Review

Pathology of perinatal and early onset nephrotic syndrome

Guido Monga[1], Lorenzo Daniele[2], Gianna Mazzucco[2]

[1]Department of Health Sciences, University of the Eastern Piedmont, Novara, Italy

[2]Department of Medical Sciences, University of Turin, Turin, Italy

Proceedings

Abstract

Nephrotic syndrome rarely occurs in the first year of life. There are some cases which share the pathological changes observed in older children or in adults, but two forms, the congenital nephrotic syndrome of the Finnish type (CNF) and the diffuse mesangial sclerosis (DMS) show peculiar morphologic findings.

CNF is characterized in its early phases by the focal dilation of the proximal tubules with formation of small cysts and by mesangial hypercellularity. With progression of the disease, tubular dilation spreads from the deep to the outer cortex and focal-segmental and global glomerulosclerosis become evident.

DMS may be renal-limited or be associated with male pseudo-hermaphroditism and Wilm's tumor (Denys-Drash syndrome). It shows the increase of the mesangial matrix and mesangial hypercellularity in the early phases of the disease and extensive glomerulosclerosis in the later ones. Podocytes are hypertrophic around the sclerotic areas and form pseudocrescents. Tubular dilations and cysts may be present, but in lesser extent compared with CNF. Interstitial fibrosis occurs with increasing severity from the inner to the outer cortex.

Apart from the negative reaction from nephrin in CNF, immuno-histochemistry has no diagnostic relevance in both diseases. Electron microscopy shows in both diseases a diffuse effacement of the foot processes and microvillous transformation of the podocytes. Glomerular basement membrane may show changes recalling those found in Alport disease.

Due to the rather similar changes in CNF and DMS, a pathological diagnosis may be difficult on small tissue specimens provided by needle biopsies. It follows that accurate clinical and genetic investigations are needed in addition to the pathological study.

Keywords

Congenital nephrotic syndrome, infantile nephrotic syndrome, nephrotic syndrome of the Finnish type, diffuse mesangial sclerosis, focal-segmental glomerulosclerosis, membranous glomerulonephritis.

Corresponding author

Guido Monga, Dipartimento di Scienze della Salute, Università del Piemonte Orientale, Novara, Italy; e-mail: guido.monga@med.unipmn.it.

How to cite

Introduction

Congenital nephrotic syndrome is a term applied to those forms which develop before or within 3 months of life, whereas the term infantile nephrotic syndrome refers to the occurrence of the disease between 3 and 12 months of age [1, 2].

Due to genetic and immunological studies, a large variety of clinocopatological entities with different etiology, course and outcome have been identified over the time (**Tab. 1**). As to the morphologic appearance, several early onset disorders share their pathologic findings with the nephrotic diseases observed in older children and adults (minimal change disease, focal-segmental glomerulosclerosis [FSGS], membranous glomerulonephritis, endocapillary or mesangial proliferative glomerulonephritis). In this setting, two entities are worth stressing: a) the autosomal recessive FSGS due to mutations of gene *NPHS2* mapped on the chromosome 1q25-q31 which encodes podocin [3], a protein expressed in the podocytes which is critical for the organization of the slit diafragm [4]; b) a severe form of membranous glomerulonephritis due to the deposition along the glomerular basement membrane of immune complexes (neutral endopeptidase-antineutral endopeptidase antibodies) produced by the pregnant woman and trasferred to her fetus [5]. Conversely, there are some other conditions such as congenital nephrotic syndrome of the Finnish type (CNF) and diffuse mesangial sclerosis (DMS) which are unique to this younger age group and show peculiar pathologic changes.

Table 1. Renal pathology in congenital and infantile nephrotic syndrome.

		Congenital	Infantile
Nephrotic syndrome of the Finnish type		Present	Absent
Diffuse mesangial sclerosis (isolated or associated to Denys-Drash Syndrome)		Present	Present
Focal segmental glomerulosclerosis	*Autosomal recessive*	Absent	Present
	Autosomal dominant	Absent	Present
	Epidermolysis bullosa	Present	Absent
	Congenital HIV infection	Absent	Present
	Idiopathic	Present	Present
Minimal change disease	*Congenital HIV infection*	Absent	Present
Mesangial proliferative glomerulonephritis	*Congenital toxoplasmosis*	Present	Absent
	Idiopathic	Present	Present
Membranous glomerulonephritis	*Congenital Syphilis*	Present	Present
	Lupus glomerulonephritis	Present	Present
	Anti-neutral endopeptidase antibodies	Present	Absent
	Mercury poisoning	Absent	Present
	Idiopathic	Present	Present
Membranoproliferative glomerulonephritis	*α-1 antitrypsin deficiency*	Absent	Present

The aim of the present work is to describe the morphologic features of the latter diseases which are of occasional occurence in routinary nephropathology and therefore less known among pathologists and clinicians.

Congenital nephrotic syndrome of the Finnish type

CNF is a disease with an autosomal recessive mode of inheritance due to mutations of *NPHS1* gene localized to the long arm of chromosome 19. The protein product of *NPHS1* is nephrin, a major component of the slit diaphragm. Since it plays a pivotal role in the normal function of the glomerular filter [6], its defective synthesis leads to the podocytes disfunction and to severe proteinuria.

CNF was described for the first time by Hallman and Hjelt in 1959 [7] and is most frequent in Finland, with an incidence of 10 to 12 x 10^5 live birth [8], but was reported with various frequency in studies from several countries [9-13].

Gross findings

The kidneys are large up to twice the normal size, pale with swollen cortex.

*Light microscopic findings (*Fig. 1 *and* Fig. 2*)*

The earliest feature is the focal dilation of the proximal tubules, with the formation of scattered small cysts, first observed in the deep cortex and at the corticomedullary junction. The dilation progressively involves a greater number of tubules and the cysts increase in size reaching 300-400 μm in diameter. The dilated tubules seem to spread radially from the deep to the outer cortex. Their epithelium becomes flattened and eventually
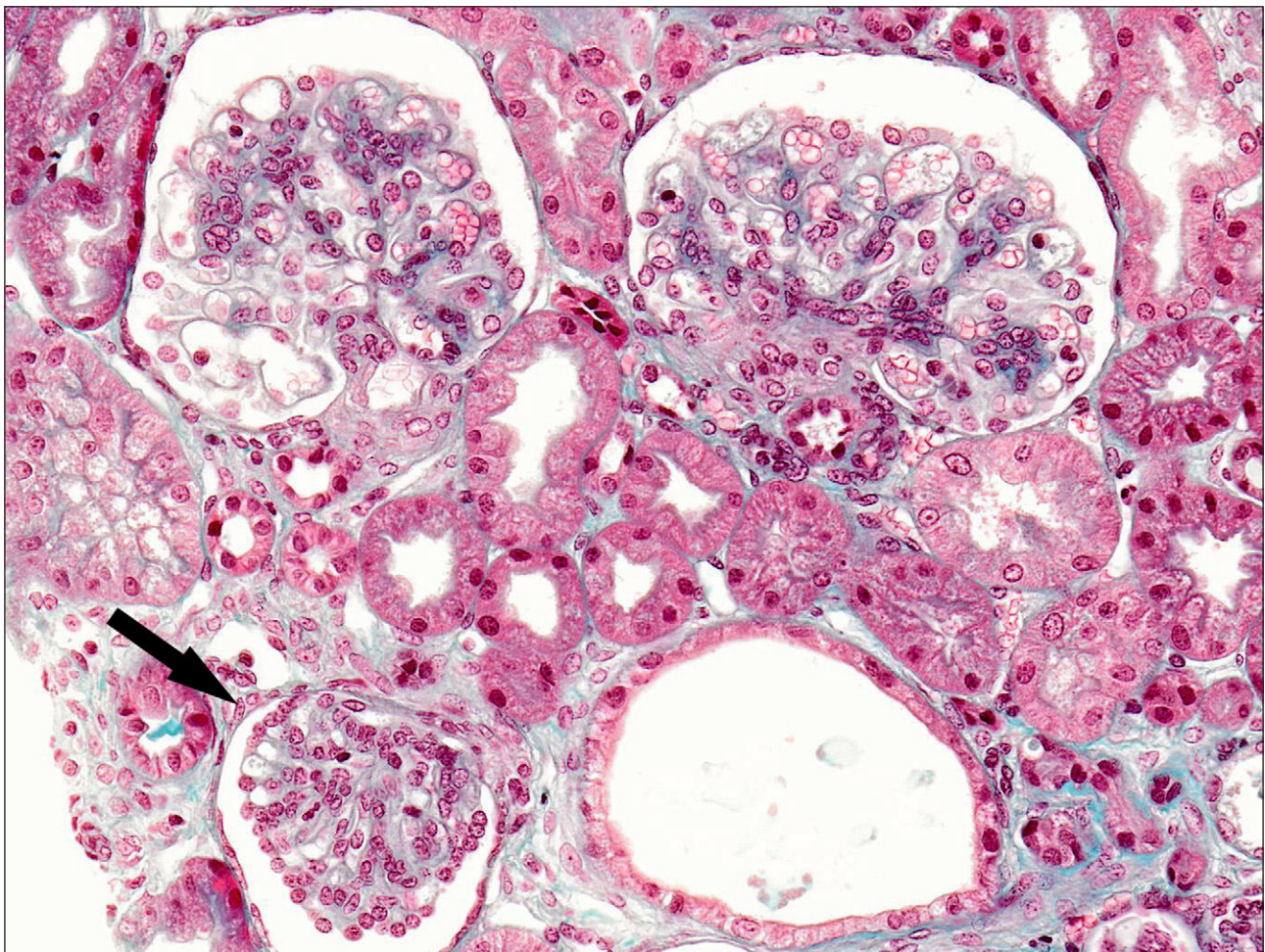

Figure 1. Congenital nephrotic syndrome of the Finnish type (CNF). Needle biopsy of a 2 month old male. Three glomeruli are present. One shows fetal appearance (arrow). The mesangial cell proliferation is evident in the two others. A single tubule is dilated to form a microcyst. Masson trichrome.
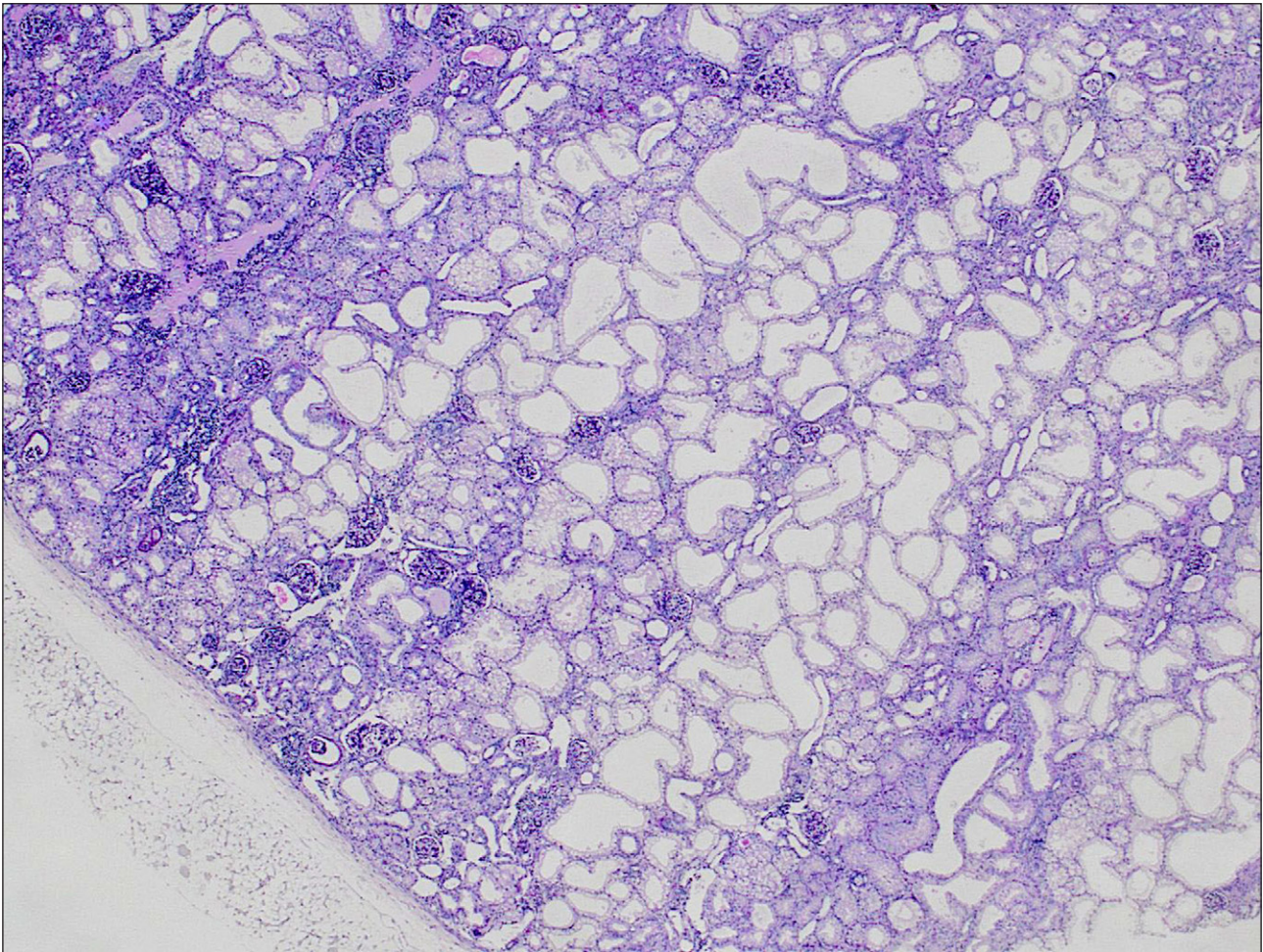
Figure 2. Congenital nephrotic syndrome of the Finnish type (CNF). Nephrectomy specimen of the same patient at the age of 4 months. Dilated tubules and microcysts are greatly increased in number and are spread in the whole cortex. PAS reaction.

atrophic. The spared tubules are lined by cells containing protein and lipid reabsorption droplets. The involvement of the proxymal tubules is not usually reported, but it was pointed out by Rapola et al. in their ultrastructural study [14].

Glomeruli may be normal in the early stages of the disease, with a number of fetal forms not exceeding that found in the normal controls. The earliest pathologic findings are the widening of the urinary spaces of the fetal glomeruli and the increase in number of the mesangial cells. Nevertheless, it must be kept in mind that mesangial hypercellularity may be difficult to judge at this age, since the mesangium is more cellular in infants than in older children [8]. With progression of the disease, focal segmental and then global glomerulosclerosis and peri-glomerular fibrosis develop. In the second half of the first year most glomeruli are sclerotic and the interstium becomes fibrotic with various amount of inflammatory cells.

Vascular changes are rare and non specific. It has occasionally been reported the increase in thickness of the muscular wall of the small cortical arteries and the arteriolar fibrinoid necrosis in the patients affected by accelerated hypertension.

Immunofluorescence findings

No immunoglobulins and complement fractions are usually detected. However, IgM and C3 lumps can be found in the sclerotic areas in the later phases of the disease. As expected, nephrin is not identifiable along the glomerular basement membranes [15, 16].

*Ultrastructural findings (***Fig. 3***)*

A widespread effacement of the foot processes is evident and the slit diafragms are not present among the residual foot processes. The glomerular basement membranes may show a widening of the lamina rara interna and occasional lamellation of
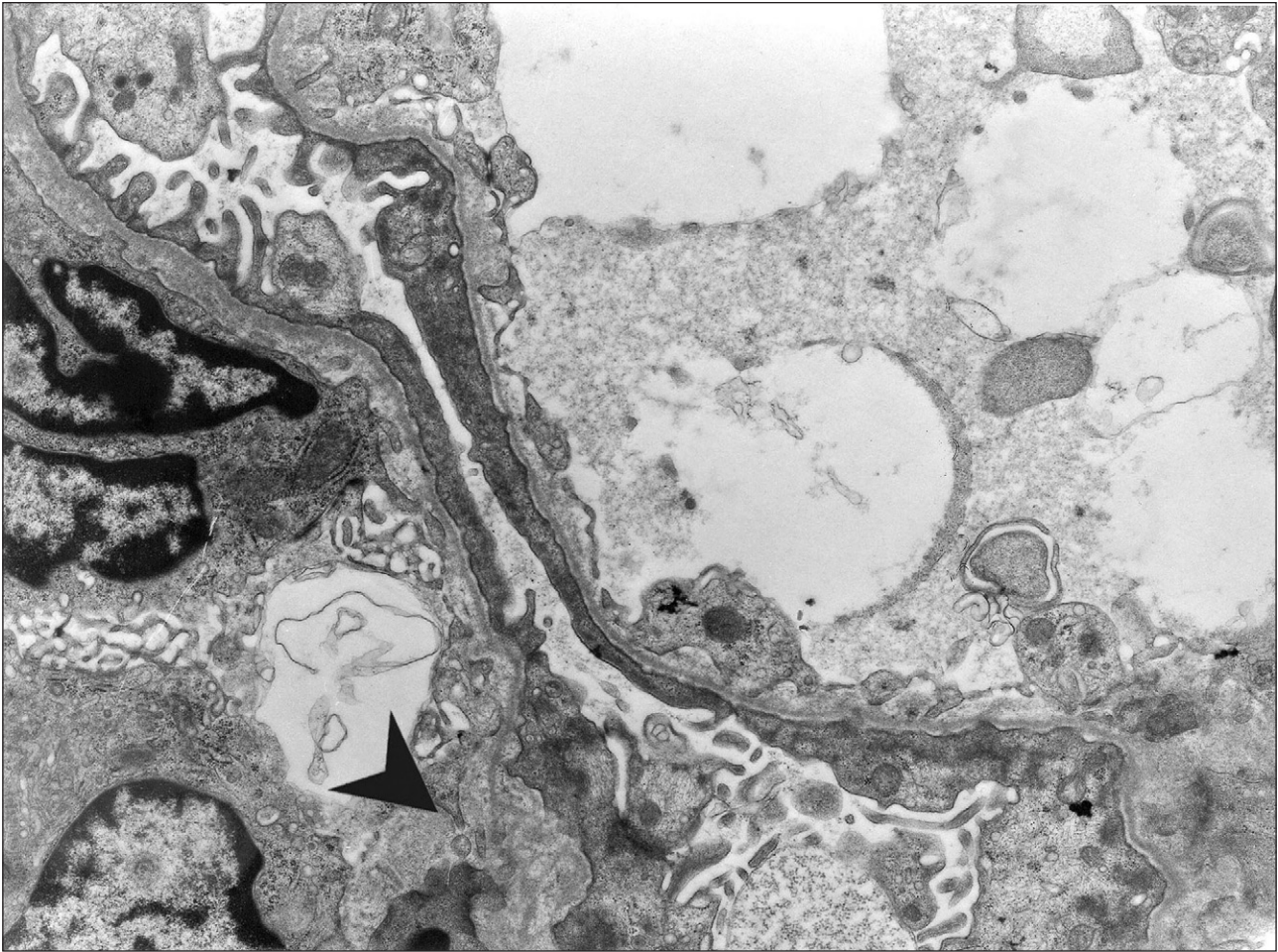
Figure 3. Congenital nephrotic syndrome of the Finnish type (CNF). The foot processes are completely effaced and the basement membranes show a widening of the lamina rara interna. Arrowhead points out the focal lamellation of the lamina densa.

the lamina densa, recalling the findings observed in Alport disease.

Diffuse mesangial sclerosis

DMS was reported for the first time by Habib and Bois in 1973 [9] and then fully described by the same French group [17]. The disease is mostly renal-limited, but may be associated with other renal and extra-renal abnormalities. The best known clinicopathologic setting is the Denys-Drash syndrome [18] characterized by male pseudohermaphroditism and Wilm's tumor in addition to DMS. The disease is related to mutations in the Wilm's tumor gene localized to chromosome 11p13 and involved in renal and gonadal development. Mutations are identified in almost all patients affected by Denis-Drash syndrome and less frequently in the subjects with isolated DMS. It must be emphasized that renal changes are the same in both cases.

*Light microscopic changes (***Fig. 4** *and* **Fig. 5***)*

The distinctive and early change is the increase of the mesangial matrix associated with mesangial hypercellularity whereas the tubulointerstitial damage is absent. As the disease progresses, first focal segmental and then global glomerulosclerosis occur. Podocytes around sclerotic areas may be hypertrophic and form the so called pseudocrescents. True epithelial cell proliferation with crescent formation has been only occasionally reported [19].

Tubulointerstitial damage becomes evident in the advanced phases and is characterized by tubular atrophy, severe fibrosis and chronic inflammatory reaction. Tubular dilation and micro-cysts may be present, but in a lesser amount compared with CNF. In their exhaustive study, Habib et al. [17] pointed out a gradient of severity of the pathologic changes from the outer to the inner cortex. The outer cortex shows severe fibrosis, tubular atrophy, an aboundant infiltration
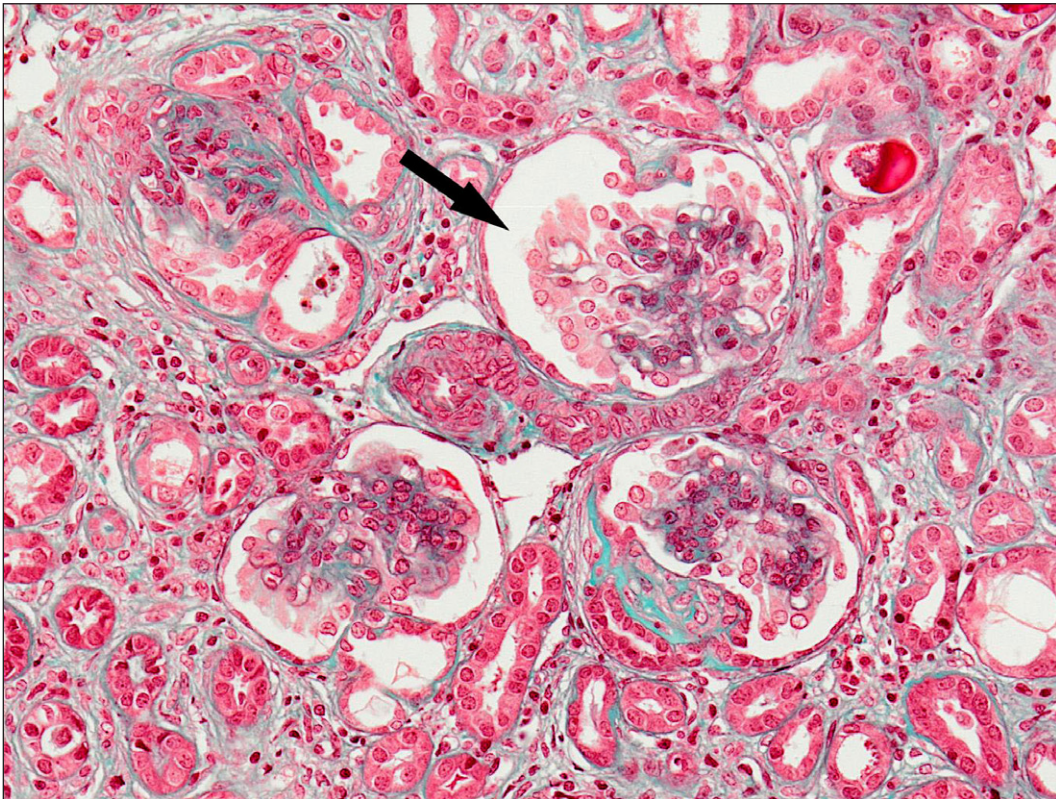
Figure 4. Diffuse mesangial sclerosis (DMS). Needle biopsy of a 4 month old male. In the early phase of the disease the glomeruli show an increase of the mesangial matrix and mesangial hypercellularity. Arrow points out hypertrophic and polystratified podocytes. There is no evidence of dilated tubules. Masson trichrome.
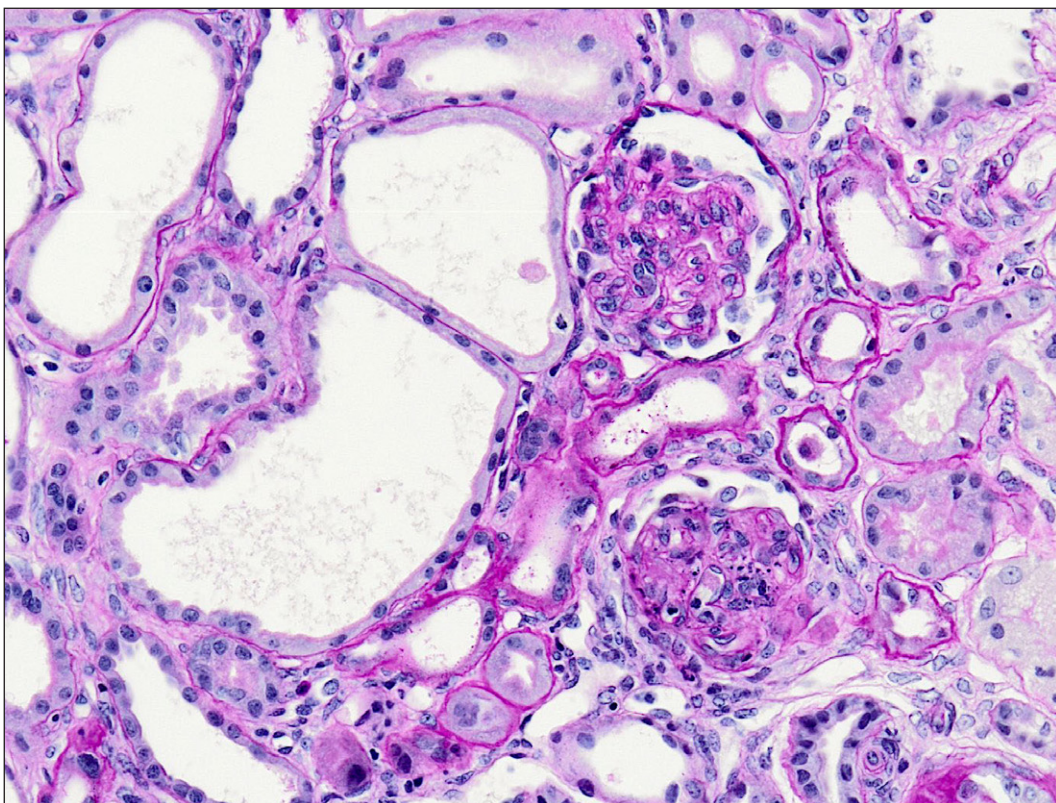

Figure 5. Diffuse mesangial sclerosis (DMS). Needle biopsy of a 4 month old female. With progression of the disease, glomeruli appear more compact with poor evidence of the capillary lumina or show severe sclerotic changes. PAS reaction.

of chronic inflammatory cells and global sclerosis of most glomeruli. Abnormalities become less extensive and severe in the inner cortex and even less evident in the iuxtamedullary areas. Due to their topographical distribution and variation in severity, the above reported lesions are difficult to be identified and graded on needle biopsies which are small and often provide only material of the outer cortex, whereas the lesions are well evident on larger histological sections from autoptical or nephrectomy specimens. In the patients affected by Denys-Drash syndrome, nephroblastoma occurs later in life, likely arising from nephrogenic rests which have an increased incidence in the kidneys of these patients.

Immunofluorescence findings

Immunofluorescence investigation usually gives negative results or may show non specific staining for IgM and C3 in the sclerotic glomeruli.

*Ultrastructural findings (***Figures 6-8***)*

Foot processes are extensively effaced and podocytes are hypertrophic with microvillous transformation of their surface. The glomerular basement membranes are thickened with waving of its external surface and presence of collagen fibers in the lamina densa [20].

Pathological findings in transplanted kidneys

Several patients affected by either DMS or CNF have been transplanted and the recurrence of the nephrotic syndrome is not known in the former, whereas it has been reported in roughly 25% of the latter [21]. The renal damage is characterized by the foot process effacement and decreased slit diaphragms, but the overall pattern observed in CNF is not present. Since the nephrin is absent in the native kidneys of these patients and antibodies anti-nephrin are found in their
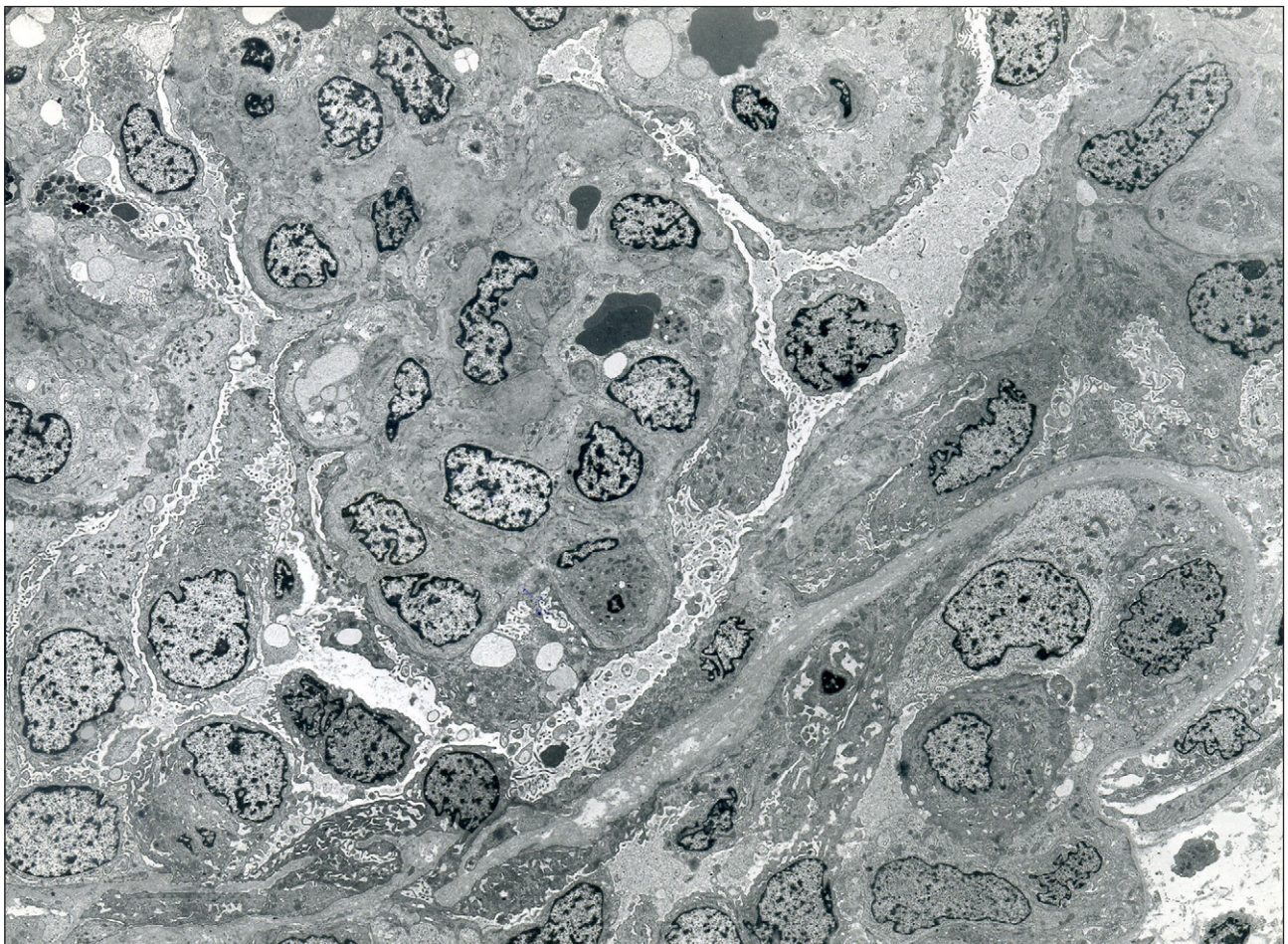

Figure 6. Diffuse mesangial sclerosis (DMS). Ultrastructural findings at low magnification. The mesangial stalk is widened and the mesangial matrix is increased. Foot processes are completely effaced and podocytes show extensive microvillous transformation.
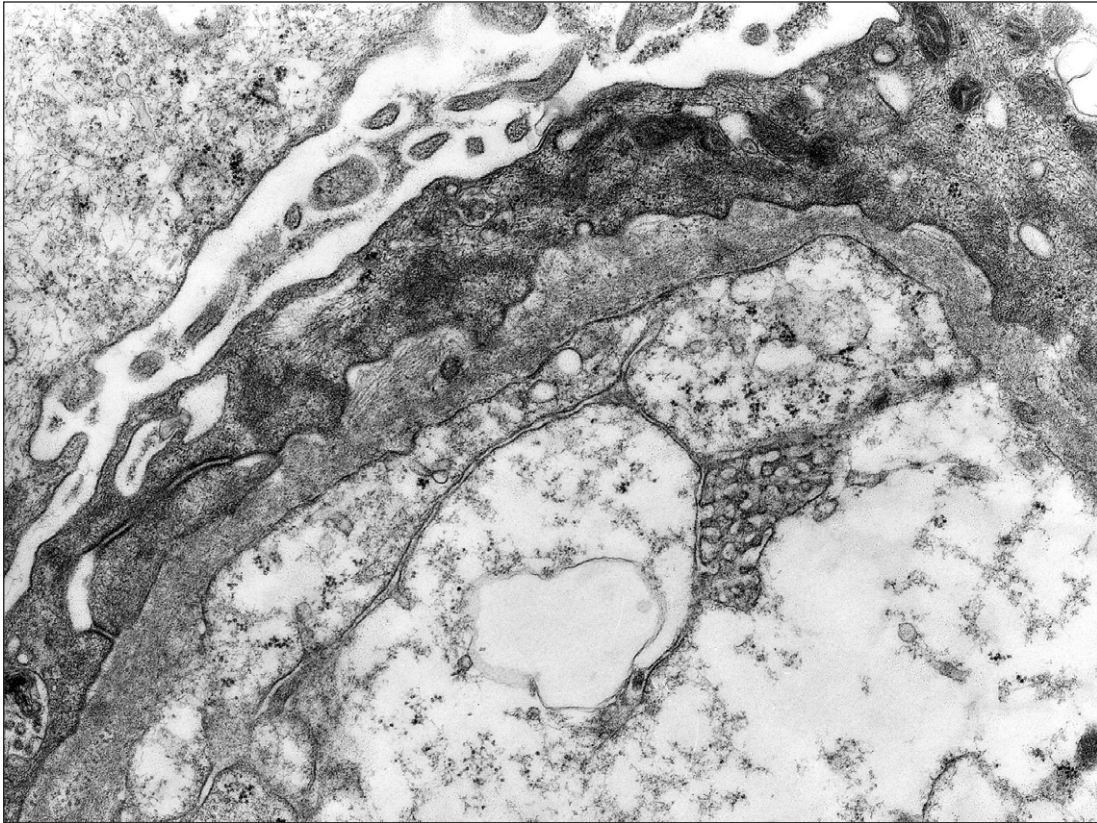
Figure 7. Diffuse mesangial sclerosis (DMS). A nonsclerotic capillary displays foot process effacement and irregular outline of the external surface of the glomerular basement membrane. Some thin fibrils are evident in the rarefied areas of glomerular basement membrane.
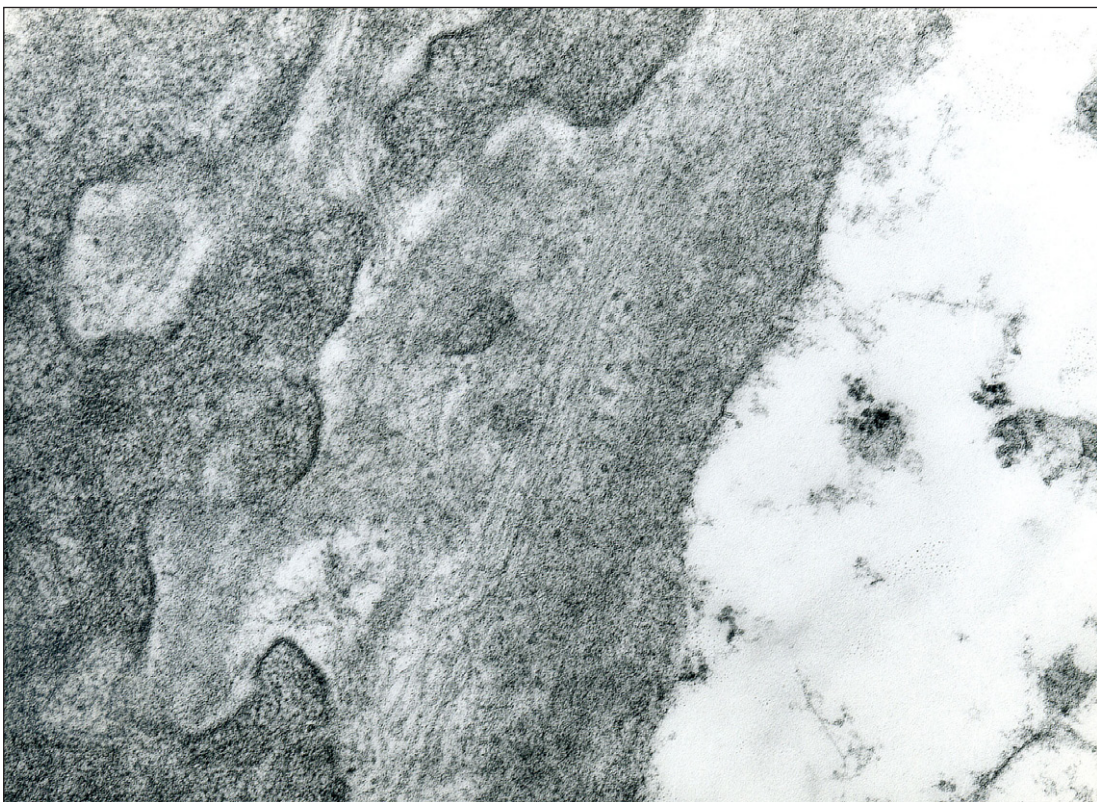

Figure 8. Diffuse mesangial sclerosis (DMS). At higher magnification fibrils show a periodic structure pointing out their collagen nature.

serum, an immunologic mechanism has been suggested.

Conclusive remarks

Nephrotic syndrome rarely occurs in the first year of life and therefore the observations of the findings reported above are absolutely occasional apart from in highly specialized institutions (e.g. the Hopital Necker Enfants Malades) where cases are sent from different countries or in specific geographic areas (e.g. Finland). In addition, some disorders share their pathological findings with the nephrotic syndrome occurring in older children or in adults, which are due to different and various pathogenetic mechanisms. On the other hand, the better known entities, the CNF and the DMS, do not display specific morphologic features, but some changes such as tubular dilation with cysts formation, glomerulosclerosis and interstitial fibrosis are present in both, even though in different percentages and in various locations. These subtle differences may not be detectable on small specimens provided by needle biopsy. It follows that cumulative data gathered from a careful clinical investigation, an exhausive genetic study and an accurate pathological evaluation are needed to achieve the correct diagnosis.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Sibley RK, Mahan J, Maurer SM, Vernier RL. A clinicopathological study of forthy-eight infants with nephrotic syndrome. Kidney Int. 1985;27:544-52.

2. Habib R. Nephrotic syndrome in the first year of life. Pediatr Nephrol. 1993;7:347-53.

3. Fuchshuber A, Jean G, Gribouval O, Gubler MC, Broyer M, Beckmann JS, Niaudet P, Antignac C. Mapping a gene (SRN1) to chromosome 1q25-q31 in idiopathic nephrotic syndrome confirms a distinctic autosomal recessive nephrosis. Hum Mol Genet. 1995;4:2155-8.

4. Boute N, Gribouval O, Roselli S, Benessy F, Lee H, Fuchshuber A, Dahan K, Gubler MC, Niaudet P, Antignac C. NPHS2, encoding the glomerular protein podicin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. Nat Genet. 2000;24:349-54.

5. Debiec H, Guigonis V, Mougenot B, Decobert F, Haymann JP, Bensman A, Deschenenes G, Ronco PM. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. N Engl J Med. 2002;346:2053-60.

6. Holzman LB, St John PL, Kovari IA, Verma R, Holthofer H, Abrahamson DR. Nephrin localizes to the slit pore of the glomerular epithelial cell. Kidney Int. 1999;56:1481-91.

7. Hallman N, Hjelt L. Congenital nephrotic syndrome. J Pediatr. 1959; 55:152-7.

8. Huttunen NP. Congenital nephrotic syndrome of Finnish type. Arch Dis Child. 1971;41:344-8.

9. Habib R, Bois E. [Heterogeneity of early onset nephrotic syndromes in infants (nephrotic syndrome "in infants"). Anatomical, clinical and genetic study of 37 cases]. [Article in French]. Helv Paediatr Acta. 1973;28(2):91-107.

10. Martul EV, Cuesta MG, Churg J. Histologic variability of the congenital nephrotic syndrome. Clin Nephrol. 1987;28:161-8.

11. Hamed RM, Shomaf M. Congenital nephrotic syndrome. A clinicopathologic study of thirty children. J Nephrol. 2001;14:104-9.

12. Mehrazma M, Otukesh H, Madani A, Hooman N, Bedayat A, Daniati Maleki N, Ehteshami A, Hoseini. Histolohic and clinical findings of congenital nephrotic syndrome in Iranian children: a study of two centers. Iran J Kidney Dis. 2012;6(6):426-31.

13. Kari JA, Montini G, Bockenhauer D, Brennan E, Rees L, Trompeter R, Tullus K, van't Hoff W, Waters A, Ashton E, Lench N, Sebire NJ, Marks SD. Clinicopathological correlations of congenital and infantile nephrotic syndrome over twenty years. Pediatr Nephrol. 2014 Jun 6. [Epub ahead of print].

14. Rapola J, Sariola H, Ekblom P. Pathology of fetal congenital nephrosis: immunohistochemical and ultrastructural studies. Kidney Int. 1984;25:701-7.

15. Routsalainen V, Ljungberg P, Vartiovara J, Lenkkeri U, Kestilä M, Jalanko H, Holmberg C, Tryggvason K. Nephrin is specifically located at the slit diafragm of glomerular podocytes. Proc Natl Acad Sci USA. 1999;96:7962-7.

16. Patrakka J, Kestila M, Wartiovara J, Ruotsalainen V, Tissari P, Lenkkeri U, Männikkö M, Visapää I, Holmberg C, Rapola J, Tryggvason K, Jalanko H. Congenital nephrotic syndrome (NPHS1): features resulting from different mutations in Finnish patients. Kidney Int. 2000;58:972-80.

17. Habib R, Gubler MC, Antignac C, Gagnadoux MF. Sclérose mésangiale diffuse: une glomérulopathie du nourrisson avec syndrome néphrotique. Actualités Néphrologiques Jean Hamburger. 1992;1992:117-31.

18. Habib R, Loirat T, Gubler MC, Niaudet P, Besman A, Levy M, Broyer M. The nephropaty associated with male pseudohermaphroditism and Wilm's tumor (Drash syndrome): a distintive glomerular lesion. Report of 10 cases. Clin Nephrol. 1985;24:269-78.

19. Swietlinski J, Mariunak-Chudek J, Niemir ZI, Wozniak W, Wilinska M, Zacharzewska J. A case of atypical congenital nephrotic syndrome. Pediatr Nephrol. 2004;19:349-52.

20. Patrakka J, Ruotsalainen V, Reponen P, Qvist E, Laine J, Holmberg C, Tryggvason K, Jalanko H. Recurrence of nephrotic syndrome in kidney grafts of patients with congenital nephrotic syndrome of the Finnish type: role of nephrin. Transplantation. 2002;73:394-403.