A child with familial glomerulonephritis

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A child with familial glomerulonephritis: Answers

1. Alport syndrome, despite the negative results given by the genetic test, seemed the most likely diagnosis given the patient's family history and the early onset of the symptoms both in the child and his mother [1]. Alport syndrome should be strongly considered in the event of persistent glomerular haematuria during the first years of life, particularly if the family history presents cases of chronic glomerulonephritis and/or renal failure without other causes or when the characteristic clinical features (hearing loss, lenticonus or retinopathy) are present [2]. As reported in the latest guidelines by Savige and colleagues (2019), the diagnosis is confirmed by the presence of lamellated glomerular basal membrane (GBM) in the examination of the renal biopsy under an electron microscope or by pathogenic mutations detected by genetic testing (one deleterious mutation in the COL4A5 gene, two in the COL4A3 or COL4A4), which has been reported to be at least 90% sensitive for X-linked Alport syndrome [3]. Furthermore, since the mother's diagnosis of mesangial proliferative glomerulonephritis was obtained by examining renal biopsy tissue, Alport syndrome cannot be excluded as the actual diagnosis, especially if the biopsy examination was conducted without the use of an electron microscope. As a matter of fact, both mesangial proliferative glomerulonephritis (MsPGN) and focal and segmental glomerulosclerosis (FSGS) were shown to be the most commonly misdiagnosed glomerulonephritis (26.9% and 19.2% of cases respectively) [4].

2. We therefore decided to perform a cutaneous biopsy. Immunofluorescence performed on the skin sample showed the complete absence of the α5-chain of type IV collagen, as typically found in X-linked Alport syndrome patients (Fig1). Further genetic analysis performed with multiplex ligation-dependent probe amplification (MLPA) highlighted the presence of a pathogenic duplication of exons 48, 49 and 50 in the COL4A5 gene, therefore confirming X-linked Alport syndrome.
   Alport syndrome is an inherited disorder of type IV collagen, the major collagenous constituent of basal membranes [5]. The majority of Alport syndrome patients (approximately 85%) present a dominant X-linked hereditary pattern caused by mutations in the COL4A5 gene, found in the Xq22 region, which codes for the α5-chain of type IV collagen [3]. On top of all cases diagnosed by standard genetic testing, there are a few cases (due to duplications, insertions and deletions which represent 5-10% of all pathogenic variants) which may evade detection during standard genetic testing due to insufficient sensitivity of the testing process, as in this case. The use of MLPA genetic testing is recommended in these cases [3].
   Mutations in the COL4A5 gene lead to a loss of the α5-chain in basal membranes and, generally, a complete lack of expression of α5 in male patients and a mosaic distribution in female patients are considered diagnostic of Alport syndrome.
   The α5-chain is found in both normal glomerular basal membrane (GBM) and normal epidermal basal membrane and its absence results in the typical GBM ultrastructural lesions, widely recognized as diagnostic of the disease [6]. As reported by Wang and colleagues (2012), using skin biopsy a negative or mosaic α5-chain staining in the epidermal basal membrane was detected in 86.2% of male and 93.5% of female X-Linked Alport syndrome patients. Immunohistochemical analysis of the α5-chain in the epidermal basal membrane (EBM) is therefore a clearly useful approach for making a diagnosis of X-Linked Alport Syndrome [7] and is currently considered the procedure of choice in the evaluation of patients with haematuria who are suspected of suffering from the disease. In this procedure, the use of confocal laser scanning microscopy (CLSM),

which produces high-resolution images of thick biological samples, could prevent the occurrence of false negatives, which is otherwise reported in a significant number of cases [6].

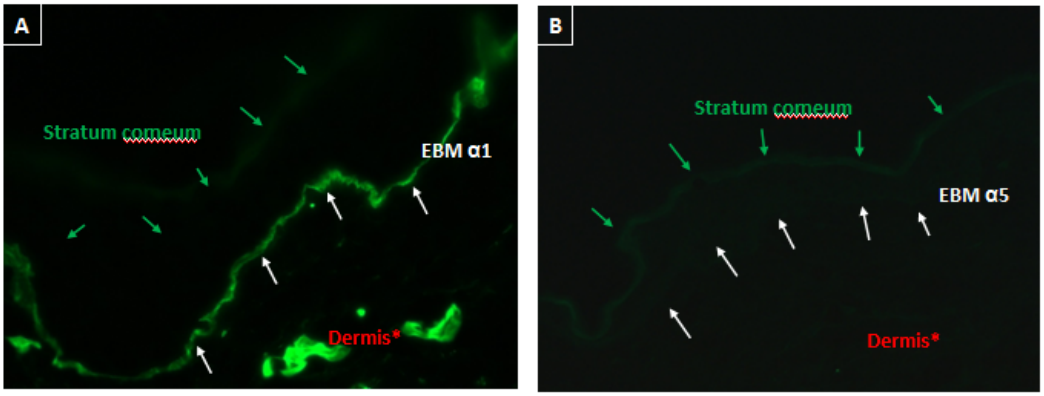

Fig. 1
A: Immunofluorescence shows normal COL4-α1 expression in epidermal basal membrane (EBM) (white arrows) and papillae basal membrane of dermis (red asterisk). Faint auto florescence of stratum corneum is visible (green arrows).

B: COL4-α5 negativity of EBM. Faint auto florescence of stratum corneum is visible (green arrows).

3. The treatment of hearing and eye anomalies can only be targeted to alleviating the symptoms in order to provide a better living standard for the patients. Hearing in fact continues to deteriorate as the patient ages, and although it is helped with hearing aids the only other precaution patients can take is to protect their hearing from additional insults throughout life [8]. The lenticonus also worsens and can be corrected with lens replacement. On the other hand, retinopathy progresses but usually does not affect the patients' vision or require treatment [9]. Proteinuria, regarded as an indicator of the progression of renal disease as in other glomerular conditions, has been shown to be reduced with the use of Angiotensin-converting enzyme (ACE) inhibitors in children with X-linked Alport syndrome [10]. Furthermore, combined administration of ACE inhibitors with angiotensin-receptor blockers and aldosterone inhibitors has shown additional therapeutic benefits in the treatment of proteinuria [11]. Treatment with ACE inhibitors, even before the onset of proteinuria, especially in individuals with genetic mutations or a family history consistent with early-onset renal failure, may delay the onset of end-stage disease and improve life expectancy [3]. In the event of end stage renal disease, the chosen treatment is kidney transplant. Patients with X-linked Alport syndrome who undergo transplantation have survival rates and graft survival rates similar to or better than those of patients with other inherited renal diseases [12]. It is however worth remembering that 3% to 5% of males develop anti-GBM disease with rapid allograft loss after transplantation [13]. Anti-GBM disease is more common with large gene deletions but can also occur with other mutations. These patients should be closely monitored and should undergo prompt allograft biopsy in order to check for new-onset glomerular haematuria, proteinuria or renal impairment.

Comment:

Alport syndrome is the most common familial chronic glomerulonephritis with onset during the first years of life. Negative results from genetic testing cannot be considered conclusive if there is strong clinical evidence pointing to the disease. In the X-linked form, the most common, cutaneous biopsy has demonstrated high diagnostic accuracy.

Furthermore, its ease-of-use and the absence of complications make this method an excellent first test to perform in case of clinical suspicion of Alport syndrome.

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