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Inflammatory changes in infantile-onset *LMNA*-associated myopathy

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Abstract

Mutations in *LMNA* cause wide variety of disorders including Emery–Dreifuss muscular dystrophy, limb girdle muscular dystrophy, and congenital muscular dystrophy. We recently found a *LMNA* mutation in a patient who was previously diagnosed as infantile onset inflammatory myopathy. In this study, we screened for *LMNA* mutations in 20 patients suspected to have inflammatory myopathy with onset at 2 years or younger. The diagnosis of inflammatory myopathy was based on muscle pathology with presence of perivascular cuffing and/or endomysial/perimysial lymphocyte infiltration. We identified heterozygous *LMNA* mutations in 11 patients (55%), who eventually developed joint contractures and/or cardiac involvement after the infantile period. Our findings suggest that *LMNA* mutation should be considered in myopathy patients with inflammatory changes during infancy, and that this may help avoid life-threatening events associated with laminopathy.

Keywords: Inflammatory myopathy; Laminopathy; Emery–Dreifuss muscular dystrophy; Limb girdle muscular dystrophy; Congenital muscular dystrophy; *LMNA*; Infantile; Pathology; Steroid therapy; Muscle image

1. Introduction

Laminopathy is a group of disorders caused by mutations in the *LMNA* gene encoding A-type lamins that includes autosomal forms of Emery–Dreifuss muscular dystrophy (AD- and AR-EDMD) and limb girdle muscular dystrophy type 1B (LGMD1B). EDMD is characterized by the triad of: (1) early contractures of the elbows, Achilles tendons, and posterior cervical muscles; (2) slowly progressive muscle weakness and atrophy that begins in a humeroperoneal distribution; and (3) cardiomyopathy with conduction defects which culminates in complete heart block and atrial paralysis [1]. LGMD1B patients show progressive proximal dominant muscle involvement and

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cardiomyopathy with conduction defects, but joint contracture is not prominent. The onset of these diseases is usually 2 years or later. Recently, *LMNA*-related congenital muscular dystrophy (L-CMD) was reported as a novel and severe form of laminopathy [2]. L-CMD has variable severity and can be divided in two main groups: a severe group with absent motor development and patients with dropped-head syndrome.

We recently came across an infantile-onset laminopathy patient with marked mononuclear cell infiltrations in his muscle mimicking inflammatory myopathy (Patient 1 in Table 1, Fig. 1A). This patient showed hypotonia and delayed motor milestones with elevation of serum CK levels from 3 months of age. Although, he became ambulant at 15 months of age, he presented proximal dominant muscle weakness and atrophy with no dropped-head at 2 years of age. Corticosteroid therapy was started based on the muscle pathological findings that had beneficial effects on his motor development. *LMNA* gene analysis was done at 6 years of age when his ankle and elbow joint contractures appeared and a heterozygous p.Glu358Lys mutation was identified.

From this result, we screened *LMNA* mutation in the 20 patients with the onset at 2 years or younger who were pathologically suspected as inflammatory myopathy.

2. Patients and methods

2.1. Patients

All clinical materials used in this study were obtained for diagnostic purposes and written informed consent was obtained from guardians of all patients. This work was approved by the Ethical Committee of National Center of Neurology and Psychiatry (NCNP). We retrospectively recruited patients with onset at 2 years or younger who were pathologically suspected to have inflammatory myopathy from a total of 10,874 muscle biopsies stored in the

Table 1
Clinical, radiological, and genetic findings of patients with *LMNA* mutations and inflammatory changes.

Patient #/gender/ *LMNA* mutations	Age at onset /age at biopsy/ age at last consultation	Initial signs/ CK at biopsy	Muscle pathology	Steroid treatment: responsiveness/ age at start of administration/ duration of administration	Age at acquired ambulation/ maximum motor ability	Cardiac involvement	Joint contracture	Respiratory dysfunction	CT/MRI (age)/imaging at thigh	CT/MRI (age)/imaging at calf
1/M/E358K*	3 m/2 y/11 y	Motor delay/900	IC: marked, diffuse; NR: moderate; Fib: mild	Effective/2 y/9 y	15 m/Ambulant	No	6 y: Ankles, elbows, 8 y: rigid spine	No	MRI (8 y)/ selective involvement of VL, VI, VM	MRI (8 y)/ selective involvement of SO, mGC
2/M/R249W*	10 m/10 m/12 y (Died by respiratory failure)	Motor delay/1000	IC: marked, pathy; NR: mild; Fib: mild	Effective/10 m/11 y	Unknown/ambulant	9 y: Heart failure	4 y: Ankles, knees	9 y: Nocturnal NPPV	ND	ND
3/M/N39D	11 m/1 y/16 y	Motor delay/1100	IC: marked, pathy; NR: marked; Fib: mild	Effective/1 y/15 y	18 m/Ambulant	13 y: 200B0 A–V block, 15 y 3° A–V block, pacemaker implantation	1 y: Ankles, knees, hips, Rigid spine from childhood	No	CT (13 y)/DI with relative sparing of RF, GR, SA	CT (13 y)/DI
4/F/R249Q*	2 y/2 y/15 y	High CK/2000	IC: moderate, focal; NR: moderate; Fib: moderate	Effective/3 y/6 m	14 m/Ambulant	12 y: 1° A–V block	3 y: Ankles, 8 y: elbows	No	CT (6 y)/DI with relative sparing of RF, GR	CT (6 y)/ selective involvement of SO, mGC
5/M/R28Q	5 m/1 y/11 y	Motor delay/800	IC: marked, pathy; NR: moderate; Fib: moderate	Ineffective/1 y/2 y	18 m/9 y: Inability to walk	Atrial fibrillation, A–V block, PAC, PVC	No	No	CT (11 y)/DI with relative sparing of RF, GR, SA	ND
6/M/R41S	9 m/1 y/13 y	Motor delay/900	IC: moderate, diffuse, NR: moderate Fib: moderate	Ineffective/1 y/8 y	16 m/9 y: Inability to walk	11 y: PSVT attack	6 y: Ankles, elbows	11 y: Nocturnal NPPV	MRI (10 y)/ DI/DI	MRI (10 y)/ DI/DI
7/F/K32del*	1 y/2 y/6 y	Unsteady gait/800	IC: mild, focal; NR: mild; Fib: mild	Ineffective/2 y/8 m	15 m/5 y: Inability to walk	No	2 y: Ankles	No	CT (4 y)/DI with relative sparing of RF, GR/Selective involvement of SO, mGC	CT (4 y)/DI with relative sparing of RF, GR/Selective involvement of SO, mGC
8/M/R249W*	11 m/1 y/24 y (Died by arrhythmia)	Motor delay/600	IC: marked, pathy; NR: mild; Fib: moderate	Ineffective/1 y/unknown	2 y/12 y: Inability to walk	17 y: 2° A–V block, 23 y complete A–V block	17 y: Ankles, knees	No	ND	ND
9/F/L292P	1 y/8 y/10 y	Motor delay/300	IC: mild, focal; NR: moderate; Fib: marked	Unadministered	16 m/4 y: Inability to walk	6 y: LV dysfunction, 8 y: PAC, PVC	No	No	MRI (8 y)/DI with relative sparing of RF, GR, SA	MRI (8 y)/DI
10/F/R377C*	2 y/4 y/7 y (Died by heart failure)	Unsteady gait/1000	IC: moderate, focal; NR: moderate; Fib: moderate	Unadministered	10 m/ambulant	7 y: DCM (EF:32%)	5 y: Ankles	No	ND	ND
11/F/N456H	2 y/5 y/10 y	Unsteady gait/3000	IC: moderate, focal; NR: moderate; Fib: marked	Unadministered	12 m/ambulant	No	6 y: Ankle, knee, neck, 8 y: rigid spine	No	MRI (10 y)/ DI with relative sparing of RF, GR, SA	MRI (10 y)/ DI

A–V block = atrioventricular conduction block, CK = creatine kinase, CT = computed tomography, DI = diffuse involvement, EF = ejection fraction, Fib = endomysial fibrosis, GR = gracilis, IC = inflammatory cellular infiltration, LV = left ventricle, mGC = medial head of gastrocnemius, MRI = magnetic resonance imaging, NPPV = noninvasive positive-pressure ventilation, NR = necrotic and regenerating process, PAC = premature atrial contraction, PSVT = paroxysmal supraventricular tachycardia, PVC = premature ventricular contraction, RF = rectus femoris, SA = Sartorius, SO = soleus, VI = vastus intermedius, VL = vastus lateralis, VM = vastus medialis.