An atypical late onset *Dysferlinopathy* mimicking ALS with *flail leg* phenotype.

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Background

Dysferlinopathies are caused by mutations in dysferlin gene (DYSF) located in chromosome 2p13 presenting an autosomal recessive inheritance. DYSF gene encodes for the dysferlin protein implicated in vesicle fusion, trafficking and muscle membrane repair [1]. Two main phenotypes have been described: **limb-girdle muscular dystrophy type 2B** (LGMD2B) and **Miyoshi myopathy** (MM). Less frequently dysferlin deficiency may lead to **distal anterior compartment myopathy** (DACM)[2] and **asymptomatic hyperCKemia**. We describe a patient with DACM phenotype presenting with clinical signs mimicking Motor Neuron Diseases (MND).

Case Report

We describe a 57 years-old patient with DACM, presenting with clinical signs mimicking Motor Neuron Diseases (MND) consisting of weakness and wasting to the lower limbs associated with fasciculations (figure 1). Laboratory tests showed only an increase in Creatine Kinase (CK) values (496 U/L). Cerebrospinal fluid did not show any alteration; brain, cervical and lumbar MRI were normal. Neurophysiological exams showed a mild neurogenic picture (figure 2).

Clinical follow up after three and six months did not show any worsening, disconfirming the diagnosis of MND. A muscular biopsy was then performed in the right tibialis anterior muscle: a chronic myopathy with a dystrophic pattern was found. Immunohistochemical studies were performed using an anti-dysferlin antibody and revealed the deficiency of the dysferlin protein.

Fig. 1

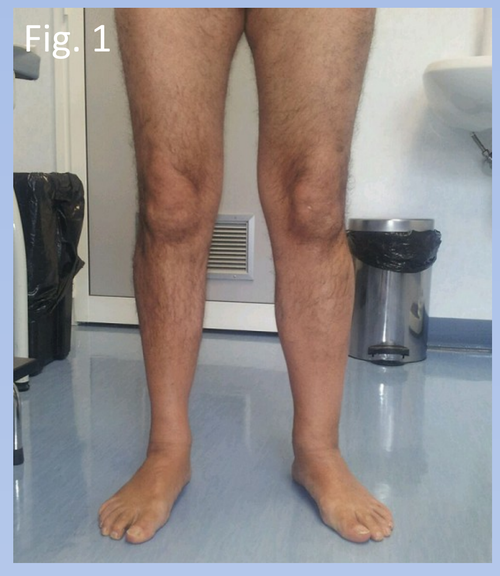
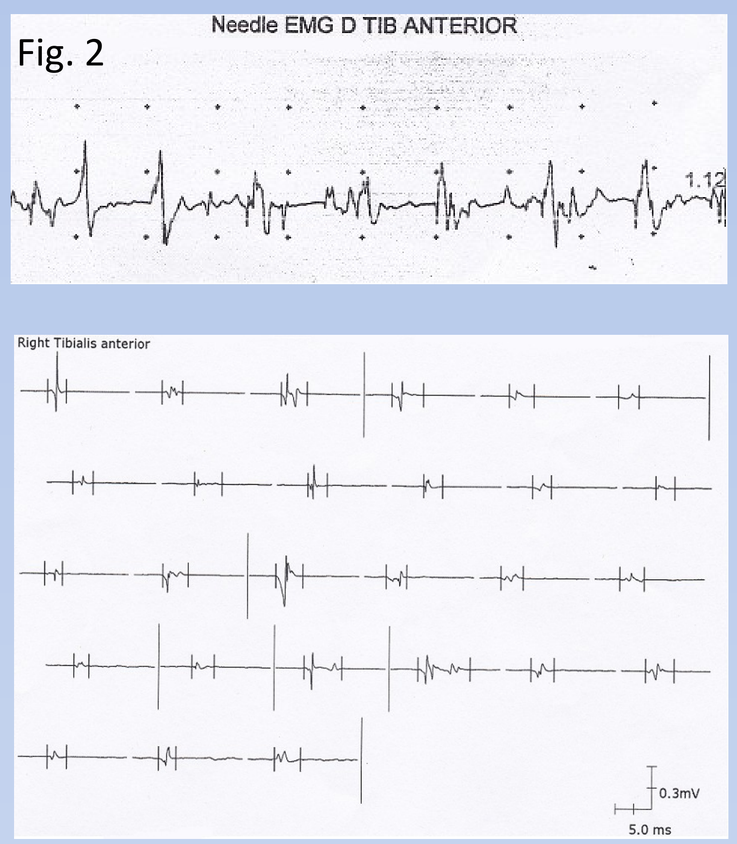


Fig. 2



Discussion

This is a rare case of late onset dysferlinopathy presenting with clinical signs and neurophysiological features resembling the flail leg variant of ALS (table 1). Dysferlin is a member of the ferlin subgroup and plays an important role in repairing sarcolemmal damage and in the maintenance of Ca++ homeostasis following cellular stress (Fig. 3). In our patient, clinical presentation could mimic a MND, especially because of the leg hypotrophy associated with fasciculations. Needle EMG in dysferlinopathy usually shows motor units of small amplitude and short duration, which are compatible with a myopathy, but sometimes, this disease could have a mixed myopathic and neuropathic pattern [3-4].

This case highlights the importance of clinical follow up in MND; moreover, in cases with a long history of focal disease, muscular biopsy and immunohistochemical studies could play an important role to avoid misdiagnosis.

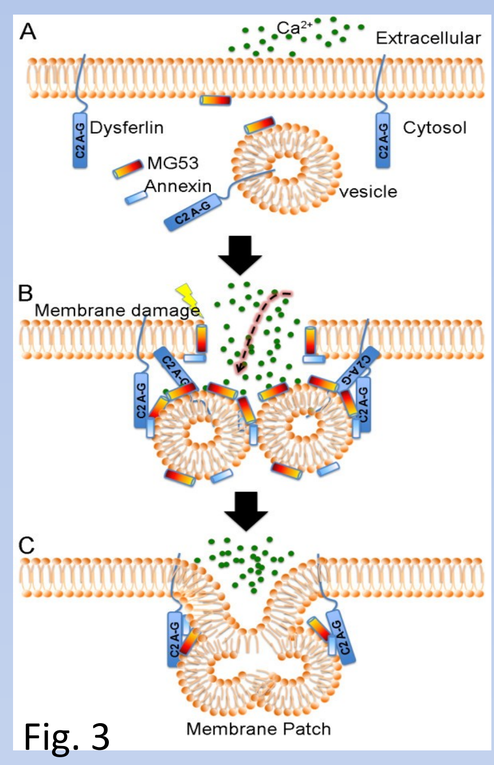


Fig. 3

	Miyoshi myopathy	LGMD2B	Dystal myopathy with anterior tibial onset	Flail leg ALS	PMA
Mean age at onset	20 (range 10-33)	20 (range 15-45)*	14-28	55-58	60-65
Clinical features	Distal muscle weakness and atrophy of the leg, mainly the posterior side; worsening at legs, forearms involvement with intrinsic hand muscles sparing. Shoulder girdle can be involved	Predominant weakness and atrophy of shoulder and pelvic girdles muscles; preservation of function of the hands in late stage; preservation of strength in the neck muscles in late stage	Weakness of the anterior compartment with foot drop	Lower limbs distal onset of weakness and wasting, without upper limbs or bulbar involvement within 12 months from onset	A pure lower MN syndrome with weakness and wasting having limbs onset, but spreading and involving a second or third region within 12 months
Wheelchair (onset)	12-23 yrs	25-35 yrs	11-22 yrs	2-4 yrs	2-4 yrs
Nerve conduction studies	Normal	Normal	Normal	Normal	Normal
Cranial nerves	Spared	Spared; rare dysphagia	Spared	Late involvement	Late involvement
EMG	Primarily myogenic pattern	Primarily myogenic pattern	Spontaneous activity, complex repetitive discharges in several muscles, myopathic MUPs	Fibrillation or PSW potentials, or both, fasciculation potentials in resting muscles; incomplete interference pattern, with abnormal large MUPs.	As Flail leg variant
MEP (central motor conduction time)	Normal	Normal	Normal	CCT prolonged despite the absence of pyramidal signs	May be altered
Muscle biopsy	Random variation in fiber size; degeneration and regeneration; inflammation	Not different from Miyoshi miopathy; no correlation between inflammation at biopsy and phenotype	Fiber-size variability, central nuclei, fibers subdivided by splitting, and infiltrates. Increased connective tissue.	classical signs of denervation (atrophic and angular fibres) and reinnervation (fibre type grouping)	classical signs of denervation and reinnervation
CK (mean values)	10-100 times normal values	2-40 times normal values	20-70 times normal values	Normal or slightly increased	Normal or slightly increased
Need for ventilation	Occasional in the very late stages	Occasional in the very late stages	A reduction of FVC has been reported	Frequent	Frequent
Survival (median)	>30 years	>30 years	>15 years	70-90 months	40 months

References

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4. Argov Z, et al. Muscular dystrophy due to dysferlindeficiency in Libyan Jews. Clinical and genetic features. Brain 2000;123: 1229-1237.