Acta Neuropathol (1991) 82: 102 – 106

Acta Neuropathologica

Intranuclear and cytoplasmic filamentous inclusions in distal myopathy (Welander)*

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Received October 22, 1990/Revised, accepted March 26, 1991

Summary. Ultrastructural examination of anterior tibial muscle from four patients with late-onset autosomal dominant distal myopathy of Welander-type revealed intrasarcoplasmic filamentous inclusions in association with rimmed vacuoles. In one of the patients, identical intranuclear filamentous inclusions were also found. These filamentous inclusions are similar to those described in inclusion body myositis (IBM). They have also been observed in hereditary neuromuscular disorders including autosomal recessive distal myopathy. Thus, the filamentous inclusions occur in different neuromuscular conditions with different etiologies. These findings further raise the question of the specificity of the filamentous inclusions in IBM.

Key words: Distal myopathy (Welander) – Muscle biopsy – Nuclear inclusions – Cytoplasmic inclusions – Rimmed vacuoles

Late-onset autosomal dominant distal myopathy, which almost exclusively occur in Sweden, was described 1951 by Welander [38] on the basis of 249 cases in 72 pedigrees. Muscle fibre abnormalities were originally described as conforming to other muscular dystrophies [38]. Rimmed vacuoles and collections of cytoplasmic filaments with a diameter of 15–20 nm have been reported in Welander distal myopathy [2, 32].

Cytoplasmic filamentous inclusions in association with rimmed vacuoles within muscle fibres have been considered as one of the characteristic features of inclusion body myositis (IBM) [5, 21, 24, 35, 39]. In IBM, the filamentous inclusions are also found within muscle fibre nuclei, although in a considerably lower frequency than in the cytoplasm. The diameters of the filamentous inclusions vary between 15 and 20 nm in different studies [5, 15, 21, 24, 35, 39]. Similar filamentous inclusions have been described in hereditary neuromuscular disorders [7, 13, 14], in distal myopathy with autosomal recessive inheritance described by japanese authors [22, 25, 31], in myotonic dystrophy [9] and in one case of polyneuropathy associated with sarcoidosis [23].

The aim of this study was to evaluate muscle fibre ultrastructure in patients with Welander distal myopathy to search for intranuclear filamentous inclusions and to characterize further the cytoplasmic filamentous inclusions.

Patients and methods

Four patients, who clinically and neurophysiologically fulfilled the criteria for Welander distal myopathy as given by Welander [38], were examined.

Case 1

Case 1 was a 49-year-old woman with a 5-year history of slowly progressive, symmetrical and distal muscle weakness. The patient's mother and maternal grandmother were affected and the mother was diagnosed by Welander. The most prominent findings on clinical examination were slight to moderate weakness of extensors of the fingers and hands and moderate atrophy of the thenar muscles. Serum creatine kinase (CK) was 372 IU/1 (normal <144 IU/1). Electromyographical (EMG) abnormalities were myopathic with mild neuropathic changes.

Case 2

Case 2 was a 51-year-old woman with a 20-year history of slowly progressive, symmetrical and distal muscle weakness beginning with clumsiness in the fingers. During the last years a gait disturbance had evolved. The patient's mother, two sisters and brother, her daughter and maternal grandmother were affected.

* Supported by grants from the Swedish Medical Research Council (proj. 3875, visiting research grant K. Borg), the Swedish MS foundation, the Swedish Society of Medicine, the Swedish Society for Traffic and Polio Disabled, Erik and Edith Fernströms Foundation for Medical Research and from the Karolinska Institute

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On clinical examination the patient had difficulties walking on the heels and a weakness for dorsal extension of the feet was found. Serum CK was normal. EMG abnormalities were of myopathic type.

Case 3

Case 3 was a 44-year-old man with a 10-year history of slowly progressive, symmetrical and distal muscle weakness. The patient's father and paternal grandfather were also affected. On clinical examination the patient was unable to walk on his heels and had slight to moderate weakness for extension of the hands. The atrophy found was slight in the thenar muscles and moderate to severe in the lower limb muscles and interosseus muscles. Serum CK was normal. EMG abnormalities were myopathic with mild neuropathic changes.

Case 4

Case 4 was a 47-year-old woman with a 1-year history of bilateral weakness and clumsiness in fingers and hands. The patient's mother and two sisters were diagnosed as having Welander distal myopathy. Clinical examination revealed a weakness for extension of fingers and hands, a moderate atrophy of the left thenar and slight atrophy of the right thenar muscles. Serum CK was normal. EMG abnormalities were of myopathic type.

Muscle biopsies

Muscle biopsies were performed in the anterior tibial muscle by the percutaneous conchotome method described by Radner [28], and slightly modified according to [20]. For light microscopical morphology and histochemistry cryostat, cross-sections of 10–15 μm were stained with hematoxylin-eosin, modified trichrome [12], adenosine triphosphatase (ATPase) according to Padykula and Herman [27], and the modifications of Brooke and Kaiser [4] and NADH-TR [30]. Specimens used for transmission electron microscopy were fixed in 2.5 % glutaraldehyde in phosphate buffer. Ultrathin Epon sections were examined in Philips 300 or 410 electron microscopes.

Results

Light microscopy

The muscle bioposies from all four patients showed similar morphological abnormalities and conformed to those described earlier [2, 10, 32], although these were less pronounced in patient 4. The abnormalities consisted of increased variation of muscle fibre diameters, centrally located nuclei, split fibres and atrophy of both type I and type II fibres. The atrophic fibres were mainly angulated but rounded atrophic fibres were also found (Fig. 1). In two patients (nos. 1 and 2) small group atrophy was present. Rimmed vacuoles were found in atrophic and in normal-sized muscle fibres in biopsies from all patients (Fig. 1). They were abundant in patients 1, 2 and 3 and occurred in a few muscle fibres in patient 4.

Electron microscopy

At the ultrastructural level the rimmed vacuoles corresponded to autophagic vacuoles which contained membranous bodies with the appearance of dense bodies and myelin figures intermingled with collections of glycogen and amorphous material (Fig. 2). The autophagic vacuoles were found in fibres with normal size and normal myofibrillar ultrastructure as well as in atrophic fibres with disorganization of myofibrils.

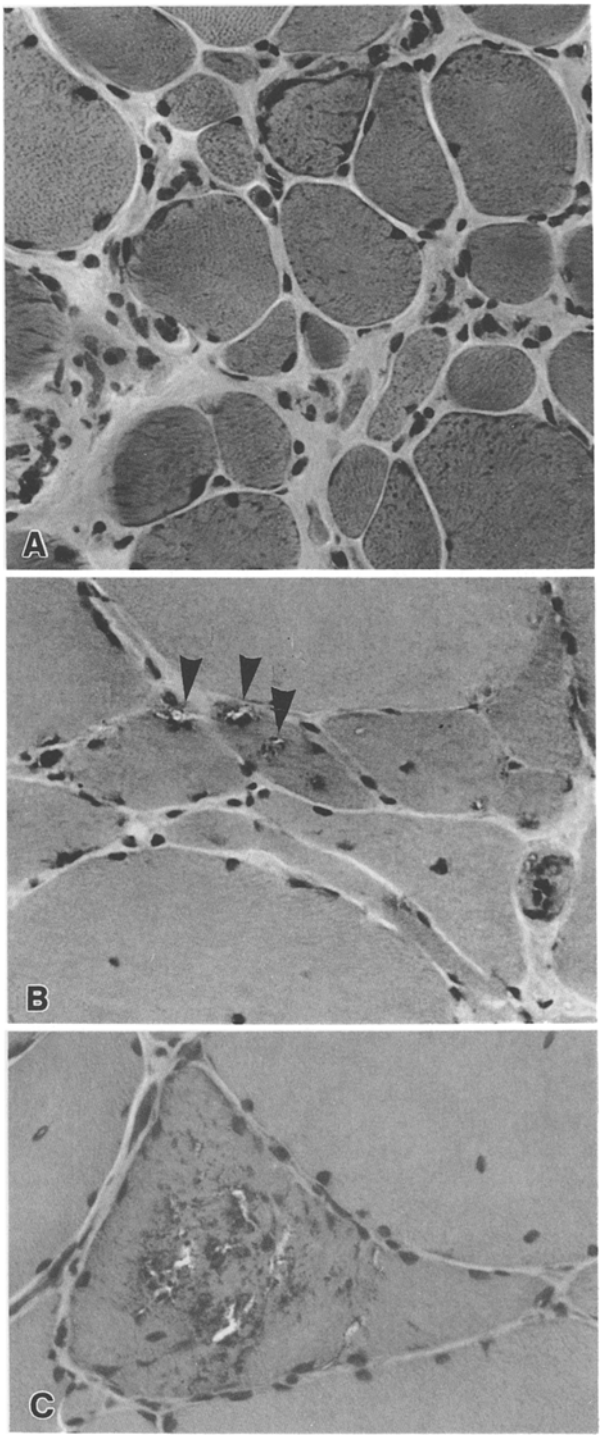

Fig. 1A–C. Cryostat cross-sections of anterior tibial (TA) muscle stained with Hematoxylin-eosin. Atrophic fibres with rounded (**A**) and angulated (**B**) appearance. Rimmed vacuoles in a normal-sized muscle fibre (**C**) and in atrophic muscle fibres (*arrowheads* in **B**). **A–C** × 320

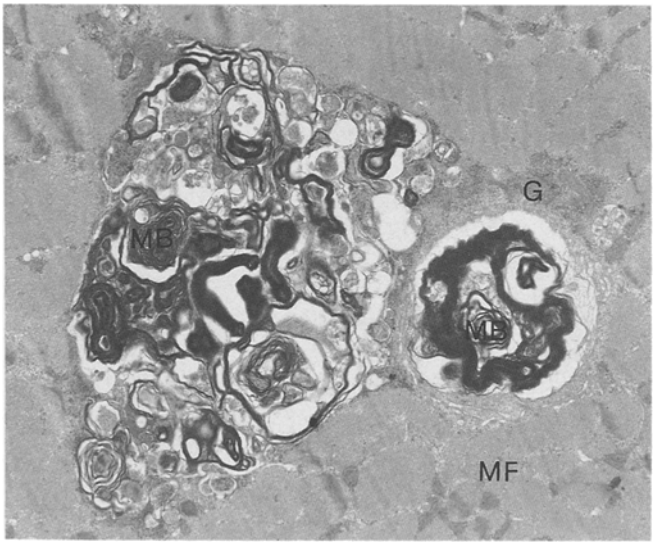

Fig. 2. Electron microscope photograph of TA muscle. Autophagic vacuole containing myelin bodies (*MB*) and collections of glycogen (*G*) surrounded by normally packed myofilaments (*MF*). × 6500

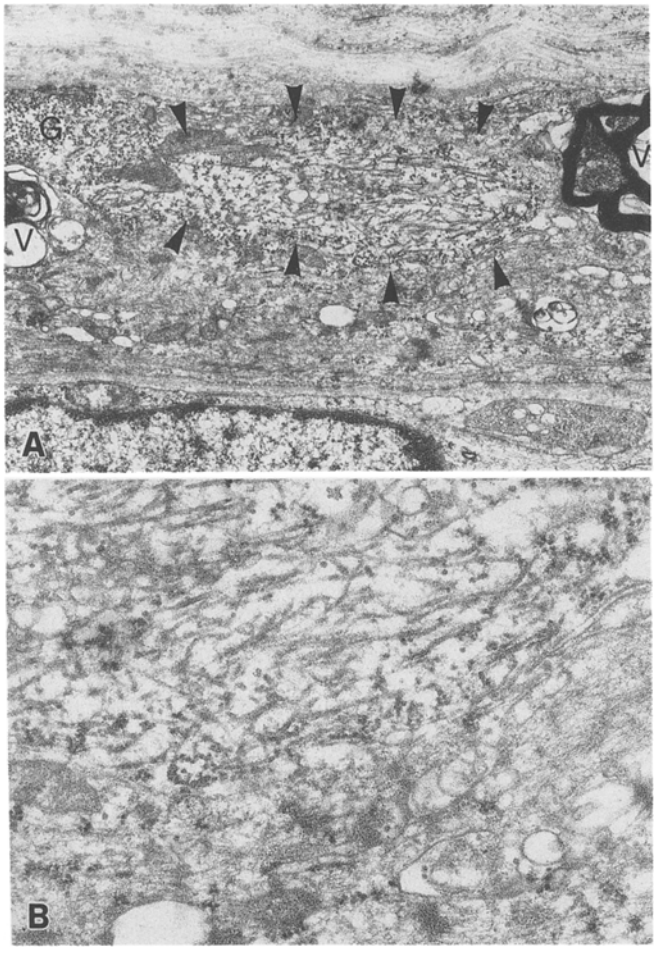

Fig. 3A,B. Electron microscope photographs of TA muscle. **A** Cytoplasmic filamentous inclusions (*arrowheads*) in association with autophagic vacuoles (*V*). **B** Higher magnification. **A** × 12 200; **B** × 35 500

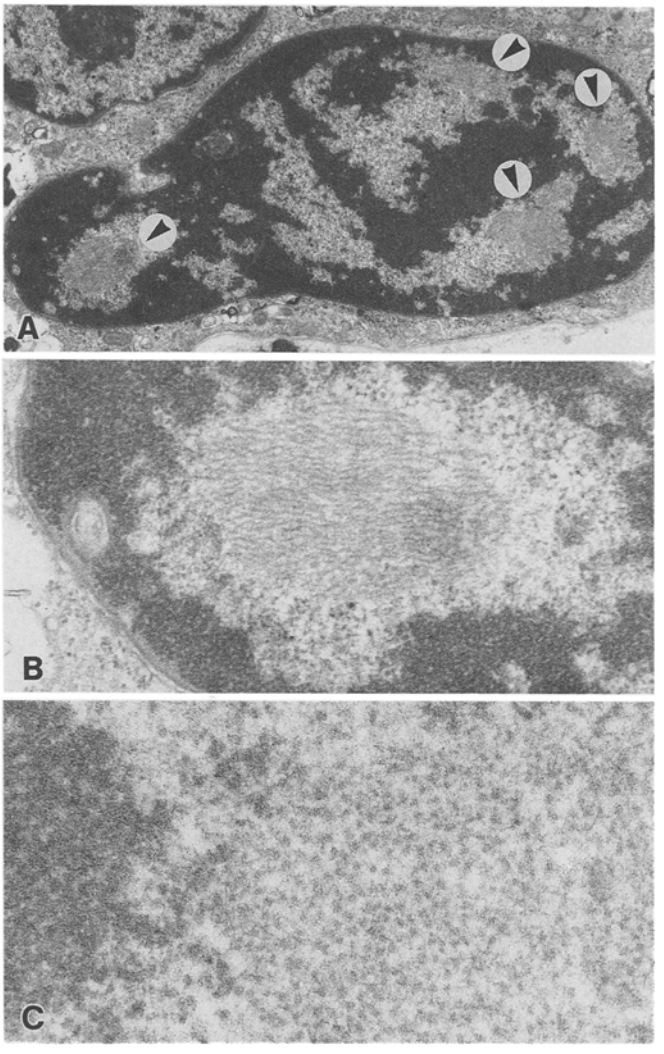

Fig.4A–C. Electron microscope photograph of TA muscle. **A** Atrophic muscle fibre containing a nucleus with collections of filamentous inclusions (*arrowheads*). Longitudinal (**B**) and transversal (**C**) sections of the filamentous inclusions. **A** × 10 200; **B** × 29 500; **C** × 69 100

Cytoplasmic filamentous inclusions were found in association with autophagic vacuoles in all four muscle biopsies. The filaments were straight or gently curved and were generally randomly dispersed but were sometimes arranged in parallel forming an interlacing meshwork (Fig. 3). The diameter of these filaments was 16–21 nm.

In patient 1 filamentous inclusions with a diameter of 13–17 nm were found in multiple sites within a nucleus in an atrophic muscle fibre containing autophagic vacuoles (Fig. 4). The intranuclear filaments were found in many serial sections. Fingerprint bodies, identical to those reported by Engel et al. [11] and Thomé et al. [33], were also seen near nuclei in two atrophic muscle fibres in this patient (Fig. 5).

Other ultrastructural abnormalities were dense collections of Z-disc material or streaming, double Z-discs, honeycomb structures and abnormal mitochondria as described previously [2, 32].

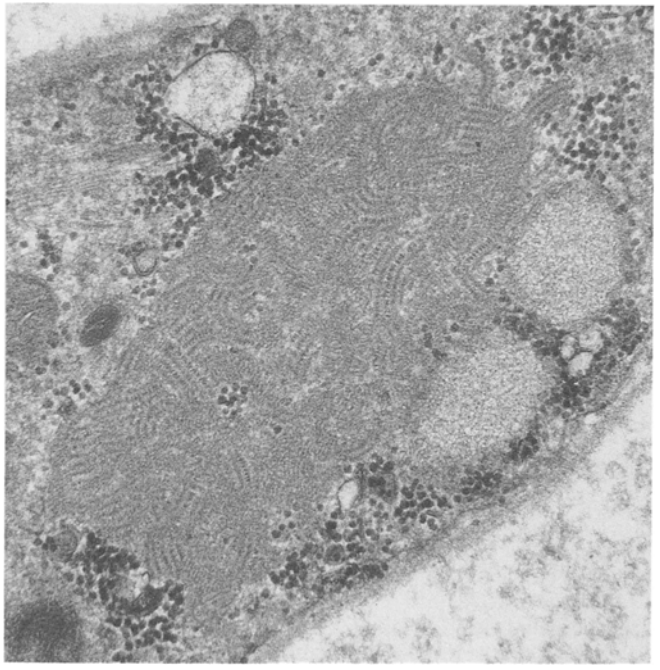

Fig.5. Electron microscope photograph of TA muscle. Fingerprint body in atrophic muscle fibre. × 33 800

Discussion

The cytoplasmic filamentous inclusions found within muscle fibres in the present patients with Welander distal myopathy had the same organization, appearance and diameters as the filaments described in IBM patients [5, 19, 21, 24, 35, 39] and in hereditary neuromuscular disorders [7, 13, 14], including autosomal recessive distal myopathy described by Japanese authors [22, 25, 31]. As in these disorders the cytoplasmic filamentous inclusions in Welander distal myopathy always occurred in association with rimmed vacuoles. In addition, rimmed vacuoles have been reported to appear in different disorders, including neurogenic conditions [1, 16, 23], in a normal, aged human [17] and in an exercise-induced myopathy with mitochondrial abnormalities [18]. Intranuclear filamentous inclusions with a diameter of 20 nm have recently been described in myotonic dystrophy [9]. Thus, filamentous inclusions and rimmed vacuoles appear in disorders with possibly different etiologies, affecting muscle as well as nerve, and they are nonspecific phenomena seen in degenerating muscle fibres, as suggested by Dieler and Schröder [9]. These inclusions and rimmed vacuoles are only significant for a given disease when they are found frequently and constitute a predominant change. This means that the filaments probably do not play a central role in the pathophysiological process of Welander distal myopathy. The finding of the filamentous inclusions in Welander distal myopathy further supports the view expressed by several authors that the filamentous inclusions are not specific for IBM.

Filamentous inclusions were also found in one nucleus in one patient with Welander distal myopathy, although a thorough examination was carried out in this and the three other patients. In IBM there is also a lower frequency of intranuclear in relation to cytoplasmic filaments. Carpenter et al. [5] found intranuclear filamentous inclusions in 3 of 6 examined IBM patients and Lotz et al. [21] in 13 of 43 patients. Tomé et al. [35] estimated that in their two cases, 2.5 % and 3.5 % of the nuclei were affected.

The intranuclear filaments described here were similar to those found in IBM but differed clearly from the 8.5-nm diameter intranuclear filaments described in oculopharyngeal muscular dystrophy [3, 8, 34]. Furthermore, they had smaller diameters than the cytoplasmic filaments. This is in accordance with the findings of Yunis and Samaha [39] and Lotz et al. [21] in IBM.

As to the nature of the filamentous inclusions in IBM, a viral origin has been suggested by several authors. Chou [6] reported that the filamentous inclusions bound antibodies against mumps virus antigens and evoked a persistent mumps virus infection. However, a specific binding of anti-mumps antibodies could not be demonstrated in in-situ hybridization studies [26, 29]. Furthermore, Yunis and Samaha [39] and Tomé et al. [35] suggested that the filaments might be of myofilament origin. In IBM and oculopharyngeal muscular dystrophy, immunocytochemical studies with antibodies against intermediate filaments and various other filamentous proteins have been negative [36, 37]. Thus, the nature of the filamentous inclusions are so far unknown and further studies are required to solve this question.

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