How early renal biopsy has to be performed in children with isolated asymptomatic proteinuria?

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An axiom in nephrology is that the treatment of renal diseases is mostly effective when the renal damage has not yet entered a sclerotic phase, hence the need for an early diagnosis to establish a timely treatment. This is considered particularly valid for the immune-mediated glomerular diseases. A point of no-return corresponds to a severe loss of functioning renal mass (∼60–70%) and the kidney lesion mostly detected at this point is a severe interstitial fibrosis, which is the monotonous pathology hallmark of conditions with irreversible chronic renal damage. In these cases, proteinuria is mostly due to glomerular hyperfiltration, which further aggravates the tubulointerstitial damage and can be only partially reduced by angiotensin–angiotensin antagonists [3]. It is clear that the diagnosis should be made long before the detection of these pathology lesions.

The wish of an early diagnosis of glomerular diseases suspected on the basis of proteinuria and/or microscopic haematuria is particularly felt when children are concerned because of the long life expectancy and the likely early stage of renal damage. There are no valid evidence-based guidelines for timing and indication to renal biopsy in children to early detection of glomerular diseases. Suggestions are mostly based on opinions, personal experience and culture. Moreover, renal biopsy is an invasive procedure, particularly in children, and it carries an emotional impact on the entire family. Biopsy-related morbidity is 8–10% [4] but complications are generally not severe, easily reversible and exceptionally life-threatening. However, there is fear of possible complaints and legal consequences, and this is particularly the case of North American nephrologists, who limit the indication to renal biopsy to cases in which there are overt risk factors for progression to renal failure (like heavy proteinuria or already reduced glomerular filtration rate), hence with obvious need of searching effective treatments. This attitude does not favour an early diagnosis. Conversely, Asian colleagues are encouraged to perform renal biopsy shortly after the detection of urinary abnormalities, particularly in children [5]. Indeed, in Japan [6], Korea [7] and Taiwan [8], mass screening programmes are well established since decades—in Japan started in 1973—aiming at the early detection of renal diseases in primary school children. A diagnostic renal biopsy is performed in all children with confirmed urinary abnormalities, and there is large consensus in these countries that the early diagnosis and timely treatment have led to positive public health results. Murakami et al. [9] reporting Japanese registry data from 1974 to 2002 observed a decrease in number of children and adolescents entering dialysis starting from 1984. Moreover, another Japanese report [10] considered the incidence of patients <20 years old who reached end-stage renal disease (ESRD) in the USA and in Japan in 2002 and found a 4:1 ratio. The data comparison was particularly impressive for the 15- to 19-year-old young subjects, as 30 per million population in USA versus 6 per million population in Japan yearly reached ESRD. The role that Japanese screening program has in obtaining these results remains to be proven; however, it seems to be confirmed also by the data from the Japanese dialysis registry, which reported that in 1980, the glomerular diseases were responsible for ESRD in 68.8% of children, but this figure dropped to 34.5% only in 1980 [11,12].

Also discussed and largely undefined is the extent to which adolescent and young adults with persistent asymptomatic microscopic haematuria should be evaluated in accurate follow-up. A recent report in Israeli healthy subjects aged 16–25 years with asymptomatic isolated microscopic haematuria detected when examined for fitness for military service, between 1975 and 1997, showed an association with significantly increased risk of ESRD needing dialysis over the following 20 years [13].

In North America and in Europe, the fear of starting an expensive screening programme without a prior assessment of cost-benefit effectiveness has impaired the establishing of such large mass screening, and the most recent unofficial recommendation is to screen children with risk factors, including familial renal or metabolic diseases, and obese adolescents [14]. It is likely that economical reasons, more than scientific conclusions, are responsible for the present European and American lack of interest for
screenings aimed at an early detection of urinary abnormalities in children.

However, in several European countries, children often perform urine analysis before entering intensive sport programmes or by chance as routine analysis before minor surgery or for other health problems. In these cases, the detection of isolated proteinuria and/or haematuria leads the pediatricians and sometimes also the nephrologists into the dilemma on whether to perform or not a renal biopsy. In these cases, a biopsy report of normal kidney tissue or of minimal mesangial proliferative changes without a definite diagnosis of a well identifiable glomerular disease is felt as having exposed the child to an unnecessary and potential dangerous procedure.

The paper of Hama et al. published in Nephrology, Dialysis, and Transplantation explores this difficult area of decision making and puts forward some indications based on a suitable statistical evaluation, even if supported by a rather limited number of observations. They analysed data obtained in children who had undergone renal biopsy because of persistent non-orthostatic and non-tubular isolated proteinuria. Persistent asymptomatic isolated proteinuria is not common in children, who, when podocytes are injured, suddenly develop a severe degree of urinary protein loss with full-blown nephrotic syndrome. Children very rarely present with mild proteinuria, rather typical of glomerular diseases with established sclerotic renal damage, or observed in aged hypertensive patients with nephroangiosclerosis. Hence, when mild asymptomatic proteinuria develops the dilemma raisers on whether to perform or not a renal biopsy, certainly scientifically of interest but which might be considered disproportionate to the child’s need.

Hama et al. calculated by receiver operating characteristic analysis a cut-off proteinuria which resulted significantly associated with minor glomerular damage, i.e. absence of light microscopy detectable glomerular lesions, without signs of podocyte damage or basement membrane alterations at electron microscopy and without significant immune deposits at immunofluorescence. The cut-off proteinuria resulted to be a urinary protein/creatinine g/g ratio (uP/Cr) <0.5. Children with uP/Cr >0.5 had a significantly increased frequency of chronic glomerular diseases which are associated with potential progression, including focal segmental glomerulosclerosis (FSGS), IgA nephropathy and other chronic glomerulonephritides which the authors found in 41% of the children. Conversely, among children with <0.5 uP/Cr, one only had a potentially progressive disease, an FSGS in an early phase, which later on developed >0.5 uP/Cr. The authors conclude suggesting to perform renal biopsy in children with persistent >0.5 uP/Cr. There is a general consensus about the significant risk of progression of cases presenting FSGS or IgA nephropathy and proteinuria, even in low amount like 0.5 uP/Cr [15]. Even though the need of starting a treatment in these early stages is still debated, the knowledge of a potentially progressive renal disease is very useful to timely start treatment in case of sudden worsening of urinary findings or of renal function.

A personalized follow-up based on a well-recognized risk factor as a definite histological diagnosis is particularly valuable for children, even if renal biopsy does not indicate a precipitous need of starting a treatment immediately after the diagnosis. Finally, if it is true that the current reading of renal biopsy frequently provides only limited information concerning ongoing injurious mechanisms, modifiable by specific focussed therapies, it is also likely that science is proceeding towards the identification of new biomarkers, such as molecular signatures expressed in renal biopsy tissues. In this context, the information provided by early renal biopsy promises to be crucial for the choice of new pharmaceutical and biological drugs.

Conflict of interest statement. None declared.

(See related article by Hama et al. Renal biopsy criterion in children with asymptomatic constant isolated proteinuria. Nephrol Dial Transplant 2012; 27: 3186–3190.)

References

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