Amyloidosis-related nephrotic syndrome due to a G654A gelsolin mutation: the first report from the Middle East

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Introduction

Several genetic mutations are associated with nephrotic syndrome, including those of genes producing proteins nephrin, podocin, alpha actinin-4, an adapter protein anchoring CD-2, canonical transient receptor potential-6 and laminin beta-2 [1]. A G654A gelsolin gene mutation has also been found to be associated with severe nephrotic syndrome in homozygote patients [2]. Such a mutation results in the formation of a conformationally abnormal gelsolin protein [3,4]. Impaired gelsolin function together with the generation of the amyloidogenic peptides by the cleavage of the mutant gelsolin causes a constellation of manifestations referred to as gelsolin-related amyloidosis, AGel amyloidosis or originally as familial amyloidosis, Finnish type [5]. The authors believe that referring to this disease as being solely an amyloidosis undermines some of its important pathogenic aspects. Because impaired gelsolin function is thought to play a critical role, even before amyloidogenesis, in the course of this disease, we used the term gelsolin dystrophy and amyloidosis disorder (GDAD) throughout this article. GDAD is an autosomal dominant systemic disorder with complete penetration, first described by Joko Meretoja in Finland in 1969 [6]. The cardinal clinical manifestations of GDAD are corneal lattice dystrophy, progressive cranial and peripheral neuropathy and cutis laxa, although every body organ could be affected [5–7]. Less frequent manifestations of this disease include, but are not limited to, macroglossia, endocrinopathies, osteoporosis, gait ataxia, autonomic dysfunction, cardiomyopathy, glaucoma and cataract [5,6]. Renal involvement is occasionally seen in GDAD, which usually manifests as intermittent proteinuria [6,7]. The disease was first considered to be limited to Finland. However, several kindreds were later found in other parts of Europe; Denmark, the Netherlands, the former Czechoslovakia and the United States and Japan [5]. The large area between the Far East and Europe, Africa and South America had no record of GDAD.

We report a patient with amyloidosis who presented with a nephrotic syndrome. Further investigations revealed a G654A gelsolin mutation and led to the discovery of a large Iranian family with GDAD. We believe that attention to this particular case may aid clinicians abroad in the identification of this under-diagnosed entity.

Case report

A 25-year-old single woman from Bonab, East Azerbaijan, a northwest province of Iran, was admitted to our university hospital for 4 weeks with periorbital and lower extremity oedema. Past medical history revealed poor night vision for 2 years. Family history was remarkable for a brother who had proteinuria, end-stage renal disease, an unknown retinal disorder and facial nerve paresis; two sisters with poor night vision and facial nerve paresis and the father, who was blind. Physical examination revealed a young woman who was alert and oriented, in no acute distress. Blood pressure was 120/80 mmHg and pulse rate was 70 per minute. Body temperature was 37.3°C. A moderate pitting oedema was found on both lower limbs. The skin of the forehead was thickened and coarse. A mask-like facial expression and facial flushing was notable. There was a considerable atrophy of the buccal musculature, which was associated with roughened facial skin folds and deepened nasolabial furrows. A mild blepharochalasis and shallow epicanthal folds also were found.

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The thyroid gland was diffusely enlarged. Slit lamp examination revealed a bilateral peripheral lattice line in the cornea and a posterior subcapsular cataract. Fundal examination showed bony spicule-like retinal pigmentations (Figure 1) and arterial narrowing that was consistent with retinitis pigmentosa (RP). Neurological examination revealed a right upper facial nerve paresis, decreased corneal sensation and fine fasciculations over the frontal muscle as well as a horizontal unidirectional nystagmus. Peripheral nerve examination revealed a distal sensory neuropathy with predominant affection of the vibratory sensation in the lower extremities.

Laboratory findings included a white blood cell (WBC) count of $8.7 \times 10^9/l$, haemoglobin of 13 g/dl, haematocrit of 38% and platelet count of $238 \times 10^9/l$. Serum creatinine and blood urea were 0.8 and 24 mg/dl, respectively. Serum triglyceride level was 129 mg/dl and cholesterol level was 201 mg/dl. Blood calcium and phosphorus level were 8.5 and 4.2 mg/dl, respectively. Fasting blood sugar was 70 mg/dl. Urinalysis showed a marked proteinuria, WBC of 56 per high power field. No haematuria or red blood cell/granular casts were found. Subsequently, a 24-h urine examination revealed a proteinuria of 3624 mg/day. Thyroid function tests revealed a total T4 level of 11.3 ng/ml (normal 4–12 ng/ml), total T3 of 1.0 ng/dl (normal 0.5–1.5 ng/l), thyroid-stimulating hormone of 32 μIU/ml (normal 0.4–5 μIU/ml), which were consistent with a subclinical hypothyroidism. Serological (antinuclear antibody, anti-double strand DNA, C3, C4, CH50, P- and C-antineutrophil cytoplasmic antibody) and viral (hepatitis B and C) markers for secondary glomerulonephritis were all negative. Visual evoked potential revealed bilateral optic nerve axonal involvement. Facial nerve conduction velocity exam demonstrated facial nerve axonal degeneration.

A renal biopsy was performed that on light microscopic inspection revealed a heavy deposition of pink amorphous material within the glomeruli, significant obliteration of the capillary loops and occasional thickening of the capillary basement membranes. Interstitium had foci of foamy histiocytes and a mixed inflammatory infiltrate. Renal tubuli and vasculature appeared normal. Congo red and periodic acid-Schiff stainings were unrevealing. Immunofluorescence study was also negative for any immunoglobulin or complement deposit within the glomeruli. Electron microscopic analysis was performed by Prof. M. Kashgarian, Yale School of Medicine, which revealed mesangial matrix deposits of non-branching fibrils of ~10 nm diameter consistent with amyloidosis (Figure 2). The amyloid tended to deposit in a nodular fashion with resultant bulging on...
the endothelial side (Figure 2). The capillary loops were patent. There was diffuse effacement of the foot processes.

Considering the patient’s family history and a history of peripheral nerve involvement, a presumptive diagnosis of familial renal amyloidosis was made and the patient’s DNA, extracted from the peripheral leukocytes, was sent to University of Helsinki, Finland for genetic analysis. Analysis of this DNA material revealed a G654A gelsolin mutation (see references 18 and 20 for more detailed information on the laboratory method) that was identical to a Finnish patient with GDAD. The patient was homozygote for this mutation. The diagnosis of GDAD was made. A survey of her family revealed that several members of the family had been suffering from various systemic manifestations characteristic for GDAD as well as RP (unpublished data). The genetic analysis of some of the afflicted patients was also positive for G654A gelsolin mutation (unpublished data).

Discussion

This report demonstrates the first case of GDAD in an Iranian family. In the present case, the renal biopsy examinations for an unexplained nephrotic syndrome and a subsequent genetic analysis led to the diagnosis of this entity. The first manifestation of this disease is corneal lattice dystrophy in the third decade of life [5–7]. The neuropathies and loose skin appear later [6]. The present patient had the cardinal manifestations of GDAD. However, to our knowledge, the retinal involvement as RP has not been previously reported in such patients. A false negative result on a conventional Congo red staining has once been reported by Maury [3] in a GDAD patient.

Gelsolin is a calcium- and polyphosphoinositide-regulated actin-modulating protein encoded by a locus on chromosome 9 at q32-q34 [3]. Circulating gelsolin is believed to take part in the clearance of actin filaments [3]. Guanine to adenine or very rarely, thymidine transversion at nucleotide 654 of gelsolin gene (G654A or G654T gelsolin mutation) causes, respectively, asparagine or tyrosine for aspartic acid substitution at codon 187 corresponding to position 15 of the mutant gelsolin [2,8]. Such amino acid substitution favours trypsin-like protease (Furin, a-gelsolinase) activity over the gelsolin molecule, which leads to the deposition of gelsolin fragments as amyloid plaques [3,4]. Chen et al. [9] revealed that the mutant gelsolin is unable to bind calcium, which renders it susceptible to furin cleavage within the trans-Golgi network. The two main accumulating amyloid peptides in GDAD correspond to the fragments of circulating gelsolin at the amino acid sequences of 173–243 and 173–225 [3].

Meretoja et al. [7] mentioned that ‘since hereditary amyloidosis is most probably a metabolic defect, it should affect all the defective cells simultaneously and lead to an even distribution of amyloid in the glomeruli’. They distinguished this type of familial amyloidosis, GDAD, from secondary amyloidosis, which is associated with huge homogenous deposits and hypothesized that amyloid fibrils are synthesized by renal mesangial cells [7]. Our findings indicate that the amyloid fragments tended to deposit in a nodular fashion within the glomerular basement membrane.

Renal disease such as nephrotic syndrome and as serious as end-stage renal disease is an under-addressed issue among GDAD patients. One out of four patients originally reported by Meretoja et al. [7] had a proteinuria of about 9 g/day. These authors found numerous vacuoles containing dark lamellar bodies within the cytoplasm of glomerular cells in this patient. They suggested that these structures may be of a mitochondrial origin [7].

A unique feature of the present case is the occurrence of RP in GDAD. Several other afflicted members of the patient’s family were also found to have RP (unpublished data). Hence, this association does not seem to be accidental. We believe that this is the first report of such an association. The combination of renal diseases and RP is rare and has been described in few genetic disorders. These include Senior–Loken syndrome (RP and juvenile nephrophthiasis), Alagille syndrome (RP and renal dysplasia), Bardet–Biedl syndrome (RP and renal malformation), Alstrom syndrome (RP, sensorineural hearing loss and progressive renal failure), Sensenbrenner syndrome (RP and interstitial nephritis) and a rare syndrome of glomerulocystic disease and RP [10,11].

Finally, we believe that GDAD is an under-diagnosed entity worldwide. A thorough knowledge of its clinical manifestations and potential complications is useful for clinicians abroad. Retinal involvement such as RP should also be considered in the clinical spectrum of this disorder. Although corneal dystrophy, peripheral neuropathy and cutis laxa are the hallmark of GDAD, nephrologists should be aware of proteinuria and nephrotic syndrome as the presenting features of this disease in a young and homozygote patient when other manifestations are minimal.

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Conflict of interest statement. None declared.

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Gelsolin dystrophy and amyloidosis disorder