Diagnosis of Alport syndrome, is there a role for skin biopsy?

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To the Editor.

We read with great interest the recommendations of Kashtan et al. [1] about the management of Alport syndrome in children. In particular, the protective effect of early treatment with ACE-inhibitors imposes a prompt diagnosis of Alport syndrome that is nowadays still a challenging aspect. As a matter of fact, standard genetic testing with the next generation sequencing approach may miss large gene rearrangements or splice site mutations which represent 5–10% of all pathogenic variants. On the other hand, the case of unfamiliar microhematuria is a frequent finding accounting for around 1% of school-age children. A diagnostic approach such as the one proposed would lead to the execution of a considerable number of kidney biopsies, which is recommended both in isolated microhematuria and in familiarity for hematuria with negative genetic analysis for Alport syndrome. In our opinion, as an intermediate step, a skin biopsy could be a reasonable choice, having small risks related to the procedure compared to kidney biopsy. The X-linked (*COL4A5*) Alport syndrome remains the most frequent form and, as reported by Wang and colleagues [2], the immunostaining analysis of $\alpha 5$ -chain in the epidermal basal membrane from skin fibroblasts gives a mutation detection rate of 83% in males and 93.5% in females heterozygous or with mosaicism for *COL4A5* mutation. A pathological skin biopsy could therefore be an indication to perform more specific genetic investigations, as with MLPA technique [3]. The kidney biopsy could therefore be

reserved for cases with negative kidney biopsy or with the suspicion of Alport syndrome due to a *COL4A3/COL4A4* mutation in which the skin biopsy is not contributive as skin collagen chains are not encoded by these two genes, or again the kidney biopsy could be reserved for cases of *COL4A5* mutation not detected by the skin biopsy. Immunostaining for type IV collagen could also be proposed for kidney biopsy showing an absence or an abnormal distribution of the α -3,4 or 5(IV) chains of the epidermal basal membrane.

References

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