Case Report

Alport syndrome and diffuse leiomyomatosis with major morbid events presenting at adult age

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Introduction

Alport syndrome (AS) is a familial nephropathy characterized by: (1) a history of haematuria with or without chronic renal failure; (2) ultrastructural evidence of irregular thickening or thinning of the glomerular basement membrane (GBM), and/or splitting of the lamina densa; (3) progressive bilateral sensorineural deafness for high tones and (4) ocular changes, including anterior lenticonus and retinal flecks [1–3]. According to Flinter et al., at least three of these four characteristics should be present to establish the diagnosis of AS in a family [4]. Conditions, such as hyperprolinaemia, hyperaminoaciduria, ichthyosis, development of serum antithyroid antibodies, hypoparathyroidism, serum IgA deficiency, granulocyte inclusions, or macrothrombocytopenia have been reported in association with AS [1,2].

AS with diffuse leiomyomatosis (ASDL) is defined by the association of AS with oesophageal, gastric, vulvovaginal, and bronchial leiomyomas, and clitoreal hypertrophy [5].

ASDL was first recognized as a specific clinical entity by Garcia-Torres and Guarner in 1983 [6]. Since then, a number of clinical reports have been published, mainly in the paediatric literature [6–20], which usually focus on a particular aspect of the disease, such as ophthalmological [14] or radiological changes [17,18] or surgical aspects [7,8,13]. Little attention in the medical literature concerning adult patients has been paid to the clinical history of ASDL [7,14,16]. As a consequence, ASDL may remain unnoticed when patients present with this syndrome at a more advanced age. However, a timely diagnosis is important, in view of the morbidity and the inheritance characteristics of the disease.

In this paper we report a family with at least four members affected by ASDL and with clinical manifestations presenting mainly during adulthood. The variable clinical expression—even within the same family—is illustrated. The clinical findings are correlated with the present knowledge on genetic and pathophysiological aspects of ASDL.

Case reports

Patient 1. (III,5) (the index patient) is a young woman, born in 1974, who at age 16 presented in the department of nephrology because of haematuria (>200 RBC/HPF). She developed dysphagia for solid food and nausea without vomiting in 1987. Her family history was positive for dysphagia and nephropathy (Figure 1).

Fig. 1. Pedigree of the present family. Squares = males; circles = females.
Clinical examination and biochemical analysis of the blood, including renal function tests, were normal. Proteinuria was 0.7 g/24 h. The urinary sediment contained 20 RBC/HPF without leukocyturia. Endogenous creatinine clearance was 113 ml/min. A chest X-ray suggested a right paracardiac mass. A barium swallow study showed narrowing of the distal oesophagus with distension of the upper segment (Figure 2). These radiological findings, together with the results of endoscopy and manometry, were found compatible with achalasia. Computerized axial tomography of the chest confirmed the oesophageal dilatation; in addition, displacement of the distal lumen from the midline to the right with filiform luminal narrowing due to the presence of a tumoural mass with focal zones of wall thickening, was observed (Figure 3). The tumour had a density of solid tissue and was located in the lower third of the oesophagus extending into the upper portion of the stomach. Echography of the kidneys and audiometry were normal. Ophthalmological investigation revealed congenital cataract and pronounced thickening of both lenses. A renal biopsy showed non-specific findings on light-microscope examination. Electron-microscopy disclosed irregular thickening of the glomerular basement membrane with splitting of the lamina densa (Figure 4A). Immunofluorescence was negative. Based on these data, the diagnosis of Alport syndrome was established.

In July 1991 a thoracotomy was performed for enucleation of a tumour (20 × 15 cm) in the lower oesophagus, which extended over a length of 10 cm in the upper stomach; an antireflux procedure (according to Belsey) was performed. Histological studies revealed an irregular pattern of smooth muscular bundles with benign appearance, compatible with the diagnosis of leiomyoma (Figure 4B). After a few months, the patient developed severe complaints of pyrosis and dysphagia. Reflux oesophagitis was discovered endoscopically, refractory to ranitidine (150 mg bidaily) and to omeprazole (20 mg daily); the patient became only asymptomatic with high doses of omeprazole and cisapride. In January 1992, a new antireflux intervention (fundoplication according to Toupet) with supraselective vagotomy was performed. Relapse of reflux oesophagitis necessitated again maximal combined pharmacological treatment. In May 1993, total oesophagectomy was performed with gastric pull-up (three-field technique). Since then the patient has been free of dysphagic complaints.

In April 1992 three vulvar leiomyomas were resected. Molecular studies in this patient demonstrated a deletion of the 5∞ part of the COL4A5 gene, extending into the COL4A6 gene, with deletion of exons 1 and 2, the deletion breakpoint being localized in intron 2 of the COL4A6 gene [21].

Until now, renal function remains normal, although haematuria and proteinuria persist.

Patient 2. (II,3), born in 1948, is the mother of the index patient. She had complaints of dysphagia with...
COL4A5 and COL4A6 genes as the lesion found in her daughter (patient 1) [21].

Besides her daughter, patient 2 has one son, born in 1972, who is in good health with a normal urinary sediment. He has no gastrointestinal, auditory, or visual complaints.

**Patient 3.** (II,2), born in 1946, is the uncle of the propositus. He developed recurrent bronchitis, dysphagia with retrosternal pain and frequent vomiting during childhood. He needed a dental prosthesis at the age of 4. Proteinuria and haematuria were detected at the age of 5. He developed progressive renal failure from 1958 and had end-stage renal disease at the age of 23 (serum creatinine 18 mg/100 ml). Bilateral cataract and bilateral high-tone sensorineural hearing loss were observed. The diagnosis of AS was retained based on the clinical and biochemical findings. Barium studies of the oesophagus revealed marked distension of the distal part with delayed transit to the stomach. A renal transplantation was performed in March 1970; the patient died from fungal peritonitis 3 months later, despite adequate graft function.

**Patient 4.** (I,2) born in 1923, is the grandmother of the propositus. She complained of dysphagia since her youth, but never had specific investigations until recently, at age 71, when her clinical condition deteriorated. A weight loss of more than 15 kg in 12 months, due to extreme dysphagia for solid food was observed. A barium oesophagogram disclosed a mega-oesophagus with narrowing of the distal part. The patient refused further examinations as well as surgical treatment. Serum creatinine has been normal up to now; urinary analysis could not be obtained. Her.

Fig. 4. A. Electron-micrograph of renal biopsy in patient 1 (III,5): parents, four brothers and one sister all lived into their seventies without clinical problems that could be split into two layers (*) (uranyl acetate, ×4000). B. Light-micrograph of oesophageal leiomyoma: irregular and disorderly arrangement of smooth muscular bundles with benign appearance (Trichrome, ×25).

Discussion

In this paper we present a family with clinical manifestations of ASDL in at least four members in three generations (Figure 1).

The present family conforms with the diagnostic criteria of AS, as proposed by Flinter et al. [4]. More severe expression of renal disease was observed in male versus female family members, as is currently observed in X-linked disorders. In contrast, the symptoms of oesophageal leiomyomatosis were as severe in the three female patients as in the male patient. This suggests that oesophageal involvement is fully expressed in females, with complete penetrance, in contrast to manifestations of renal disease, which are in general more pronounced in men [22].

The mother of the propositus (patient 2) showed no proteinuria and only sporadic haematuria. It should be remembered that in women with AS, renal involvement can be mild or even absent. At least one female has been reported who presented with DL but without signs of nephropathy, in whom the molecular gene
Alport syndrome and diffuse leiomyomatosis at adult age

defect associated with ASDL was found, thus establishing that this patient was a carrier of AS [22].

Most of the ASDL patients reported so far needed surgical interventions during childhood [6,9,11–13, 15–16,18–20]. In contrast, in the index patient and her mother, surgery was performed only at the age of 17 and 30 years respectively, whereas the grandmother lived for more than 70 years without surgery. Also the only affected male (patient 3) had no surgical intervention for his oesophageal problems.

The diagnosis of oesophageal leiomyomatosis may be delayed or may be mistaken as achalasia, based on the clinical presentation and the results of radiographic studies, endoscopy, and manometry [5,13,15,18]. Computerized tomography is more appropriate to establish the diagnosis and to evaluate the extension of the leiomyomas, especially when they present as nodular masses. Diffuse invasion of the oesophageal wall by leiomyomatosis may be more difficult to recognize and the real extent may be underestimated.

In view of the important clinical and genetic implications, renal function and urinary status should be controlled in any patient with oesophageal leiomyomatosis. Conversely, the possibility of ASDL should be considered in AS patients with dysphagia.

Potentially fatal pulmonary complications have been observed in several patients and were attributed to tracheobronchial localization of leiomyomas [6]. Recurrent bronchitis disappeared after oesophageal surgery in the mother of our index patient, suggesting that the pulmonary problems were due to aspiration pneumonia, secondary to the mega-oesophagus.

Better insights have recently been obtained in the genetics of AS and ASDL. X-linked inheritance is present in 85% of patients with classical AS [23]. AS is characterized by structural changes in the glomerular basement membrane, of which collagen type IV is the major component. Type IV collagen are molecules with a triple helical structure containing three polypeptides or α-chains. Six different α-chains, which differ considerably with respect to tissue distribution, have already been identified [24]. The α5(IV) and α6(IV) chains are encoded by the COL4A5 and COL4A6 genes, located in the Xq.22 region in a head to head configuration [21]. A range of deletions, point mutations and gene rearrangements in the COL4A5 gene have been identified in AS patients [25–27]. Mutations involving only the COL4A6 gene have not yet been reported.

Antignac et al. [19] and Zhou et al. [21] demonstrated that ASDL deletions including the 5′ region of the COL4A5 gene extended into the COL4A6 gene. Heidet et al. [28] reported the consistent presence of a deletion breakpoint in the second intron of the COL4A6 gene in seven patients with ASDL. The molecular studies performed in the present family disclosed similar findings. Hence, it has been hypothesized that mutations of the COL4A6 gene play an essential role in the development of leiomyomatosis. Recently, however, combined deletions in the COL4A5 and COL4A6 genes have been demonstrated in some patients with classical AS without leiomyomatosis. In some, the deletion included an even larger part of the COL4A6 gene than was seen in ASDL patients. It has therefore been suggested that localization of the breakpoint in intron 2 of the COL4A6 gene, as is the case in this family, is specifically related to the development of DL. It is thought that localization of the deletion breakpoint in intron 2 may trigger the activation of a cryptic promoter, resulting in the transcription of otherwise non-expressed sequences [28]. This mechanism may explain the high penetrance and similar phenotypic expression of DL in women and men.

Expression studies in fetal tissues of a 24-week-old human fetus showed the presence of an α5(IV) mRNA in the BM of most tissues, whereas α6(IV) mRNA was found only in meninges, oesophagus, choroid plexus, and stomach [21]. This tissue distribution may explain the clinical picture of ASDL, with leiomyomatosis of the oesophagus as an almost obligatory feature.

Bilateral congenital or juvenile cataract has been observed in a substantial number of patients with ASDL [5], although it is rare in classical AS [3,14]. In contrast to the nephropathy, the cataract may be severe in women as in men. The presence of cataract in ASDL is possibly also related to the specific localization of the deletion breakpoint in the COL4A6 gene, triggering the activation of a cryptic cataract-causing gene.

Several members in this pedigree developed severe early dental loss. In patient 3, a dental prosthesis was already required at the age of 4. As collagen type IV is present in the biochemical composition of the periodontal ligament [29], which is part of the tooth attachment apparatus, a structural defect of this collagen type may explain the early dental loss.

In conclusion, diffuse leiomyomatosis associated with AS is an X-linked genetic disorder with important clinical complications, in children as well as in adults. So far, this syndrome comes to attention mainly in the paediatric literature. The present report underscores the point that the first major morbid events of the disease may be delayed until adulthood. Patients with AS should be examined for signs of leiomyomatosis and vice versa. Genetic studies in this family have shed new light on the molecular basis underlying AS and DL as well as on tumorigenesis in general.

References


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