A case of amyloid myopathy in a patient with familial Mediterranean fever

Sirs,

Amyloid myopathy (AM), an increasingly recognized muscle disorder (1, 2) is reported in familial and AL-amyloidoses, associated with lymphoproliferative disorders (1-3). To our knowledge, AM has not been previously described in familial Mediterranean fever (FMF), though amyloidosis represents its most severe complication, or in other AA-amyloidoses. We report the case of a 28-year-old Italian male patient with AM in FMF. He complained of previously undiagnosed recurrent episodes of fever, lymphadenopathy, monoarthritis, thoracical/abdominal pain over the past twenty years, and presented with persistent myalgia, fatigueability and creatine kinase (CK) increase. The duration of attacks (about 20/year) was 1-2 days; symptom-free intervals lasted up to 3 months. In his medical history there was no consanguinity, nor autoimmune or neuromuscular disorders. Neurological examination detected mild weakness of the leg muscles. Electrodagnostic studies showed normal nerve responses and myopathic changes bilaterally on anterior tibialis muscles. Laboratory investigations showed, during attacks, leukocytosis (15.65 x 10^9/mm^3), ESR 120 mm/hour (v.n< 25), CRP 4.13 mg/dl (v.n<0.5), CK 1465 U/l (v.n<170).

Acute phase serum amyloid A (SAA) was 141 mg/dl (v.n<0.5). CK decreased to 250 U/l between fever episodes. Kidney function, liver and urinary were normal. Antinuclear and antineutrophic cytoplasmic antibodies were absent. No cardiac abnormalities nor organomegaly were present.

PCR analysis for mutations in MEFV and TNFRSF1A genes identified a heterozygous K695R MEFV mutation. Fulfilling the Tel-Hashomer criteria, the patient was diagnosed with FMF (4).

Tibialis anterior muscle biopsy showed myopathic changes, sarcoclemmal deposits of the terminal complex of complement and amyloid deposition on endomysium and around vessels, confirmed by transmission electron microscopy (Fig. 1).

Colchicine treatment (1 mg/daily) was started and led to a complete resolution of fever attacks, thus confirming the clinical diagnosis of FMF, SAA decrease to normal values after 2 months and CK decrease to 250 U/L. Skeletal muscle involvement in FMF is rarely reported as protracted febrile myalgia (5). CK elevation, is to be investigated in FMF, for a possible AM.

Proximal weakness is the most common clinical presentation of AM (2, 7), though distal weakness, as in our patient, and nodules within muscle are also recognized (2). Respiratory muscles involvement is sporadic; macroglossia and muscle pseudo-hyper trophy are characteristic but inconsistent features (2, 7).

Unusual phenotypes, with a slow evolution over decades, are described in juvenile cases (2). A significant CK increase, as in our report, occurs in 3% of cases and rhabdomyolysis is described (2, 3).

Histopathology shows amyloid deposits in perimysium/endomysium, as well as surrounding vessels and myopathic changes of variable severity with possible neurogenic changes and inflammation (1, 2, 7). The mechanisms of myofiber damage are not fully elucidated; they may involve ischemia, impaired diffusion of nutrients, sarcoclemmal dysfunction or disruption (8).

Cytotoxicity of the complement cascade is also suggested by sarcoclemmal localization of the terminal complex on non-necrotic fibers (3). AM can be the first or rarely the only organ manifestation of genetic transthyretin (7) or gelsolin (1) amyloidosis and AL systemic amyloidosis (2, 7). Speculating why AM occurred in our patient, the prolonged diagnosis delay (20 years) and the subsequent lack of treatment may have been determinant. Country of origin, M694V homozygous mutation, disease duration, and consanguinity are risk factors for development of renal amyloidosis in FMF (9, 10). It is yet to be determined if these factors, or different MFEV mutations, may also be relevant to other organ localisations, such as AM. However, it has been proposed that selective tissue deposition of amyloid may depend on the types or folding of amyloid proteins and AA type might have a low affinity to skeletal muscle (11). Our case suggests that AM may occur as a presenting manifestation of amyloidosis in FMF, therefore we propose that clinical involvement of skeletal muscle, with CK elevation, is to be investigated in FMF, for a possible AM.

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References