

Hereditary Gelsolin Amyloidosis: A New Japanese Case with Cutis Laxa as a Diagnostic Clue

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Accepted September 6, 2010.

Hereditary gelsolin amyloidosis (1), also known as familial amyloidosis of the Finnish type (FAF) or familial amyloid polyneuropathy type IV, is a very rare disease that normally occurs in Finland. Only four affected families have previously been identified in Japan (2–5). In our patient, the characteristic cutaneous presentation of cutis laxa served as a major clue to the diagnosis of FAF.

CASE REPORT

A 65-year-old Japanese man became aware of loose skin on his face in his forties. Prominent around the mouth and eyes, it progressed gradually with slight muscle weakness. He had consulted a neurologist two decades ago, but the results of needle electromyography performed at that time were negative. He subsequently became aware of reduced sweating in hot weather, and pruritus of the extremities that worsened in winter. On physical examination, he had atrophic skin, and presented a facial appearance of bilateral blepharochalasia, sagging and loose cheeks, and drooping lips (Fig. 1a). After pinching for a minute, the facial skin retained its deformed position (Fig. 1b). The patient complained of water occasionally spilling out of his mouth when he drank. He had macroglossia with a central furrow (Fig. 1c). His back also showed slightly diminished elasticity, but was much less severely affected than his face. His dorsal hands showed pigmentation, purpura, and multiple tiny scars caused by minor mechanical traumas (Fig. 1d).

Like two previously described FAF families (2, 3), his grandmother had originated from Nagano Prefecture. He himself had a daughter and son, who were 34 and 31 years of age, respectively. Thus far, they had not shown major neurological or cutaneous problems, although his daughter had complained of reduced sweating. He disclosed that his mother, who had died at the age of 83, and two of her eleven siblings, one male and one female, both of whom had died at the age of 78, had also suffered from similar laxity or muscle weakness of the facial skin. One of his

cousins, aged 72 and the daughter of the uncle mentioned above, had been followed by a neurologist in another hospital because of similar cutaneous symptoms and dysphagia. Although an electromyogram had revealed neurological change of her facial muscles, a diagnosis had not been made. A routine blood examination in our own patient, which assessed, among other things, renal function, was non-contributory. Biopsy specimens from the loose skin in the mandibular area and the back showed a normal epidermis and minimal perivascular inflammatory cell infiltration in the dermis. However, elastic fibre abundance was reduced, and the fibres that were present displayed abnormal fragmentation and conspicuous aggregation, especially in the lower reticular dermis of mandibular skin (Fig. 2a). The internal elastic laminae of the arteries were not affected. Congo red staining showed focal deposits of amyloid in the basement membranes of the epidermis, eccrine sweat glands and hair follicles, which produced red-green birefringence under polarised light (Fig. 2b). The results of immunohistochemical staining with an anti-gelsolin amyloid (AGel) antibody (Sigma-Aldrich, St. Louis, MO, USA) correlated with those of Congo red staining (Fig. 2c). Electron microscopic examination revealed non-branching amyloid fibrils (data not shown).

A slit-lamp ophthalmologic examination revealed bilateral corneal lattice dystrophy, despite the absence of visual disturbances. Neurological examination revealed slight weakness in the orbicularis oculi and orbicularis oris muscles. The patient also showed slight dysarthria and dysphagia, but otherwise presented with no muscle weakness or atrophy of the four limbs. He exhibited no sensory deficits or ataxia of any kind. In a nerve conduction study, a compound muscle action potential could not be evoked in the facial nerve. The early component of the blink reflex was minimal, and a delay in the late component was noted on stimulation of the right eye. Needle electromyography showed motor unit potentials of a long duration and high amplitude in the tongue and orbicularis oculi and orbicularis oris muscles. Finally, genetic analysis of a DNA sample extracted from peripheral leukocytes (5) revealed a heterozygous G654A gelsolin mutation (Fig. S1) (<http://adv.medicaljournals.se/article/abstract/10.2340.00015555-1011>).



Fig. 1. Clinical features of the patient. (a) Characteristic sagging cheeks and drooping lips. (b) Loss of elasticity of the skin, with retention of its deformed position after pinching. (c) Macroglossia and a central furrow. (d) The dorsal hand showing purpura and multiple tiny scars.

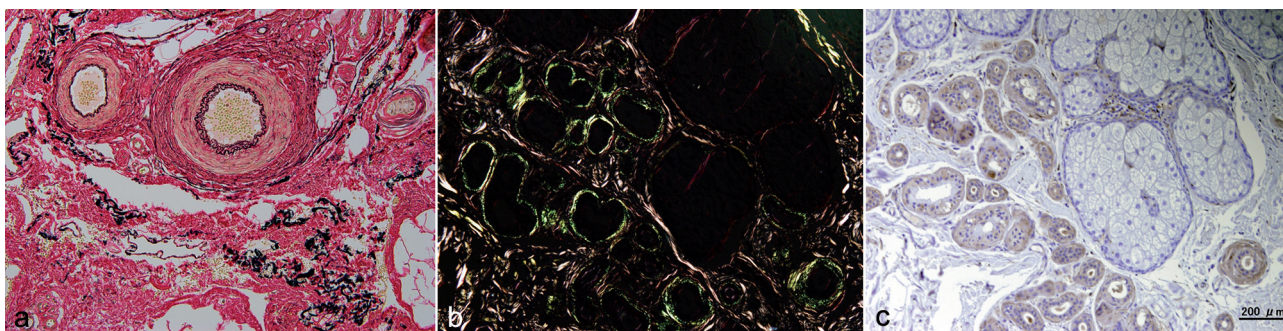


Fig. 2. Histopathological analysis of a biopsy specimen. (a) Aggregation of elastic fibres in the lower reticular dermis of mandibular skin (elastin staining, original magnification $\times 200$). Note the normal appearance of the internal elastic laminae of the arteries. (b) Red-green birefringence under polarised light after Congo red staining (original magnification $\times 200$). (c) Immunohistochemical staining of the basement membranes of eccrine sweat glands with an anti-gelsolin amyloid antibody (original magnification $\times 200$). Stained regions correspond to the Congo red-reactive deposits in (b).

DISCUSSION

FAF is characterised by a triad of ophthalmologic, neurologic and dermatologic findings (1). The G654A mutation in the *gelsolin* gene responsible for FAF is common to all Japanese and Finnish patients (6). Cranial neuropathy starts as facial nerve palsy that often becomes apparent in the fourth or fifth decade, before slowly progressing to involve other cranial nerves (1). Thus, the neurologic symptoms in our patient were mild for his age. With no visual disturbances, the dermatologic findings greatly assisted the correct diagnosis. Cutis laxa usually becomes apparent in the scalp and forehead in the fifth decade, and hanging of the eyelids, facial skin and/or lower lip in the sixth or seventh decade (1). The characteristic facial appearance is remarkably consistent, despite different ethnic origins (1, 7). It is not caused merely by facial palsy and muscle atrophy, and careful palpation is advisable to recognise cutis laxa.

Degeneration and abnormal aggregation of elastic fibres was clearly demonstrated by elastin staining of a biopsy specimen. Cutis laxa is often associated with decreased perspiration, dry, itchy skin, intracutaneous bleeding, loss of body hair, thinning of the eyebrows and scalp hair, and macroglossia (7). Our patient exhibited most of these symptoms. Of note, skin laxity was found to be relatively mild in areas other than the scalp and face, although amyloid deposits and elastic fibre degeneration were also detected histologically in skin from his back.

It is imperative to exclude other possible causes of cutis laxa. With familial clustering of cases, hereditary cutis laxa, which is caused by mutations in different genes and shows considerable heterogeneity, may initially be considered (8). Acquired cutis laxa may be generalised or localised. It usually develops in adulthood following episodes of inflammatory skin disease, hypersensitivity reactions to insect bites or drugs, or in association with particular diseases or haematologic malignancies, such as multiple myeloma and cutaneous lymphoma (9).

Localised acquired cutis laxa may be confined to the face (9). Interestingly, Van Gerpen et al. (10) reported a 55-year-old woman with progressive lower facial drooping, in whom electromyography revealed bilateral facial neuropathies. However, cutaneous T-cell lymphoma was diagnosed following analysis of a buccal biopsy.

The precise pathogenesis of elastolysis in FAF is not well understood. Gelsolin amyloid fibrils often encase elastic fibres, and elastic fibre-associated amyloid P component may act as a matrix for the assembly of these fibrils. Elastolysis may result from altered elastic fibrillogenesis or accelerated enzymatic degradation, while deposits of mutant *gelsolin* may alter the organisation of the elastin-associated microfibrils or other elastic fibre components. In addition, a direct toxic effect of amyloid fibril formation on tissues must be considered (7).

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