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A case report of hereditary apolipoprotein A-I amyloidosis associated with a novel APOA1 mutation and variable phenotype

Birgitte G. Tougaard [a, *], Katja Venborg Pedersen [c], Søren Rasmus Krag [b], Janet A. Gilbertson [d], Dorota Rowczenio [d], Julian D. Gillmore [d], Henrik Birn [a]

[a] Department of Renal Medicine, Aarhus University Hospital, Aarhus, Denmark
[b] Department of Pathology, Aarhus University Hospital, Aarhus, Denmark
[c] Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark
[d] National Amyloidosis Centre, UCL Division of Medicine, Royal Free Hospital, London, United Kingdom

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ABSTRACT

Apolipoprotein A-I (apo A-I) amyloidosis is a non-AL, non-AA, and non-transthyretin type of amyloidosis associated with mutations in the *APOA1* gene inherited in an autosomal dominant fashion. It is a form of systemic amyloidosis, but at presentation, can also mimic localized amyloidosis. The renal presentation generally involves interstitial and medullary deposition of apo A-I amyloid protein. We describe the identification of apo A-I amyloidosis by mass spectrometry in a 52-year old male, with no family history of amyloidosis, presenting with nephrotic syndrome and associated with heterozygosity for a novel *APOA1* mutation (c.220 T > A) which encodes the known amyloidogenic Trp50Arg variant. Renal amyloid deposits in this case were confined to the glomeruli alone, and the patient developed progressive renal impairment. One year after diagnosis, the patient had a successful kidney transplant from an unrelated donor. Pathogenic mutations in the APOA1 gene are generally associated with symptoms of amyloidosis. In this family however, genotyping of family members identified several unaffected carriers suggesting a variable disease penetrance, which has not been described before in this form of amyloidosis and has implications when counselling those with *APOA1* mutations.

1. Introduction

Amyloidosis is characterized by extracellular deposition of insoluble protein and peptides. Accumulation of amyloid in tissues, as well as oligomers of amyloid protein may cause organ damage, and if affecting the kidney, often is associated with progression to end stage renal disease (Bergesio et al., 2008).

Hereditary amyloidosis is caused by mutations in specific, protein encoding genes leading to misfolding and aggregation of the protein. Several proteins have been identified including fibrinogen A-α chain (Benson, 2003) transthyretin (Ando et al., 2013), apolipoprotein A-I (apo A-I) (Obici et al., 2006), apolipoprotein A-II (apoAII) (Yazaki et al., 2001), lysosome (Booth et al., 1995) and gelsolin (Benson, 2003).

Mutations in the *APOA1* gene are associated with autosomal dominant inherited amyloidosis (Van Allen et al., 1969). To date, 20 different amyloidogenic mutations in *APOA1* are listed in the Human Genome Database (HGMD: http://www.hgmd.cf.ac.uk/ac/index.php; accessed on June 2015). The majority of these are missense/nonsense mutations but small deletions/insertions have also been reported. The *APOA1* gene mutations are associated with systemic amyloidosis, but can initially present as localized disease, particularly in the larynx and skin. Multiple organs including liver, kidneys, peripheral nerves, gastrointestinal tract, testes, spleen, heart, larynx, and skin may be involved. The clinical presentation varies from severe and progressive cardiac failure at the age of 20 and death in the late 4th decade, to late onset disease presenting in the 5th decade with gradually progressing renal failure. Renal involvement is common and most often characterized by amyloid deposition in the medullary interstitium and/or vasculature. In most cases of apoAI amyloidosis caused by *APOA1* mutations, there is a prior family history of similar disease (Table 1) and so far, unaffected mutation carriers have not been described (Eriksson et al., 2009).

* Corresponding author. Department of Renal Medicine, Aarhus University Hospital, Brendstrupsgaardsvej 100, DK-8200, Aarhus N, Denmark.
E-mail address: bgtougaard@gmail.com (B.G. Tougaard).

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2. Results

A 52-year old Danish male with no family history of renal disease presented with hypertension, renal insufficiency, and nephrotic syndrome. At presentation, he had an eGFR of 36 ml/min/1,73 m^2 and proteinuria in the range of ~7 g/24 h. A kidney biopsy revealed amyloid with extensive glomerular involvement (Fig. 1A). Immunostaining for serum amyloid A protein (SAA), kappa and lambda immunoglobulin light chains and transthyretin were all negative. A bone marrow aspirate and trephine biopsy were normal without clonal plasma cells or amyloid. Nerve conduction studies were normal and cardiac investigations, including echocardiography and cardiac biomarkers did not suggest cardiac infiltration by amyloid. Proteomic analysis of microdissected amyloid deposits from a kidney biopsy revealed large amounts of apoAI, which scored as number one, in conjunction with the amyloid 'signature' proteins serum amyloid P component and apolipoprotein E (Fig. 1D). Simultaneously, specific staining of glomeruli with antibodies against apoAI (Fig. 1B) also confirmed the presence of apoAI protein. Subsequent sequencing of *APOA1* revealed heterozygosity for a mutation encoding the Trp50Arg variant, c.220 T > A (cDNA reference sequence NM_000039.1). No mutations in other amyloid genes were identified. Except for paresthesia, there were no symptoms of extra-renal involvement by amyloid. Serum amyloid P component (SAP) scintigraphy revealed a large total body amyloid load with deposits in the liver, spleen, and kidneys (Fig. 1C). Despite treatment, including an angiotensin II receptor blocker and a statin, significant albuminuria persisted and kidney function declined to end-stage kidney disease within 10 months of diagnosis. Genetic analysis of the patient's family identified the mother, two older brothers, and a younger sister as mutation carriers but with no symptoms or signs of amyloidosis. The proband received a

Table 1
Variants of *APOA1* mutations.

Variant (reference)	Age at presentation	Nephrotic range proteinuria	Organs involved	Amyloid deposits in kidney biopsy	Outcome
Gly26Arg (Van Allen et al., 1969), (Nichols et al., 1988), (Vigushin et al., 1994)	20–46/+FH[1]	No	Kidneys, liver, Peripheral nerves, spleen, GI tract	Extensive and diffuse peritubular and interstitial amyloid deposits in cortex and medulla. No glomerular deposits.	Slowly progressing CKD and ESRD within 10–20 years. Excellent outcome after K-TX.
Glu34Lys (Rowczenio et al., 2011)	29	No	Kidneys, liver, spleen	Location of amyloid within the kidney not described.	Slowly progressing CKD
Trp50Arg (Booth et al., 1995)	34–35/+FH	No	Kidneys, liver, spleen, GI tract	Location of amyloid within the kidney not described.	Progressive CKD. Died 10 years after presentation and two months after K-TX from CMV infection and liver failure.
Trp50Arg (Current case)	50	Yes	Kidneys.	Amyloid deposits only in glomeruli	Progressive CKD, ESDR 9 months after pressentation.
Leu60Arg (Soutar et al., 1992)	20–60/+FH	No	Kidneys, liver, spleen, testes, heart	Location of amyloid within the kidney not described.	Death at 35–65 years of age and up to 12 years after presentation. Splenectomy. H-TX and K-TX.
Leu60-Phe71delins 60Val_61Thr (Booth et al., 1996)	35–45/+FH	No	Liver, kidney, spleen	Diffuse interstitial amyloid limited to medulla (autopsy).	Slowly progressing lever disease in 15–20 years. Death at 48–66 years of age of liver failure.
Leu64Pro (Murphy et al., 2004)	58 + FH	Yes	Kidneys, liver, spleen,	Amyloid deposits in glomeruli, interstitium and vessels	ESRD 1 year after presentation. Good outcome with K-TX.
Glu70_Trp72del (Persey et al., 1998)	18–21/+FH	Yes	Kidneys, liver, spleen, choroid vessel	Location of amyloid within the kidney not described.	ESRD 5 years after presentation. The renal graft continues to function after 17 years.
Phe71Tyr (Rowczenio et al., 2011)	51	No	Liver and palate	Not reported	Short follow-up.
Asn74Lysfs (Eriksson et al., 2009)	48	No	kidneys, uterus, ovaries, pelvic lymph nodes, GI tract	Not reported	Not described.
Leu75Pro (Coriu et al., 2003), (Eriksson et al., 2009), (Gregorini et al., 2005)	42–70/+FH	No	Kidneys, liver, testes	Medullary deposition of amyloid	Slowly progressing liver disease and CKD. Death at 67–90 years of age.
Leu90Pro (Hamidi Asl et al., 1999)	37–51/+FH	No	Skin, heart, larynx	Not reported	Progressive cardiac failure. Death at 41–70 years of age.
Lys107Del (Amarzguioui et al., 1998)	45	No	Aortic intima amyloid	Not reported	Coronary heart disease at early age. CABG at 48 years of age. Died at 68 of age.
Ala154fs (Eriksson et al., 2009)	58	Yes	Kidneys	Glomerular amyloid deposits.	Not described
His155Metfs × 46 (Rowczenio et al., 2011)	77/+FH	Yes	Kidneys	Glomerular and interstitial deposits of amyloid	CKD. Not further described
Arg173Pre (Hamidi Asl et al., 1999)	20–45/+FH	No	Kidneys, skin, heart, larynx	Location of amyloid within the kidney not described.	Progressive cardiomyopathy and CKD. Death at 52 years of age.
Leu174Ser (Obici et al., 1999)	42–45/+FH	No	Skin, testes, heart, larynx, peripheral Nerves	Not reported	Progressive cardiomyopathy. Death at 50–52 years of age.
Ala175Pro (Rowczenio et al., 2011)	38	No	Larynx, testes	Not reported	No progression of organ damage at age 42.
Leu178His (Hazenberg et al., 2009)	34/+FH	No	Larynx, Skin, heart, peripheral? nerves	Not reported	Progressive cardiomyopathy. Death at 39 years of age.

Summary of reported findings and outcome in amyloidosis associated with *APOAI* gene mutations and variants in the mature apoA1-protein. Cases with nephrotic proteinuria are highlighted in gray. FH = family history reported, GI = gastro-intestinal, K-TX, and H-TX = kidney, and heart transplantation, respectively, CKD = chronic kidney disease, ESRD = end stage renal disease.