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Case Report

Spontaneous Subarachnoid Haemorrhage in an Adult with Alport's Disease: A Case Report and Review of the Literature -

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ABSTRACT

Aneurysmal subarachnoid haemorrhage constitutes a common clinic-pathological entity carrying significant mortality and morbidity. We present a 34-year-old patient with Alport's disease-induced chronic renal failure, presenting with a gradual loss of consciousness following a thunderclap headache, after a dialysis session. The patient's head CT scan showed a severe subarachnoid haemorrhage, with increased thickness of blood in basal cisterns and diffuse intraventricular haemorrhage. Her CTA revealed a fusiform aneurysm of the left vertebral artery. Bilateral ventriculostomies were inserted for controlling her increased intracranial pressure and her hydrocephalus, and was managed in the ICU. She finally passed away after developing diffuse cerebral edema. The potential role of type IV collagen deficiency along with the renin-angiotensin complex dysfunction of Alport's disease in the pathogenesis of the cerebral aneurysm is examined in our current report. The pertinent literature is reviewed with emphasis on the association of kidney diseases with the formation of intracranial aneurysms.

INTRODUCTION

Aneurysmal subarachnoid haemorrhage (aSAH) is a well-described clinic-pathological entity, which is associated with high mortality and poor outcome [1]. There is a difference in aSAH epidemiology throughout the world, and there are several adjusted population studies, which demonstrate quite variable rates [2,3]. A relatively recent systematic review revealed an increased aSAH incidence in Finland and Japan [4]. A nationwide study performed in the USA demonstrated an annual estimate of 14.5% discharges for aSAH per 100,000 adults [5]. However, this rate may be an underestimation, since 12-15% of patients suffering SAH die before even reaching the hospital [6,7]. The most common early risks associated with aSAH are a high re-bleeding risk, and vasospasm development and subsequent ischemia.

Various conditions have been shown to predispose to spontaneous SAH such as female gender, presence of a non-ruptured cerebral aneurysm (particularly those that are symptomatic, large, and are located either on the posterior communicating or the vertebra-basilar arteries), history of a previous SAH, familial history of cerebral aneurysms (at least one first-degree family member with an intracranial aneurysm, especially if two first-degree relatives are affected), and family history of aSAH [8,9]. Moreover, certain genetic syndromes, such as the autosomal dominant polycystic kidney disease, and the type IV Ehlers-Danlos syndrome have been associated with spontaneous SAH [10,11].

Alport syndrome is a basement membrane disorder, which presents with delayed onset and progressive glomerular dysfunction [12]. It has been associated with progressive sensorineural hearing loss, sometimes with retinal flecks, while more rarely with aortic aneurysms [12]. It is caused by mutations in type IV collagen genes, with approximately 85% of cases associated with mutations in the COL4A5 gene (X-linked), and the remaining cases associated with mutations in either the COL4A3 or the COL4A4 genes. It is well known that type IV collagen networks are the structural foundation for all basement membranes. There are six different genes encoding type IV collagen chains, which are designated as COL4A1-COL4A6 [13]. During the last few years, new insights on the pathophysiology of Alport's disease, imply that hypertension and especially the renin-angiotensin-complex may play a crucial role in the development of this clinical entity [14,15,16]. Interestingly, recent studies have revealed suspicious genetic polymorphisms in the renin-angiotensin-aldosterone complex, among patients suffering aSAH [17]. Therefore, an association between Alport's syndrome and aSAH may be possible, since there is a common ground in their underlying pathophysiological mechanisms.

In our current report we present a patient with Alport's syndrome, who suffered aSAH, and with this opportunity we review the pertinent literature.

CASE DESCRIPTION

After a routine dialysis session, a 33-year-old female with established Alport's syndrome presented to the ER with acute onset headache. The patient had a long history with Alport's disease diagnosed from early childhood. She had been on dialysis for the past ten years. Her past medical history revealed that she underwent kidney transplantation twice, because of graft failure the first time. She was not on anticoagulant therapy and she had received heparin after the dialysis session that evening. A few hours later that night she experienced an excruciating headache. This was followed by a rapid and dramatic deterioration of her level of consciousness, for which the patient was intubated on a Glasgow Coma Scale of 6/15, on an emergent basis. Her CBC and clotting studies were within normal limits. She had elevated urea and creatinine levels and the nephrologist on call consulted about handling properly hydration and medicine given according to her glomerular filtration rate. An emergent CT scan of the head was obtained, revealing a Fisher 4 diffuse subarachnoid haemorrhage, with an obstructed 4th ventricle and presence of blood into both the lateral and the 3rd ventricles, causing ventricular dilatation. The obtained CT angiogram, revealed a left vertebral artery fusiform aneurysm. Due to the eminent obstructive hydrocephalus and the need for intracranial pressure monitoring, bilateral External Ventricular Drains (EVDs) were inserted prior to her admission to the ICU. The patient was stable and the nephrologists recommended another dialysis session. One day later, she acutely deteriorated, her pupils became fixed and dilated, and she became highly hypertensive and tachycardic. We emergently obtained a new head CT scan, which revealed diffuse cerebral edema. The patient's family did not want any further interventions, and the patient passed away one day later (Figure 1).

DISCUSSION

Alport syndrome is a genetic disorder [18], affecting approximately 1 in 50,000 children, characterized by glomerulonephritis, end-stage kidney disease, and hearing loss [19]. It may also affect the eyes, although the underlying changes do not usually affect the patient's sight, except when changes to the lens occur in later life. The presence of blood in the urine is a universal feature of the Alport syndrome. Proteinuria constitutes another feature of this syndrome, as the

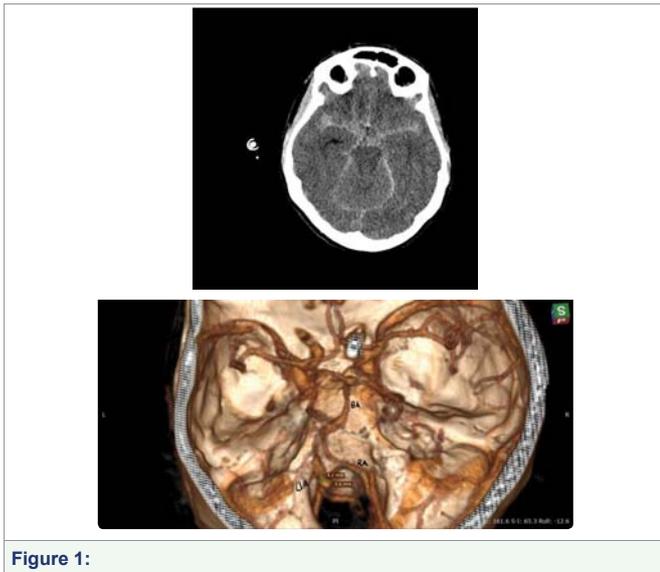


Figure 1:

underlying kidney disease progresses. It is an X-linked disease in most of the affected patients (85%), and renal transplantation is necessary in the vast majority of cases.

Alport's disease is a genetic disease, associated with collagen type IV deficiency, which affects the vessel wall, and this has a multi-systemic effect. One of the key pathophysiological components of the Alport syndrome is the type IV collagen deficiency, which causes a basement membrane defect, and is responsible for the associated kidney failure.

Numerous theories have been proposed for the pathophysiological explanation of cerebral aneurysm formation. It is generally accepted that collagen plays a fundamental role in preserving the vessel wall integrity. A growing body of evidence supports the concept that cerebral aneurysm formation may well be associated with an altered DNA translation process, affecting the collagen formation, and thus the integrity of the cerebral vessel walls.

To our knowledge this, is the first time an adult patient with Alport's disease presents with aSAH. There is another case described 17 years ago with an aSAH in an adolescent suffering from Alport's [20]. Moreover, another case of a patient with Fabry's disease, a genetic kidney disease, who died of aSAH due to a fusiform basilar artery rupture, has also been reported. In our current report the type IV collagen deficiency associated with the Alport syndrome may also be responsible for the cerebral wall deficiency, which could be implicated in the cerebral aneurysm formation. It is known that various collagen deficiencies have been associated with cerebral aneurysms. There were implications in the literature that a collagen-deficiency pathophysiologic process might be the common underlying mechanism of polycystic kidney disease and cerebral aneurysms. Furthermore, it has been demonstrated that people with long-standing hypertension have a bigger chance of suffering a SAH compared to normotensive controls. It has been postulated that the renin-angiotensin-aldosterone complex may have an impact on cerebral aneurysm formation.

Interestingly, patients with kidney diseases affecting the glomerular membrane may be the perfect population for further studying in regard to the exact role of the collagen deficiencies and/or of the renin/angiotensin complex in the cerebral aneurysm

pathogenesis [21]. Further data are necessary in order to establish a possible pathophysiologic mechanism between kidney diseases and cerebral aneurysms. Until then, the controversial issue of screening for cerebral aneurysms the patients with kidney diseases will be remaining unresolved.

CONCLUSIONS

This is the first, as far as we know, report of a ruptured cerebral aneurysm in an adult patient with Alport's syndrome. In this case, the type IV collagenopathy of Alport's syndrome, the long-standing hypertensive effect, and the renin-angiotensin genetic defects may have contributed to the pathogenesis of her intracranial aneurysm. It may be considerable to establish a screening process for intracranial aneurysms among patients with chronic kidney disease.

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