*J Clin Pathol* 1988;**41**:188–194

# Autosomal recessive distal myopathy

H ISAACS, MARGARET E BADENHORST, T WHISTLER

*From the Neuromuscular Research Laboratory, Department of Physiology, Witwatersrand University Medical School, Johannesburg, South Africa*

SUMMARY Five patients with an autosomally recessively transmitted distal myopathy were investigated. Of these, three belonged to a single sibship. Studies included electromyography, histological examination of muscle tissue, histochemical, electron microscopical, and biochemical analyses. One of the cases resembled the Nonaka form while the others were regarded as expressions of the commoner variety of recessive distal dystrophy.

Distal myopathies, though common in Scandinavian countries, are rare in other parts of the world. The Scandinavian distal myopathy described by Welander in 1951 is an inherited disorder with autosomal dominance.[1] Rare examples of distal myopathy of the dominantly inherited non-Scandinavian variety have been reported from remarkably few other areas in the world, and in these the disease seems to be less benign.[2,3] Rare infantile forms of this disorder have also been recorded.[4-6]

Sporadic and autosomal recessive inherited distal myopathies are extremely rare, but, unlike the autosomal dominant, have been reported from many parts of the world.[3,7-10] The similarity between the reported sporadic and recessive inherited cases makes it likely that the sporadic cases belong to the recessively inherited group where only one member of a sibship has inherited the disease.

Because of the relative rarity of this disorder, detailed muscle and nerve studies were carried out on a sporadic case of distal muscular myopathy, on sibships of three, and two patients with the disorder.

## Case reports

CASE 1

A 25 year old white man of Scottish extraction complained of thinning and weakness in both legs which affected all the muscles below the level of the knees. There was no history of neuromuscular disorder in the family, the patient was an only child, and had been aware of the progressive nature of his disorder for two years.

Examination of him in the standing position showed mild lumbar lordosis; his feet were flat and the small muscles undetectable. The anterior, lateral, and posterior compartment muscles in both legs were abnormally thin and weak so that the patient was neither able to stand on his toes or dorsiflex his toes or feet. Inversion and eversion of the ankles was absent. From the knee level upwards he was well built, though the proximal muscles were slightly weaker than expected. Slight weakness was noted in the small muscles of the hands and in the dorsiflexors of the wrists, fingers, and thumb. The tendon reflexes with the exception of the ankles were present and equal. All modalities of sensation were normal and no other abnormalities were found. Both parents were examined and found to be normal.

Accepted for publication 18 August 1987

CASE 2

A 35 year old woman gave a 10 year history of progressive weakness of the legs and feet. Her parents and other members of the family, apart from one brother and a sister, were healthy. She was one of six siblings, four of whom were male. Her elder sister, aged 46, had a similar complaint as did her brother aged 40 years. Examination of both parents confirmed that they were unsymptomatic and this was supported by electromyography.

She showed severe weakness in the muscles affecting the lower legs, particularly those below the level of the knees, while mild weakness was present in the more proximal muscles. The small muscles of the hands were also mildly affected. Reflexes were absent at the level of the ankle joint but were present and equal above this level.

Sensation and coordination was intact and the facial musculature was not affected. Intellectual development was normal.

CASE 3

The physical findings were similar to those of her

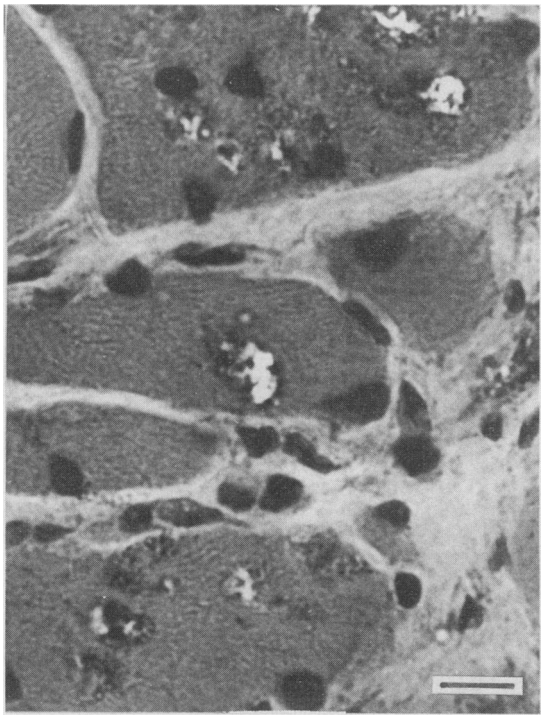

Fig 1 *Evidence of centralisation of nuclei in affected fibres, fibrous tissue infiltration, and vacuolar formation. Bar = 5 um. (Haematoxylin and eosin.)*

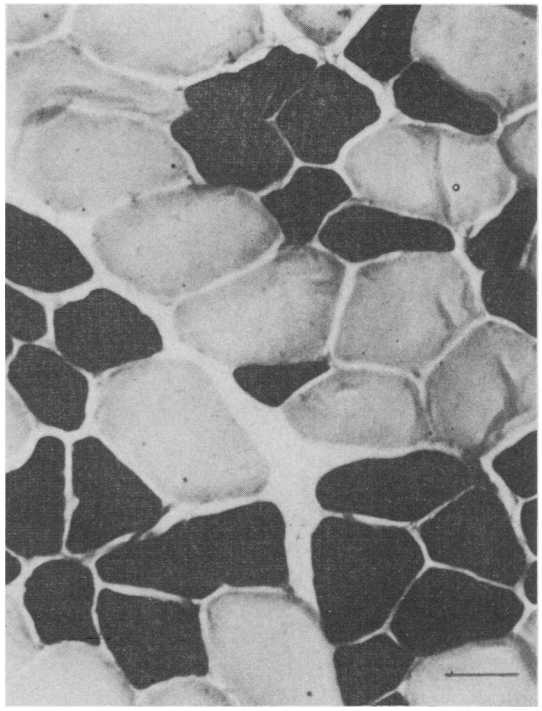

Fig 2 *Smallness of many of type 1 fibres and absence of grouping. (ATPase stain at pH 4·3.) Bar = 20 um.*

younger sister though the changes were more advanced.

CASE 4

The 40 year old brother of cases 2 and 3 had had his progressive weakness, affecting mainly his legs, for 20 years. The left leg was more affected than the right. He also complained of some degree of discomfort in his arms and in the small muscles of the hands.

On examination there was generalised thinning and weakness of the muscles of the legs, mild lumbar lordosis, and slight weakness of the small muscles of his hands. The ankle jerks were absent, the other tendon jerks were depressed but obtainable bilaterally, and the plantar responses were normal. The electrocardiogram was normal.

CASES 5 AND 6

A 49 year old man developed distal muscular weakness, which had been progressive for 10 years. Wasting and weakness particularly affected the muscles of the legs and extended up to the mid-thigh. Sensation and coordination were normal and the cranial nerves were intact. He was one of four siblings, and his 39 year old brother (case 6) was similarly affected. He had two normal sisters.

## Pathology

CASE 1

An electrocardiogram yielded normal results, and an *x*-ray of the chest was normal. Lung function studies were normal. The routine blood tests of liver, renal, and endocrine glands yielded normal results.

Electromyography showed a pronounced increase in low voltage polyphasic activity in the peripheral muscles of the lower extremities. There was no evidence of myotonia or of fasciculation. There was, however, evidence of occasional fibrillation. Motor nerve conduction studies recorded velocities in the right median nerve of 59 metres/second and the right ulnar nerve of 60 metres/second. The delay from the popliteal fossa to the anterior tibial and gastrocnemius muscles 10 cm below was normal at 5·4 metres/second. Conduction to the small muscles of the feet was not possible as the muscles were totally wasted. Sensory conduction velocity of the right median nerve was 66 metres/second and the lateral popliteal nerves 55 metres/second.

Muscle was removed from the anterior tibial under local anaesthesia. The haematoxylin and eosin stained sections showed considerable variation in fibre size,

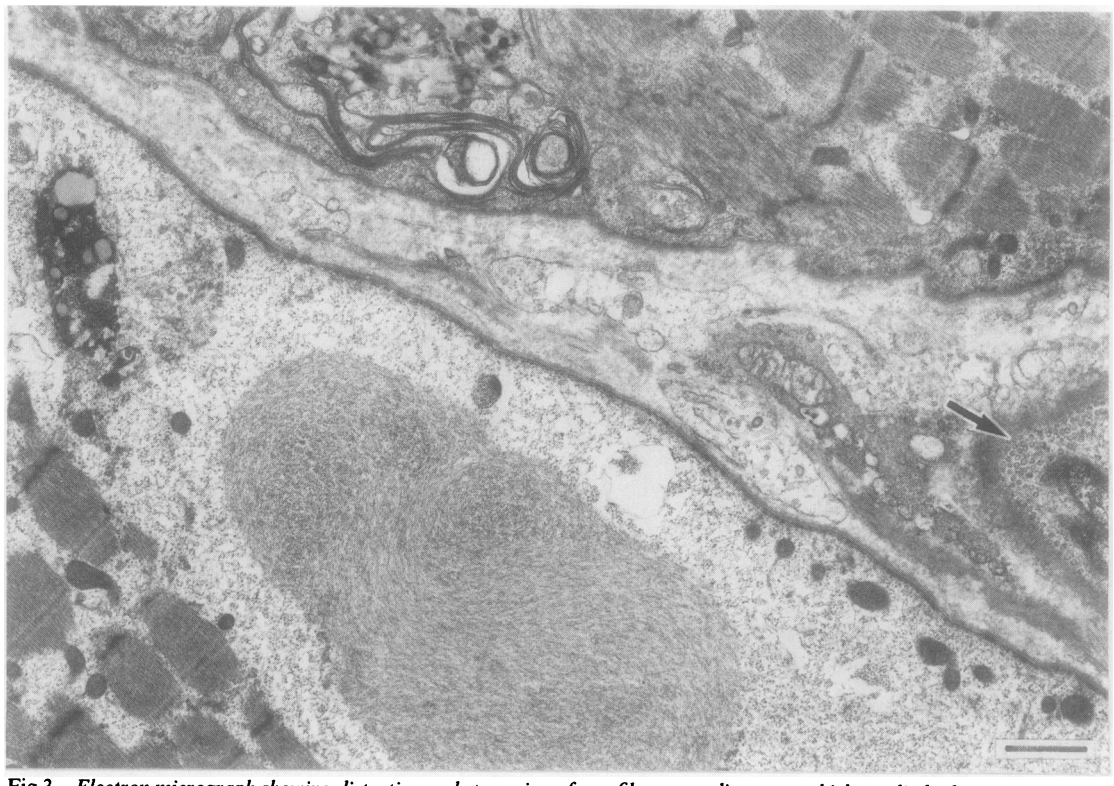

Fig 3 *Electron micrograph showing distortion and streaming of myofilaments adjacent to which myelin bodies are seen. Pynocytotic vescicles in blood vessel are indicated (arrow). Large, fine, filamentous body is seen in subsarcolemmal area. Bar = 1 um.*

and there was evidence of infiltration of fibrous and fatty tissue, and abnormal centralisation of nuclei. Fibre splitting was evident and many of the fibres appeared vacuolated (fig 1). The vacuoles observed on histochemical staining were most commonly seen in the type 1 fibres. Type 1 fibres were small and somewhat irregular; they appeared to be pock-marked, excessive in number, and the areas of vacuole formation were surrounded by a dense layer of enzymatic activity which stained positively for acid phosphatase. Type 2 fibres were also affected but to a lesser extent; these changes were most prominently seen in the nicotinamide adenine dinucleotide (NAD) disphorase stain and there was no evidence of grouping of fibre types (fig 2). Creatine kinase and myoadenylate deaminase staining were noticeably reduced.

The electron microscopic study showed gross distortion and loss of myofibrils; there were numerous fine filamentous bodies (fig 3), and in many areas the sarcoplasm was packed with laminated myelin bodies (fig 4). Z-line streaming was prominent and in many regions striation was lost. Many mitochondria were non-functioning, distended, with ruptured cristae and large clusters of mitochondria present in the subsarcolemmal regions. Occasional mitochondria were elongated and others showed the dense early conformation of paracrystalline change (fig 5). Autophagic vacuoles were prominent in the sarcoplasm and occasional zebra bodies were seen (fig 6). The appearance was typical of the disorder described by Nonaka *et al.*[11]

A segment of sural nerve was removed at the same time as the muscle biopsy and prepared for electron microscopic study. The axonal population and myelination, apart from occasional splitting of the myelin, was normal (fig 7), and counts of both myelinated and non-myelinated fibres were normal. Biochemical study of muscle tissue showed that the glycogen content was normal. Assays of myoadenylate deaminase,[12] phosphofructokinase,[13] phosphorylase[13] are shown in the table. The myoadenylate deaminase activity was below normal, confirming the histological appearances. Serum creatine kinase was raised at 642 IU/l (normal 1–150 IU/l).

Table *Muscle enzyme activities (μmol/min/mg)*

| | *Case 1* | *Case 2* | *Case 5* | *Mean (SD)* |
|---|---|---|---|---|
| Phosphorylase | 0·0650 | 0·0422 | 0·0325 | 0·0546 (0·0218) |
| Phosphoglucomutase | 0·0390 | 0·0187 | 0·0142 | 0·0601 (0·0155) |
| Phosphohexoisomerase | 1·3040 | 0·990 | 0·7308 | 1·4608 (0·3321) |
| Phosphofructokinase | 0·0621 | 0·0308 | 0·1939 | 0·1810 (0·1071) |
| Aldolase | 0·1765 | 0·1454 | 0·2074 | 0·3685 (0·1156) |
| Glyceraldehyde-3-P-dehydrogenase | | | 0·6454 | 1·5555 (0·5243) |
| Phosphoglycerate kinase | 1·3430 | 2·1555 | 2·7760 | 3·5699 (0·6727) |
| Enolase | 0·7085 | 0·3957 | 0·8451 | 0·7477 (0·2087) |
| Pyruvate kinase | 3·3192 | 1·4619 | 1·1489 | 3·2356 (0·7853) |
| Lactate dehydrogenase | 1·4859 | 1·1725 | 1·5950 | 3·0105 (1·2063) |
| Adenylate deaminae | 0·0445 | 0·0332 | 0·1218 | 0·1577 (0·0759) |
| Creatine kinase | 10·78 | 13·72 | 18·56 | 27·07 (7·86) |
| Adenylate kinase | 0·2990 | 0·8480 | 0·6573 | 1·2068 (0·4224) |
| Percentage of type 2 fibres | 60 | 32 | 55 | 60 (60) |

CASE 2

Electromyographic investigations showed increased low voltage polyphasic activity, particularly in the more badly affected muscles. There was no evidence of denervation activity.

Nerve conduction was found to be within normal limits for both upper and lower limbs; the motor velocity for the right and left median nerve was 52 and 54 metres/second, respectively, and the right lateral popliteal nerve 47 metres/second. The sensory velocity for the median nerves averaged at 61 metres/second and the lateral popliteals at 53 metres/second.

As very little muscle existed below knee level, the lower aspect of the left vastus lateralis was biopsied under local anaesthesia. Histological examination of muscle tissue showed severe loss of muscle fibre, an increase in fibrous tissue, and fatty infiltration. There was no evidence of grouping of individual fibres on histochemical analysis, and in the larger fibres central nuclei were prominent. The cytoarchitecture, par-

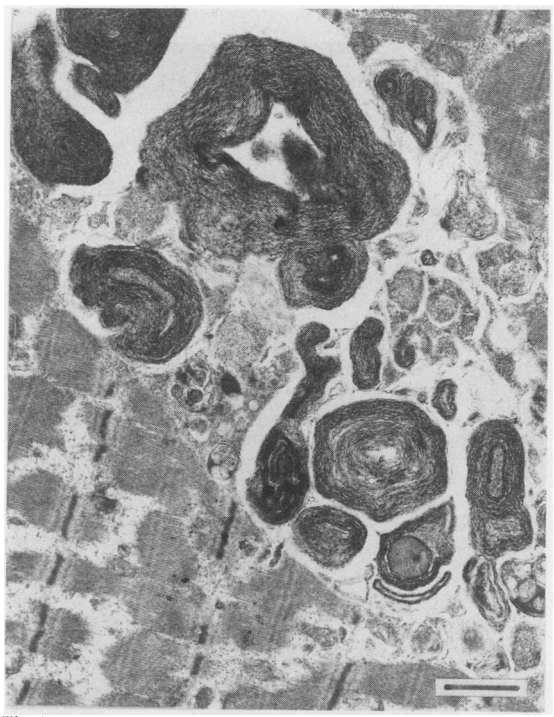

Fig 4 *Area containing numerous concentric laminated bodies situated within a vacuole. Bar = 1·25 um.*

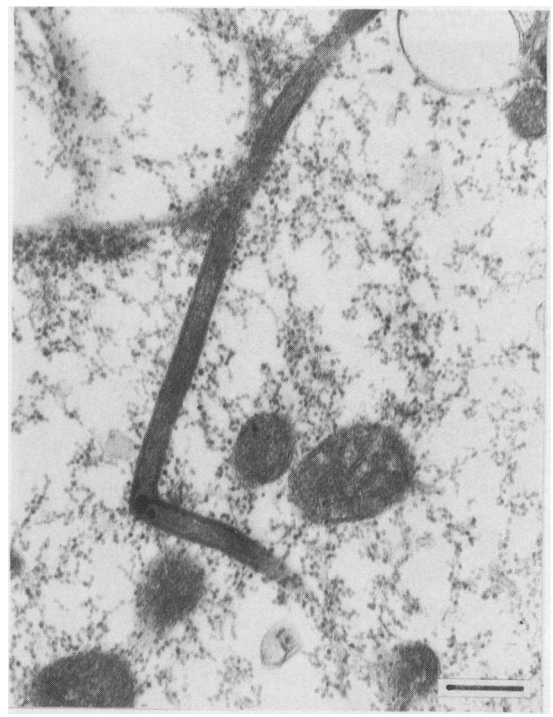

Fig 5 *Elongated mitochondrion with early paracrystalline change occurring within a vacuole. Bar = 0·33 um.*

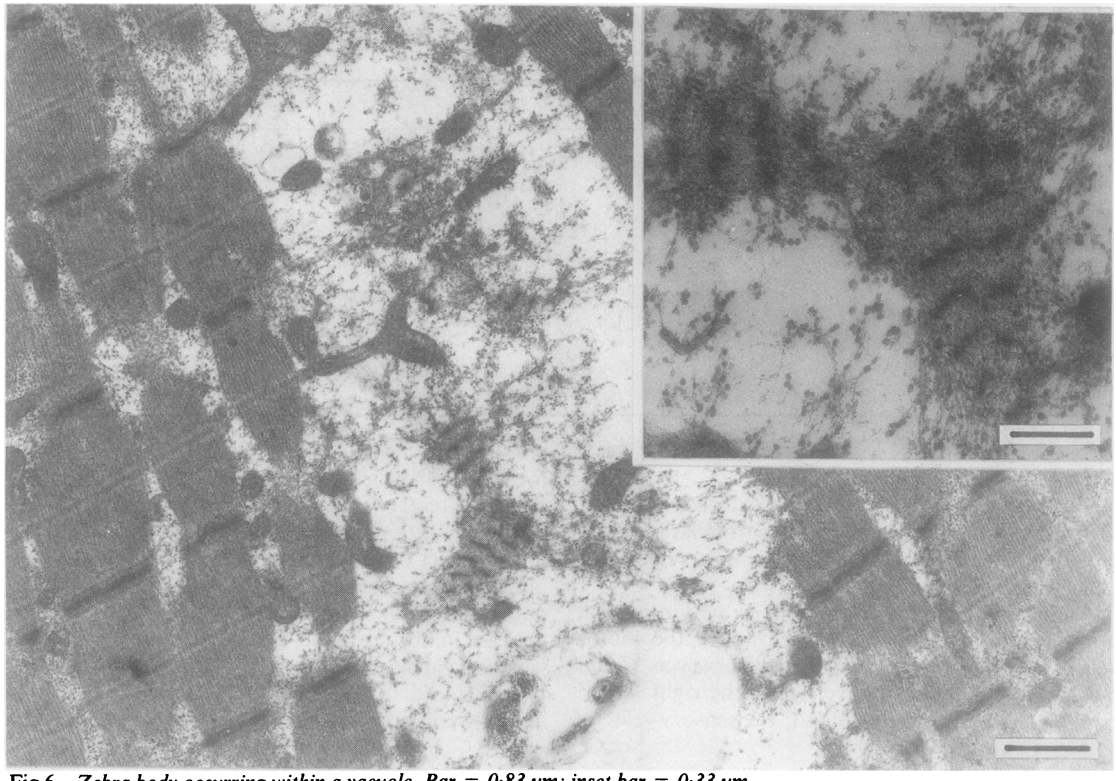

Fig 6 *Zebra body occurring within a vacuole. Bar = 0·83 um; inset bar = 0·33 um.*

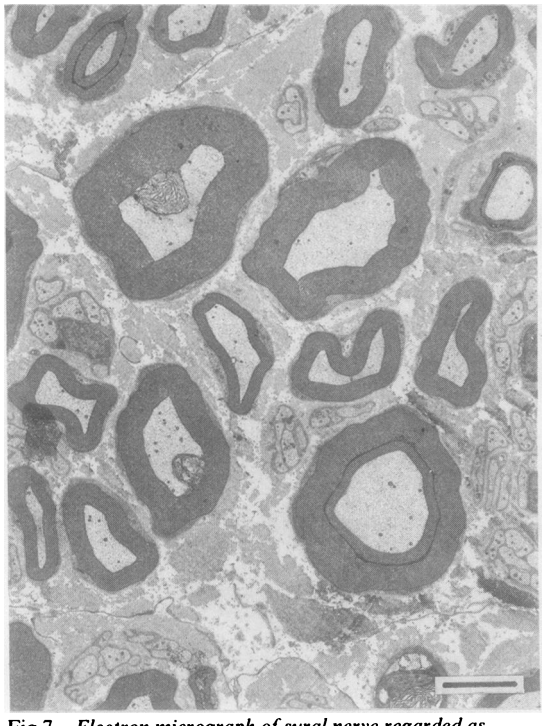

Fig 7 *Electron micrograph of sural nerve regarded as normal. Bar = 5 um.*

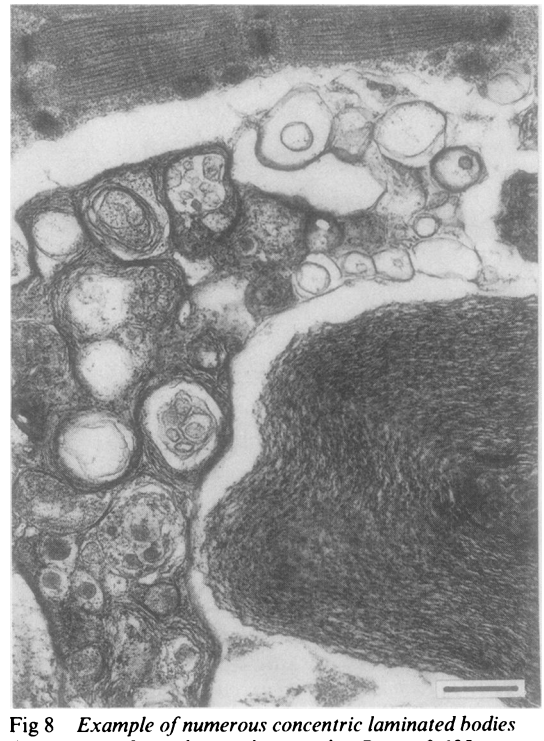

Fig 8 *Example of numerous concentric laminated bodies from a case of spinal muscular atrophy. Bar = 0·625 um.*

ticularly of the smaller fibres, most of which were of the type I variety, was grossly disturbed, and subsarcolemmal collections of oxidative material were obvious on electron microscopical examination.

Muscle enzyme activities were found to be generally normal apart from a slight decrease in the content of myoadenylate deaminase (table). Creatine kinase activity was raised and fluctuated between 2800 IU and 3300 IU/l.

CASE 3

The histochemical findings were similar, and it was again noted that most of the fibres were type 1 and these displayed a severe disturbance of cytoarchitecture. On electron microscopy the changes were more severe than those seen in case 2, and occasional mitochondria showed evidence of condensation of glycogen encased within lysosomes, while in other areas paracrystalline inclusions were found. The sural nerve study was considered to be within normal limits on both physical appearance and on axonal counts.

Muscle enzyme activities were normal. Creatine kinase activity was 3800 IU/l.

CASE 4

Electromyographic findings were similar to those of cases 2 and 3: there was increased low voltage polyphasic activity in the more severely affected muscles, and no evidence of denervation or spontaneous activity was noted. The nerve conduction velocity in the right lateral popliteal was 49·3 metres/second, left lateral popliteal 50 metres/second, and the right median 60·9 metres/second. Sensory conduction of the right median nerve was 62 metres/second, and 64 metres/second in the right lateral popliteal.

Muscle biopsy studies of the vastus lateralis and the left sural nerve were similar to those of cases 2 and 3. Selective muscle enzyme activities were normal. Creatine kinase activity was 3150 IU/l. Mitochondrial kinetics were examined and gave normal results at all stages.

CASES 5 AND 6

Electromyography showed evidence of low voltage polyphasic activity, particularly in the more severely affected muscles. The right median nerve motor conduction velocity was 57 metres/second, the right lateral popliteal 44·4 metres/second, the left lateral popliteal 50 metres/second. The sensory velocity for the right median nerve was 66 metres/second and 50 metres/second for the right lateral popliteal.

A muscle biopsy specimen of the left vastus lateralis showed fatty and fibrous tissue infiltration. There was considerable variation in fibre size, and many of the fibres had centralised nuclei. Several fibres were of hyaline appearance and showed evidence of splitting. Histochemical analysis showed that both fibres were affected, type 1 fibres more severely so. No evidence of fibre type grouping was noted. The muscle electron microscopical findings were similar to those of cases 2, 3 and 4. The sural nerve study, which included electron microscopy, single fibre study, and nerve counts of both myelinated and non-myelinated fibres, yielded normal results. The brother (case 6) was not biopsied as his clinical picture was identical.

## Discussion

In 1975 Miyoshi *et al* showed that a recessive form of distal dystrophy existed in Japan and documented 30 such cases.[10] In 1981 Kuhn and Schroder published findings on "a new type of distal myopathy in two brothers".[7] These patients with recessively inherited dystrophy had distal leg muscle weakness beginning in early adult life, associated with a pronounced increase in creatine kinase activity, and closely resembled sporadic cases described by other authors.[3 8 9 14] Edstrom *et al* described the presence of intermediate skeletin filaments in cases of distal myopathy,[15] and a similar finding was recorded by Matsubara and Tanabe.[16]

Nonaka *et al* described three cases from two families of Japanese origin which appear to fit into the autosomal recessive variety and which were characterised by the presence of rimmed vacuoles seen in the muscle biopsy sections, which possessed an acid phosphatase positive autophagic activity.[11] These findings are similar to those seen in case 1 and in other cases.[16 17] Sarcoplasmic filamentous inclusions as well as concentric lamella bodies have also been noted, and it is thought that the continued destruction of the myofibrils is achieved by the activation of lysosomal proteolytic enzymes. Rimmed vacuoles, however, should not be regarded as a specific finding as they may be seen in other myopathic disorders. Concentric laminated bodies of various forms are common in distal myopathy, are a non-specific finding, and may be seen on occasions in other diseases such as limb girdle dystrophy, and particularly in spinal muscular atrophy (fig 8).

Scopetta *et al* suggested that the recessive inheritance for distal dystrophy as opposed to the dominant inheritance exhibited the following features[18]: (i) onset in early adult life; (ii) distal leg muscles affected first; (iii) moderate to severe increase in creatine kinase activity; (iv) electromyographic evidence of myopathic damage despite the presence of fibrillation; and (v) a histological picture of a dystrophic myopathy.

Case 1 fits into the category of the sporadic distal muscular dystrophy of the Nonaka variety; cases 2–6 are regarded as examples of the commoner form of

recessive distal dystrophy in South Africans of European extraction.

We feel that these forms of distal myopathy, though not seen often, have distinctive features which require their inclusion into all modern classifications of muscular dystrophy.

We gratefully acknowledge the financial support of the Medical Research Council of South Africa, the University of the Witwatersrand, and the Muscular Dystrophy Research Foundation of South Africa.

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Requests for reprints to: Dr H Isaacs, NMRL, Department of Physiology, University of the Witwatersrand Medical School, Johannesburg, South Africa 2001.