2 (right m. biceps brachii): severe fiber type-I atrophy and moderate fiber type-II hypertrophy. x = mean fiber diameter, SD = standard deviation, AF = atrophy factor, HF = hypertrophy factor, VAR = variation coefficient (AF and HF calculated according to the method described by Brooke and Engel 1969a and b)

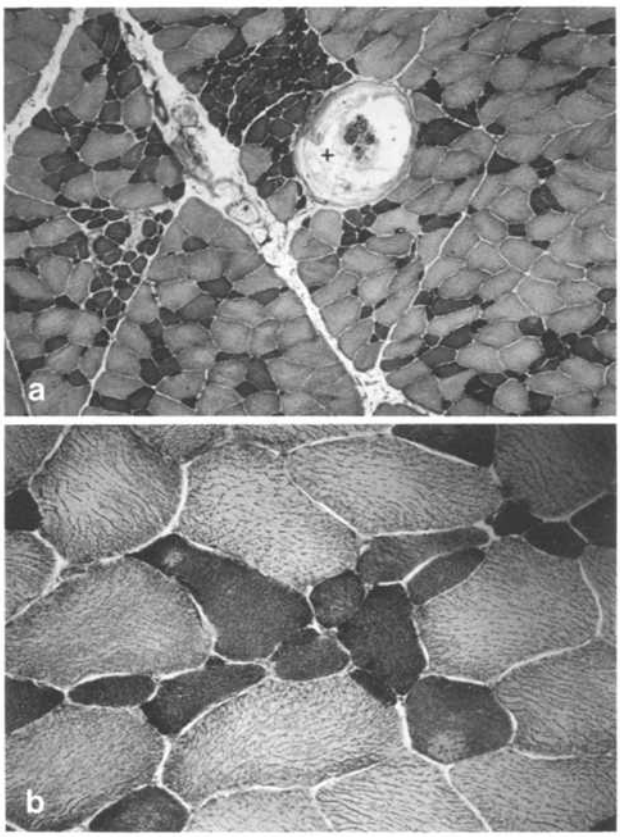

Fig. 5a and b. Case 2, NADH reaction, m. biceps brachii. Fiber type-1 dark, fiber type-II light. **a** small and large group atrophy of fiber type-I, pathologic grouping of type-I fibers (120×). **b** Small group atrophy, single target fibers, type-II hypertrophy (200×). + Muscle spindle

there was a reduced amplitude/turn. A typical example is shown in Fig. 2.

Single-fiber EMG. Single-fiber EMG recordings were carried out in the m. biceps brachii in all three cases, additionally in the m. tibialis anterior in cases 1 and 2. In the m. biceps brachii significantly increased jitter and moderate blocking were seen in all cases. In the m. tibialis anterior, only case 2 showed increased jitter in 4 of 20 single-fiber recordings. Fiber density was moderately increased in all muscles. For details see Tables 3 and Fig. 3.

Histologic Results

The histopathologic and morphometric results of a muscle biopsy performed near the site examined in the EMG from the right m. biceps brachii in cases 1 and 2 are summarized in Table 4. Case 3 refused a muscle biopsy. Histometric analysis of fiber type distribution and the calculation of atrophy and hypertrophy factors is shown in Fig. 4. Figure 5a and b represent typical histological findings. In both cases examined histologically the most striking findings were marked fiber type-I atrophy along with fiber type-II hypertrophy and scattered small group atrophy. Additionally a slight predominance of type-I fibers was seen. Degenerative fiber anomalies and interstitial connective tissue proliferation were only minor findings.

Discussion

Emery-Dreifuss syndrome is a well-defined clinical entity with slow progressive scapulohumeroperoneal atrophic paresis, early contractures, and severe cardiomyopathy. The majority of the cases reported followed a X-linked transmission (Merlini et al. 1986), autsomal dominant inheritance of the syndrome is a rare finding. Rotthauwe et al. (1972) and Camman et al. (1974) reported two German families with X-linked EDS, we present a quantitative electrodiagnostic and myopathologic study of the first German family with autosomal dominant EDS (Baur et al. 1987).

All three cases showed typical features of the syndrome to varying degrees. Two cases suffered from severe cardiomyopathy with conduction heart block. Because of progressive heart failure a heart transplant was done in case 1 in autumn 1986. Pathologic investigation of the explanted heart showed a dilatative cardiomyopathy with marked fibrosis of the muscle, especially in the septum of the ventricles. The macroscopic and microscopic findings were the same as those in common dilatative cardiomyopathy (Baur et al. 1987). More than 1 year after heart transplantation this patient is clinically in good condition.

In the literature the origin of the disease is regarded to be myopathic. Most authors suggest classifying the disease as a certain type of the muscular dystrophies (Emery and Dreifuss 1966; Rotthauwe et al. 1972; Thomas et al. 1972; Camman et al. 1974; Rowland et al. 1979; Hopkins et al. 1981; Fenichel et al. 1982; Miller et al. 1985). However, the EMG results described do not strictly correspond to a myopathy. Some authors described a mixed or even a pure neurogenic EMG pattern (Emery and Dreifuss 1966; Mawatari and Katayama 1973; Takahashi et al. 1974; Waters et al. 1975; Rowland et al. 1981; Sulaiman et al. 1981; Hopkins et al. 1981; Fenichel et al. 1982; Takamato et al. 1984; Petty et al. 1986; Witt et al. 1987). Most reports only included a qualitative EMG report of motor unit potentials and activity patterns, quantitative methods were only seldom used (Thomas et al. 1972; Rowland et al. 1979; Lin 1982). We also found a reduced mean duration and an increased rate of polyphasic motor unit potentials, findings regarded to suggest a myopathic disease. Surprisingly, quantitative analysis of the activity pattern showed normal values for amplitudes per turn and turns per second with medium innervation; but with strong innervation, amplitudes per turn were significantly increased, suggesting neurogenic muscular changes. In all cases the m. biceps brachii showed a reduced interference pattern, also indicating a neurogenic type of disease. Similar findings – myopathic motor unit potentials in combination with reduced recruitment with maximum effort with high amplitudes – have been described several times and usually regarded as mixed pattern (Takahashi et al. 1974; Rowland et al. 1979; Sulaiman et al. 1981; Chakrabarti and Pearce 1981; Takamoto et al. 1984). According to Engel (1975), brief, small, and abundant motor unit action potentials are not pathognomonic for a myopathy, but can also be found in certain primary neurogenic situations, e.g., in acquired selective fiber type-I atrophy. It is well-known that type-I fibers fire first with light voluntary effort (Warmolts and Engel 1972). So, our findings of so-called myopathic motor unit potentials with low effort and neurogenic activity pattern can be explained by the histologically proven selective fiber type-I atrophy.

Increased jitter and fiber density in the single-fiber EMG was a nonspecific result, which is found in neurogenic and myopathic disorders. However, with respect to the histologically well-preserved muscle tissue with lack of dystrophic changes and fiber splitting these results may better be interpreted as a sign of a neurogenic lesion. In particular the increased fiber density can be explained by fiber type-I atrophy. The entirely normal motor and sensory conduction velocity tests and the unimpaired evoked potential latencies disclose a demyelinating neuropathy as previously described (Rotthauwe et al. 1972; Rowland et al. 1979; Fenichel et al. 1982; Miller et al. 1985; Hara et al. 1987). The histologic and myopathologic results with marked fiber type-I atrophy, slight fiber type-II hypertrophy, small group atrophy, and fiber type grouping are strong arguments for a primary chronic, slow progressive neurogenic disease (Sulaiman et al. 1981). The pathologic fiber type grouping together with the rare incidence of target fibers indicates an accompanying reinnervation process.

Finally, fiber type-I atrophy and myopathic muscle unit potentials have also been described in the neurogenic scapuloperoneal syndrome of type Kaeser (Ricker et al. 1968; Scarlato et al. 1978; Mercelis et al. 1980; Reiter et al. 1984), a neuromuscular disorder, generally accepted to be a variant of spinal muscular atrophy on the basis of autoptic investigations of the spinal cord (Kaeser 1964, 1975; Probst et al. 1977). To date the histologic results of postmortem examination of the spinal cord in four patients with clinically proven EDS have been published (Takahashi et al. 1974; Charkabarti and Pearce 1981; Kudo et al. 1982; Hara et al. 1987), and the results are contradictory. Whereas Charkrabarti and Pearce (1981) and Hara et al. (1987) disclosed no abnormality of the spinal cord, Tagahashi et al. (1974) described a large number of lipofuscin granules in the

anterior horn cells with no reduction in the total number of these cells. Kudo et al. (1982) reveiled focal neuronal and axonal changes in lower cervical and lumbar spinal segments in combination with a reduction in the number of anterior horn cells.

On the basis of the presented electrodiagnostic and myopathologic data, we conclude, that there are two variants of autosomal dominant transmitted EDS, one myopathic, the other neurogenic in origin. This concept corresponds to the classification of the scapuloperoneal syndrome without cardiomyopathy and contractures, where a spinal scapuloperoneal muscular atrophy with dominant inheritance (type Kaeser) is established. For the EDS further postmortem examinations of the spinal cord are necessary to confirm this hypothesis. In agreement with Serratrice and Pouget (1986) we suggest avoiding the term Emery-Dreifuss disease. Instead, each case of EDS should be classified as myopathic or neurogenic EDS with X chromosome recessive or autosomal dominant inheritance.

Acknowledgement. We are indebted to Mrs. Franziska Anneser for her expert assistence with the histology stainings and histochemistry preparations.

References

Baur X, Witt THN, Pongratz D, Gokel M, Rosenbeiger P, Steinbeck G (1987) Autosomal dominantes Humero-Peroneales Syndrom mit frühzeitigen Kontrakturen und Kardiomyopathie (Emery-Dreifuss-Syndrom) Klin Wochenschr 65:738–745

Brenni G, Jerusalem F, Schiller H (1981) Myopathologie chronischer Denervationsprozesse. Nervenarzt 52:692–702

Brooke MH, Engel WK (1969a) The histographic analysis of human muscle biopsies with regard to fiber types. I. Adult male and female. Neurology (Minneap) 19:221–233

Brooke MH, Engel WK (1969b) The histographic analysis of human muscle biopsies with regard to fiber types. II. Diseases of the upper and lower motor neuron. Neurology (Minneap) 19:378–393

Camman R, Vehreschild R, Ernst K (1974) Eine neue Sippe von X-chromosomaler benigner Muskeldystrophie mit Frühkontrakturen (Emery-Dreifuss) Psychiatr Neurol Med Psychol 26:431–438

Chakrabarti A, Pearce JMS (1981) Scapuloperoneal syndrome with cardiomyopathy: report of a family with autosomal dominant inheritance and unusual features. J Neurol Neurosurg Psychiatry 44:1146–1152

Dreifuss FE, Hogan GR (1961) Survival in X-chromosomal muscular dystrophy. Neurology (Minneap) 11:734–737

Dubowitz V (1985) Muscle biopsy. A practical approach, 2nd edn, Chap IV. Baillere Tindall, London Philadelphia Toronto Mexico City Rio de Janeiro Sydney Hong Kong

Emery AEH, Dreifuss FE (1966) Unusual type of benign X-linked muscular dystrophy. J Neurol Neurosurg Psychiatry 29:338–342

Engel WK (1975) Brief, small, abundant motor-unit action potentials. A further critique of electromyographic interpretation. Neurology 25:173–176

Fenichel GM, Sul YC, Kilroy AW, Blouin R (1982) An autosomal-dominant dystrophy with humeropelvic distribution and cardiomyopathy. Neurology 32:1399–1401

Hara H, Nagara H, Mawatari S, Kondo A, Sato H (1987) Emery-Dreifuss muscular dystrophy. An autopsy case. J Neurol Sci 79:23–31

Hopkins LC, Jackson JA, Elsas LJ (1981) Emery-Dreifuss humeroperoneal muscular dystrophy: an X-linked myopathy with unusual contractures and bradycardia. Ann Neurol 10:230–237

Kaeser HE (1964) Die familiäre scapuloperoneale Muskelatrophie. Dtsch Z Nervenheilkd 186:379–394

Kaeser HE (1975) Scapuloperoneal syndrome. In: Vinken PJ, Bruyn GW (Eds) Handbook of clinical neurology, vol 22. Elsevier North Holland, Amsterdam, pp 57–65

Kudo H, Yano S, Saito K, Yanagisawa M, Kamoshita S (1982) Spinal cord involvement in Emery-Dreifuss muscular atrophy (X-linked recessive scapuloperoneal muscular atrophy) Brain Dev 14:363–369

Lin JT (1982) EMG in Emery-Dreifuss syndrome. Muscle Nerve 5:562

Mawatari S, Katayama K (1973) Scapuloperoneal muscular atrophy with cardiomyopathy. Arch Neurol 28:55–59

Mercelis R, Demeester J, Martin JJ (1980) Neurogenic scapuloperoneal syndrome in childhood. J Neurol Neurosurg Psychiatry 43:888–896

Merlini L, Granata C, Dominici P, Bonfiglioli S (1986) Emery-Dreifuss muscular dystrophy: Report of five cases in a family and review of the literature. Muscle Nerve 9:481–485

Miller RG, Layzer RB, Mellenthin MA, Golabi M, Francoz RA, Mall JC (1985) Emery-Dreifuss muscular dystrophy with autosomal dominant transmission. Neurology 35: 1230–1233

Petty RKH, Thomas PK, Landon DN (1986) Emery-Dreifuss syndrome. J Neurol 233:108–114

Probst A, Ulrich J, Kaeser HE, Heitz P (1977) Scapuloperoneal muscular-atrophy. Full autopsy report. Unusual findings in the anterior horn of the spinal cord. Lipid storage in muscle. Eur Neurol 16:181–196

Reiter M, Witt THN, Koller A (1984) Scapuloperoneales Syndrom (SPS) – neurogene und myopathische Befunde. In: Fortschritte der Myologie, Deutsche Gesellschaft „Bekämpfung der Muskelkrankheiten e.V." Freiburg Bd VII, pp 274–288

Ricker K, Mertens HG, Schimrigk K (1968) Neurogenic scapuloperoneal syndrome. Eur Neurol 1:257–274

Rotthauwe HW, Mortier W, Beyer H (1972) Neuer Typ einer rezessiv X-chromosomal vererbten Muskeldystrophie: Scapulo-humero-distale Muskeldystrophie mit frühzeitigen Kontrakturen und Herzrhythmusstörungen. Humangenetik 16:181–200

Rowland LP, Fetell M, Olarte M, Hays A, Singh N, Wanat FE (1979) Emery-Dreifuss muscular dystrophy. Ann Neurol 5:111–117

Scarlato G, Valli G, Bracchi M (1978) Quantitative histological and neurophysiological studies in scapuloperoneal syndrome. Acta Neurol (Napoli) 33:327–341

Serratrice G, Pouget J (1986) Maladie d'Emery-Dreifuss ou syndrome d'amyotrophie avec retractions precocés et troubles secondaires de la conduction cardiaque d'herédité variable. Rev Neurol (Paris) 142,10:766–770

Stalberg E, Chu J, Bril V, Nandekar S, Stalberg S, Ericsson M (1983) Automatic analysis of the EMG interference

pattern. Electroencephalogr Clin Neurophysiol 56:672–681

Sulaiman AR, McQuillen MP, Viste KM, Hughes CV (1981) Scapuloperoneal syndrome. Report on two families with neurogenic muscular atrophy. J Neurol Sci 52:305–325

Takahashi K, Nakamura H, Nakashima R (1974) Scapuloperoneal dystrophy associated with neurogenic changes. J Neurol Sci 23:575–583

Takamoto K, Hirose K, Uono M, Nonaka I (1984) A genetic variant of Emery-Dreifuss disease. Arch Neurol 41:1292–1293

Thomas PK, Calne DB, Elliott CF (1972) X-linked scapuloperoneal syndrome. J Neurol Neurosurg Psychiatry 35:208–215

Warmolts JR, Engel WK (1972) Open-biopsy electromyography: I. Correlation of motor unit behavior with histochemical muscle fiber type in human limb muscle. Arch Neurol 27:512–517

Waters DD, Nuffer DO, Hopkins LC, Dorney ER (1975) Cardiac features of an unusual X-linked humero-peroneal neuromuscular disease. N Engl J Med 293:1017–1022

Witt THN, Garner CG, Pongratz D (1987) Emery-Dreifuss-Syndrome: A comparative electrophysiological and myopathiological study in three cases. Electroencephalogr Clin Neurophysiol 66:112–113

Received December 10, 1987