

21.8.3 Minimal- change nephropathy and focal segme

21.8.3 Minimal- change nephropathy and focal segmental glomerulosclerosis 4919 Moin Saleem and Lisa Willcocks

21.8.3 Minimal-change nephropathy and focal segmental glomerulosclerosis 4919 also be sporadic. Persistent nonvisible haematuria is usually lifelong, and episodic visible haematuria may also occur in up to one-fifth of patients, sometimes in association with upper respiratory tract infection. Flank pain occurs in up to 30% of patients and a small number of cases with loin-pain haematuria syndrome have been de- scribed. Hypertension may be more common than in the general population, although this is not confirmed in all studies. Proteinuria is uncommon and patients with nephrotic-range proteinuria usually have a second, additional renal diagnosis. Progressive renal impair- ment is rare but has been described in several families. Heterozygous G1334E and G187C mutations of COL4A3 protein have been iden- tified in families with TMN that progresses to proteinuria after age 30 years and renal insufficiency after age 50 years. This is associ- ated with

the development of focal segmental glomerulosclerosis on renal biopsy. Deafness and other extrarenal manifestations seen in Alport's syndrome are absent. There is no specific treatment. Differential diagnosis TMN can only be distinguished from IgA nephropathy (IgAN) by renal biopsy. The coexistence of TMN and IgAN is well recorded and it is a matter of debate whether this merely represents the coincidence of two common glomerular diseases or is more than a chance occurrence. TMN must be distinguished from Alport's syndrome (hereditary nephritis with deafness), of which the commonest form is X-linked. If there is a clear autosomal dominant pattern of haematuria without renal impairment or extrarenal problems, then a clinical diagnosis of TMN may be established with reasonable confidence, but a renal biopsy in at least one family member is still preferable. Once the diagnosis is established in a kindred, biopsy is not required unless there are unexpected clinical changes. Differentiation from the less common autosomal forms of Alport's syndrome is less straightforward. Subclinical deafness must be excluded by audiography, and the renal biopsy must be carefully assessed. In TMN there is uniform thinning, whereas early in the course of Alport's syndrome marked variability in GBM width is typical, even if the characteristic structural disruption of the GBM has not yet developed. Staining of GBM for the α -chains of type IV collagen is highly informative since in Alport's syndrome $\alpha 3$, $\alpha 4$, and $\alpha 5$ are absent, whereas normal α -chain distribution is preserved in TMN. Genetic testing for COL4A3 or COL4A4 mutations to diagnose TMN is clinically not practical because of the huge size of these genes, their frequent polymorphisms, and the likelihood of the existence of further gene loci. Familial C3 glomerulonephritis caused by mutation of complement factor H-related protein 5 (CFHR5) has recently been described in kindreds of Cypriot descent. Affected individuals invariably have nonvisible haematuria, and recurrent (often synpharyngitic) visible haematuria is present in about 50% of patients. Impaired renal function ensues in most affected males but is much less common in females. Prognosis The prognosis is excellent in the great majority of families with TMN, but there is a small but real risk of developing progressive renal insufficiency, heralded by the onset of proteinuria and hypertension. Long-term follow-up of those with TMN is therefore mandatory; urinalysis and measurement of blood pressure and renal function are recommended every 1 to 2 years.

FURTHER READING Dische FE, et al. (1990). Incidence of thin membrane nephropathy: morphometric investigation of a population sample. *J Clin Pathol*, 43, 457-60. Gale DP, et al. (2010). Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with glomerulonephritis. *Lancet*, 376, 794-801. Nieuwhof CM, et al. (1997). Thin GBM nephropathy. Premature glomerular obsolescence is associated with hypertension and late onset renal failure. *Kidney Int*, 51, 1596-601. Pierides A, et al. (2009). Clinico-pathological correlations in 127 patients in 11 large pedigrees, segregating one of three heterozygous mutations in the COL4A3/COL4A4 genes associated with familial haematuria and significant late progression to proteinuria and chronic kidney disease from focal segmental glomerulosclerosis. *Nephrol Dial Transplant*, 24, 2721-9. Tiebosch AT, et al. (1989). Thin-basement-membrane nephropathy in adults with persistent hematuria. *N Engl J Med*, 320, 14-18. Tryggvason K, Patrakka J (2006). Thin basement membrane nephropathy. *J Am Soc Nephrol*, 17, 813-22.

21.8.3 Minimal-change nephropathy and focal segmental glomerulosclerosis

Moin Saleem and Lisa Willcocks

ESSENTIALS

Minimal-change nephrotic syndrome Minimal-change nephrotic syndrome (MCNS) is an immune-mediated condition, usually of unknown cause. On light microscopy the glomeruli appear normal, and on electron microscopy there is effacement of epithelial cell foot processes over the outer surface of the glomerular basement membrane. MCNS is the cause of about 75% of cases of nephrotic syndrome in children and 17% in adults. Management and prognosis—treatment in adults is with prednisolone at an initial dose of 80 mg/day, then tapering. This leads to complete

remission in 90 to 95% of patients, but 50 to 75% of glucocorticoid-responsive adults will have a relapse. Occasional relapses are treated in the same manner as initial presentations, but frequent relapses (more than three per year) occur in 10 to 25%, and in a further 25 to 30% the prednisolone dose cannot be reduced below 0.2 to 0.3 mg/kg per day without relapse (steroid dependence). Treatment options then include cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil, and rituximab. Progression to renal

section 21 Disorders of the kidney and urinary tract 4920 failure is not expected and would call the diagnosis of MCNS into question. Focal segmental glomerulosclerosis Focal segmental glomerulosclerosis (FSGS) is not a specific disease entity but a histological lesion, often of unknown aetiology, which is characterized by segmental areas of glomerular sclerosis. It may be (1) primary—either due to genetic mutation, or associated with an unknown circulating plasma factor that causes an increase in glomerular permeability; or (2) secondary—the end product of a variety of pathological processes including glomerular hyperfiltration, healed glomerulonephritis, viral (including HIV) infection, or parasitic infection. Based on the site of the lesions and other histological features, the primary condition can be divided into five variants: (1) perihilar; (2) glomerular tip; (3) collapsing variant; (4) cellular variant; and (5) ‘not otherwise specified’, when the other variants have been excluded. Most patients with FSGS present with nephrotic syndrome (FSGS is the diagnosis in 20% of adults with nephrotic syndrome), some with persistent proteinuria, and a few have haematuria as well as proteinuria. Management and prognosis—corticosteroid and immunosuppressive therapy should be considered only in patients with primary FSGS and nephrotic syndrome. The steroid regimen is as used for MCNS, but with lesser success: response rates for complete remission range from 28 to 74%, and partial remission rates from 0 to 50%. Steroid-resistant cases are treated with ciclosporin (for which there is most published evidence), mycophenolate mofetil, or cyclophosphamide. Prognosis depends on histology and response to treatment. Glomerular tip lesions have the best prognosis and collapsing FSGS the worst. Patients who achieve a complete remission have a 5-year survival off dialysis of 94%, as compared with 53% in those who do not achieve remission. The nephrotic syndrome recurs—often within days—after renal transplantation in about 30% of patients with primary FSGS, leading to early graft failure in approximately 50% of cases. Introduction Nephrotic syndrome is defined by the triad of urinary protein excretion greater than 3.5 g/24 h (>200 mg/mmol creatinine in children), hypoalbuminaemia (<25 g/litre), and tissue oedema. General aspects and clinical features of this condition are discussed in Chapter 21.3, as is the fact that it can be caused by a range of glomerular pathologies. In adults, minimal-change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS) are together responsible for a third of cases of nephrotic syndrome, while in children these two conditions cause over 80% of cases, the vast majority of which will be steroid sensitive. This has led to muddled terminology in paediatric practice, with MCNS patients frequently called steroid-sensitive nephrotic syndrome, with steroid-resistant nephrotic syndrome used interchangeably with FSGS, indicating the lack of response to steroids in most of these patients. In this chapter, the terms MCNS and FSGS will be used, and although this is a textbook of adult medicine it will include some discussion of paediatric presentations and management because some will continue to be affected in adolescence and adulthood. MCNS and FSGS may be primary or secondary. There continues to be debate as to whether primary MCNS and FSGS are variants of the same disease, or whether they represent separate pathogenetic entities. Both disorders are characterized by diffuse foot process effacement on electron microscopy, the absence of immune deposits, and a severe functional defect in glomerular permselectivity.

Minimal-change nephrotic syndrome Aetiology and pathogenesis The cause of MCNS is unknown, although it is thought to be caused by circulating factor(s) released by activated immune cells, particularly at the time of intercurrent infections. In a landmark hypothesis paper in 1974, Shalhoub proposed T-cell release of circulating mediators that affect the glomerulus. It is a relapsing and remitting condition, with relapse triggers including viral infections, pollen and other allergens, meningococcal C vaccination, and an association with active Hodgkin's disease and other T-cell malignancies. Between 30 and 60% of nephrotic children are atopic, and a genetic association with HLA-DRB and DQA/B loci has been reported across different populations. Measles infections have been observed to induce remission in some cases. The success of B-cell depletion therapies in a subset of patients suggests that B cells are also involved in pathogenesis. In adults, a number of drugs can induce MCNS, including nonsteroidal anti-inflammatory drugs, some antimicrobial drugs (ampicillin, rifampicin, cephalosporins), lithium, d-penicillamine and tiopronin, bisphosphonates, and sulfasalazine.

Pathology MCNS describes the observation that on light microscopy there is no evident change: the glomerulus looks normal (Fig. 21.8.3.1). The pathology can only be seen by electron microscopy, where there is effacement of the podocyte cell foot processes (Fig. 21.8.3.2).

Epidemiology In children, estimates of incidence of nephrotic syndrome are relatively consistent, at around two to seven new paediatric cases (under 16 years) per 100 000 total population per year, with 76% of cases being due to MCNS. The peak incidence of MCNS is in preschool-age children, with a male-to-female childhood ratio of 2:1. In adults, MCNS accounts for 17% of cases of the nephrotic syndrome, and Fig. 21.8.3.1 Minimal-change nephropathy. The glomerulus looks normal on light microscopy. Periodic acid-methenamine silver staining, magnification $\times 64$. By courtesy of Professor A.J. Howie

21.8.3 Minimal-change nephropathy and focal segmental glomerulosclerosis 4921 data from an adult Caucasian population in Northern Europe revealed that MCNS accounted for 10% of primary glomerulonephritis, with—as expected—the incidence falling with increasing patient age. Genetics Familial MCNS is rare, but has been reported. One pedigree to date has been found to have a monogenic mutation responsible for the disease, affecting the epithelial membrane protein-2 (EMP2) gene, and other gene mutations have been reported, although most can cause SRNS as well as SSNS. Clinical features See Chapter 21.3. Treatment The clinical trial evidence base is relatively sparse, but stronger in children. It has been comprehensively reviewed in the most recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on glomerulonephritis (in 2012). General approach Adults with MCNS are typically oedematous and often hypertensive. Sodium restriction and diuretics are often required to manage the oedema, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are advocated for blood pressure control, with the additional advantage of a reduction in proteinuria. Close monitoring is required if initiating ACE inhibitors in hypovolaemic patients undergoing diuresis, because of the risk of acute kidney injury. Statin therapy for hyperlipidaemia and anticoagulation for severe hypoalbuminaemia should be considered for the long-term management of patients whose nephrosis is refractory to treatment. See Chapter 21.3 for further discussion. MCNS is a condition with a propensity to remissions and relapses. Standard definitions of treatment response are shown in Table 21.8.3.1. Immunosuppression—initial strategy Immunosuppression with corticosteroids is recommended for initial treatment of nephrotic syndrome, based on evidence from large, prospective randomized controlled trials (RCTs) in children, smaller RCTs in adults, and observational data from adults and children. Adults According to the KDIGO recommendations, prednisone or prednisolone should be given at a daily single dose of 1 mg/kg (maximum 80 mg)

or an alternate-day single dose of 2 mg/kg (maximum 120 mg). The initial high dose of corticosteroids, if tolerated, should be maintained for a minimum period of 4 weeks if complete remission is achieved, and for a maximum period of 16 weeks if complete remission is not achieved. In patients who remit, corticosteroids should be tapered slowly over a total period of up to 6 months after achieving remission. This prolonged course of high-dose prednisolone is often associated with significant toxicity. As a result, prophylactic measures are recommended, comprising an H₂-receptor antagonist or proton pump inhibitor to prevent peptic ulceration, and bisphosphonate to prevent osteoporosis. Blood sugar level monitoring is required to identify corticosteroid-induced diabetes mellitus. For patients with relative contraindications or intolerance to high-dose corticosteroids (e.g. pre-existing uncontrolled diabetes mellitus, psychiatric conditions, severe osteoporosis, or morbid obesity), alternative therapy for which there is some evidence include daily oral cyclophosphamide or calcineurin inhibitors as discussed in frequently relapsing MCNS (see 'Frequently relapsing and steroid-dependent disease'). Glucocorticoid therapy leads to complete remission in 90 to 95% of cases. The time course to a complete remission is generally longer in adults than in children, with 50% responding by 4 weeks and 10 to 25% requiring more than 3 to 4 months of therapy (Fig. 21.8.3.2). In most cases, response to therapy of nephrotic MCNS is of an 'all or nothing' type. Partial responses are not characteristic of MCNS and, when seen, one should suspect a possible misdiagnosis, most often FSGS that was missed by biopsy sampling error. Deciding how long to pursue treatment with high-dose steroid in the grossly nephrotic patient who is not responding and yet ac-

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section 21 Disorders of the kidney and urinary tract 4922 is achieved, and for a maximum period of 16 weeks if complete remission is not achieved. In patients who remit, corticosteroids should be tapered slowly over a total period of up to 6 months after achieving remission. This prolonged course of high-dose prednisolone is often associated with significant toxicity. As a result, prophylactic measures are recommended, comprising an H₂-receptor antagonist or proton pump inhibitor to prevent peptic ulceration, and bisphosphonate to prevent osteoporosis. Blood sugar level monitoring is required to identify corticosteroid-induced diabetes mellitus. For patients with relative contraindications or intolerance to high-dose corticosteroids (e.g. pre-existing uncontrolled diabetes mellitus, psychiatric conditions, severe osteoporosis, or morbid obesity), alternative therapy for which there is some evidence include daily oral cyclophosphamide or calcineurin inhibitors as discussed in frequently relapsing MCNS (see 'Frequently relapsing and steroid-dependent disease'). Glucocorticoid therapy leads to complete remission in 90 to 95% of cases. The time course to a complete remission is generally longer in adults than in children, with 50% responding by 4 weeks and 10 to 25% requiring more than 3 to 4 months of therapy (Fig. 21.8.3.2). In most cases, response to therapy of nephrotic MCNS is of an 'all or nothing' type. Partial responses are not characteristic of MCNS and, when seen, one should suspect a possible misdiagnosis, most often FSGS that was missed by biopsy sampling error. Deciding how long to pursue treatment with high-dose steroid in the grossly nephrotic patient who is not responding and yet ac-

quiring significant side effects is one of the most difficult judgments in nephrology. Children

Corticosteroid therapy (prednisone or prednisolone) is given initially for at least 8 weeks. Oral prednisone is administered as a single daily dose starting at 60 mg/m² per day or 2 mg/kg per day to a maximum of 60 mg/day. The regimen is daily oral prednisone for 4 to 6 weeks followed by alternate-day medication as a single daily dose starting at 40 mg/m² or 1.5 mg/kg (maximum 40 mg) on alternate days and continued for 4–8 weeks. Children tend to remit rapidly, with 50% responding within 2 weeks and almost all within 8 weeks. Treatment of relapses Approximately 50 to 75% of glucocorticoid-responsive adults will have a relapse. The same initial dose and duration of corticosteroids as previously described is generally used for infrequent relapses. However, in certain circumstances, such as if there is a viral or allergic trigger for the relapse, a shorter course of prednisolone may be sufficient, for example, oral prednisone at a daily dose of 1 mg/kg (maximum dose of 80 mg per day) for 4 weeks; if remission is attained, the dose may then be tapered in 5 mg decrements every 3 to 5 days to discontinuation within 1 to 2 months. Frequently relapsing and steroid-dependent disease

In adults, frequent relapses (more than three per year) occur in 10 to 25% of patients with MCNS, and in a further 25 to 30% of patients the prednisolone dose cannot be reduced below 0.2 to 0.3 mg/kg per day without relapse (steroid dependence). Due to the high morbidity of prolonged courses of glucocorticoids, steroid-sparing therapy needs to be considered in these groups of patients. There is evidence for and considerable experience with the use of oral cyclophosphamide 2 to 2.5 mg/kg per day for 8 weeks, which is effective in approximately 75% adults with frequently relapsing or steroid-dependent disease. However, side effects are potentially serious, including infertility and malignancy, and consideration of alternative agents as first line is reasonable. A calcineurin inhibitor may be used (ciclosporin 3–5 mg/kg per day or tacrolimus 0.05–0.1 mg/kg per day in divided doses) for 1 to 2 years for frequently relapsing or steroid-dependent MCNS patients who have relapsed despite cyclophosphamide, or for people who wish to preserve their fertility. Although there is limited evidence to support it, mycophenolate mofetil 500 to 1000 mg twice daily for 1 to 2 years may be effective for patients who are intolerant of corticosteroids, cyclophosphamide, and calcineurin inhibitors, and is suggested in this situation by KDIGO. However, there is no RCT evidence for which a steroid-sparing agent should be used first in frequently relapsing or steroid-dependent disease, although mycophenolate mofetil is generally well tolerated, with its main potential side effect being gastrointestinal disturbance. All these agents are also used in paediatric practice, where only one course of cyclophosphamide is given, with a maximum cumulative dose of 168 mg/kg. Rituximab is an anti-CD20 monoclonal antibody that has been used for the treatment of various glomerulopathies, including MCNS in adults. It depletes circulating B lymphocytes and thus has a more specific mode of action than glucocorticoids and cyclophosphamide. There are no RCTs assessing the efficacy of rituximab in adult MCNS, but in retrospective series it appears to achieve remission without the need for ongoing immunosuppressive therapy with other agents in about half of patients treated. It is generally regarded as a safe and well-tolerated therapy, but is not completely without complications, with a reported mortality rate across a range of autoimmune disease of about 3% in the 3 years following initiation. Rituximab is also considered in children with steroid-dependent disease who have continuing frequent relapses despite optimal combinations of prednisone and corticosteroid-sparing agents, and/or who have serious adverse effects of therapy. A recent trial of rituximab in frequently relapsing or steroid-dependent disease (in patients who had tried other second-line treatments) suggests a median relapse time of 267 days in the rituximab group versus 101 days in a placebo group. There is evidence that recovery of B-cell counts (monitored by CD19/20 levels in peripheral blood) coincides with relapse risk, so

repeated doses of rituximab may be needed to maintain adequate protection. Another agent used in paediatric practice is levamisole, an immunostimulant, which can be given as a corticosteroid-sparing agent to prevent frequency of relapses. It is used at a dose of 2.5 mg/kg on alternate days, given for at least 12 months as most children will relapse when levamisole is stopped. There is very limited published experience of levamisole in adults; hence, this treatment should be reserved to paediatric nephrology units with expertise in its use. The long-term benefits and risks of treatment with this agent are largely unknown.

21.8.3 Minimal-change nephropathy and focal segmental glomerulosclerosis 4923

Steroid refractory MCNS Steroid refractory MCNS is defined as no reduction in proteinuria despite more than 16 weeks of high-dose glucocorticoid therapy and occurs in 5 to 10% of adults with MCNS. It may be due to initial inadequate glucocorticoid therapy (e.g. for <16 weeks), the use of prescribed or over-the-counter aluminium-containing antacids that can decrease the bioavailability of the glucocorticoid, or an incorrect diagnosis, most often FSGS. This may result from sampling error, particularly if the kidney biopsy comprises few glomeruli and only superficial cortical tufts. Reassessment of the original biopsy, or a repeat biopsy, may be helpful from a prognostic perspective. The recommended treatment based on one small study in these patients is ciclosporin (5 mg/kg per day in two divided doses) with prednisone (10–15 mg/day). This approach could be used even if a repeat biopsy showed FSGS, hence such a biopsy is not mandatory.

Prognosis Historically, morbidity and mortality from untreated MCNS was high due to complications such as infection and thromboembolic disease. However, patients did spontaneously remit, possibly as many as 70% by 3 years. With glucocorticoids, remission rates rise to 90 to 95%, although as many as three-quarters may relapse. Most relapses occur within 1 year after glucocorticoid therapy has been tapered or discontinued, although occasional patients have a glucocorticoid-responsive relapse after as long as 25 years in remission. Renal function remains well preserved. Although the glomerular filtration rate (GFR) may fall during a relapse, it will generally return to within normal limits once remission is achieved. A progressive fall in GFR would be regarded by most nephrologists as an indication that the diagnosis of MCNS is incorrect and that some other glomerular pathology, most likely FSGS, is present. Up to 80% of children presenting with nephrotic syndrome will respond initially to steroids, and approximately a third of those will have no further relapses. Of the rest, 10 to 20% will have only a few relapses, but the rest will have frequently relapsing or steroid-dependent disease. Data regarding how many children will continue to relapse into adulthood are sparse, with some studies suggesting up to 42% will do so.

Focal segmental glomerulosclerosis Aetiology and pathogenesis FSGS can be split into primary (idiopathic) and secondary forms. The primary forms are divided into those caused by a Mendelian monogenic gene disorder (Table 21.8.3.2), and idiopathic cases, some of which are likely to be due to as yet undiscovered genetic mutations, and most if not all of the rest due to unidentified circulating factor(s), so-called circulating factor disease. The definitive clinical evidence of a circulating factor in some (if not all) patients with primary FSGS is the phenomenon of post-transplant recurrence of nephrotic syndrome, which affects 30 to 40% of patients with this condition, often within minutes or hours of transplant. Other evidence comes from fascinating cases of mother-to-child transfer of proteinuric disease, also a case report of recurrence in a graft in an FSGS recipient, where the transplanted kidney was then removed and donated to a non-FSGS recipient, and fully recovered function without proteinuria. One potential candidate for this circulating factor is the soluble urokinase-type plasminogen activator receptor (suPAR). This receptor acts via activation of podocyte $\alpha V\beta 3$ integrin, which plays an important role both in the

dynamic regulation of mature foot processes and their controlled adhesion to the glomerular basement membrane. Certain forms of suPAR can induce FSGS lesions in mice. In some patients with recurrent FSGS, plasmapheresis induced clinical remission and decreased both serum suPAR levels and $\beta 3$ integrin activity. In another study, suPAR was significantly elevated in sera from patients with FSGS compared both with normal controls and with patients with other proteinuric glomerular disease, and the highest serum suPAR levels were detected in pretransplant sera of patients who developed recurrent FSGS after transplantation. However, suPAR levels rise with falling GFR and are high in patients with stage 5 chronic kidney disease, which may explain why some studies using suPAR have failed to show an association with FSGS. Three large cohorts with a combined total of 1151 patients found that suPAR levels did not discriminate between primary FSGS and other causes of renal disease, the major predictor of suPAR in these studies being the level of kidney function. By contrast, a study that only included patients with estimated GFR (eGFR) greater than 40 mL/min per 1.73 m² found that suPAR levels were significantly higher in patients with FSGS than in patients with membranous nephropathy and minimal change disease, and eGFR was not correlated with levels of suPAR. Measurement of circulating suPAR using the commercially available enzyme-linked immunosorbent assay should not be used in clinical practice to distinguish primary FSGS from other renal diseases. Secondary FSGS may be caused by a number of systemic disorders in which segmental scarring of glomeruli is the end product of a variety of pathological processes (Table 21.8.3.2). Secondary FSGS may also result from an adaptive response to glomerular hyperfiltration (e.g. reduced renal mass such as unilateral renal agenesis), or increased renal vasodilatation (e.g. in diabetic nephropathy and sickle cell anaemia). Secondary FSGS is often associated with lower levels of proteinuria, which may not be in the nephrotic range, as well as reduced GFR. Table 21.8.3.2 Aetiology of FSGS Cause Comment Primary Idiopathic 'Circulating factor disease' Genetic Mutations in one of at least 60 different genes, e.g. α -actinin 4, podocin, nephrin, ion-receptor protein transient receptor potential cation channel 6 (TRPC6) Secondary Healed glomerulonephritis IgA nephropathy, vasculitis, systemic lupus erythematosus Viral infection HIV, parvovirus B19 Drugs Heroin, pamidronate, lithium Glomerular hyperfiltration (with or without reduced renal mass) Reduced renal mass, reflux nephropathy, renal agenesis, sickle cell anaemia, obesity, diabetes mellitus Parasitic infection *Schistosoma mansoni*

section 21 Disorders of the kidney and urinary tract 4924 Pathology FSGS is so named because there is focal (i.e. in some areas of the kidney cortex) and segmental (segments of the glomerulus are affected) fibrosis and occlusion of the glomerular capillaries. Different histological features denote different prognoses and steroid responsiveness: the Columbia FSGS classification is shown in Table 21.8.3.3, with an indication of how management may be affected. Several variants are described, based on the site of the segmental sclerosing lesion (perihilar variant and glomerular tip lesion), the presence of glomerular collapse (collapsing variant), and endocapillary cellularity with visceral epithelial cell hyperplasia (cellular variant), leaving 'FSGS (not otherwise specified)' when these have been excluded. This latter lesion is equivalent to classic nephrotic-associated FSGS, when the areas of segmental sclerosis are typically randomly distributed within the glomerular tuft, with a predilection for the hilar regions (Figs. 21.8.3.3 and 21.8.3.4). Focal areas of tubular atrophy and interstitial nephritis are prominent. On immunofluorescence microscopy, deposits of IgM and complement C3 may be seen in the sclerotic areas. Electron microscopy shows diffuse foot process effacement in apparently unaffected glomeruli. Epidemiology In children, FSGS incidence peaks in the 1 to 3 years age range, with a smaller peak in the early teenage years. However, if patients with a genetic cause are studied separately (c.24% of the

total), the peak incidence of age at presentation of these is in the first year of life, reflecting the prevalence of severe phenotypes due to genetic mutations. In adult registries in the United Kingdom and the United States of America, FSGS accounts for 10% of the patients in renal failure requiring transplantation. In some parts of the world, including the United States of America, Brazil, and India, the incidence of FSGS is increasing, with a particularly high incidence (up to 80% of biopsies performed for primary glomerulonephritis) in black and Hispanic patients. By contrast, data from a Caucasian population in Northern Europe revealed a relatively low proportion of FSGS, accounting for 6% of all primary glomerulonephritis, with the population incidence of FSGS remaining unchanged over the past two decades at 0.18 per 100 000 population/year. FSGS incidence peaks in middle age, with 30% of cases occurring between the ages of 46 and 55 years.

Genetics In paediatric nephrology, genetic analysis is becoming integral to diagnosis and management of FSGS. The discovery of single gene mutations responsible for hereditary FSGS has continued apace since the discovery of mutations in *NPHS1*, the gene coding for nephrin, in 1998 (Table 21.8.3.4). This transmembrane protein, a putative member of the immunoglobulin super family, appears to be at the heart of the working slit diaphragm and integral to podocyte functioning. Since then over 50 different genes have been identified as causing FSGS when affected by mutations. Many of the proteins encoded by these genes function as key components of the slit diaphragm or actin patterning complex (Fig. 21.8.3.5). Some of the mutations affect only the glomerulus, others have broader effects and the nephrotic syndrome appears as part of a wider clinical syndrome. In paediatric practice, next-generation sequencing has transformed the ability to make the diagnosis of genetic disorders in this patient group, and clinical sequencing services are now available (e.g. <http://www.nbt.nhs.uk/severn-pathology/pathology-services/bristol-genetics-laboratory-bgl>). A genetic diagnosis is clearly important for counselling and prognostic implications, but also for immediate management decisions. Results are available within a few weeks, and the rate of mutations in childhood (0–18 years) is >30%, meaning that there is a significant chance of picking up a positive result and therefore modifying therapy because the vast majority of patients with a genetic cause of nephrotic syndrome do not respond to any kind of immunosuppression. In contrast to children with FSGS, adults with nonfamilial FSGS are far less likely to have an identifiable monogenic cause of disease, Table 21.8.3.3

Idiopathic FSGS, classification and treatment

Variant	based on site of segmental sclerosing lesion	Treatment
FSGS, not otherwise specified	Steroids if nephrotic, ACE inhibitors	Perihilar variant
ACE inhibitors	Cellular variant	Steroids if nephrotic, ACE inhibitors
Glomerular tip lesion	Steroids if nephrotic, ACE inhibitors	Collapsing variant
ACE inhibitors		

Fig. 21.8.3.3 Classic segmental sclerosing glomerulonephritis at an early stage. The glomerulus shows an erratic increase in mesangium with a segmental area of foamy cells and sclerosis opposite the vascular pole, next to the tubular origin (between 12 and 1 o'clock). Haematoxylin and eosin staining, magnification ×50. By courtesy of Professor A.J. Howie.

Fig. 21.8.3.4 Classic segmental sclerosing glomerulonephritis at a late stage. Four glomeruli show an erratic increase in mesangium and segmental lesions at various sites. Periodic acid-methenamine silver staining, magnification ×64. By courtesy of Professor A.J. Howie.

21.8.3 Minimal-change nephropathy and focal segmental glomerulosclerosis 4925

Table 21.8.3.4

List of genes associated with the nephrotic syndrome

Gene	Inheritance	Accession #	Disease
ACTN4	AD	NM_004924	Familial and sporadic SRNS (usually adult)
ADCK4	AR	NM_024876	SRNS
ALG1	AR	NM_019109	Congenital disorder of glycosylation
ANLN	AD	NM_018685	FSGS (mainly adult)
ARHGAP24	AD	NM_001025616	FSGS
ARHGDI1	AR	NM_001185078	Congenital nephrotic syndrome
CD151	AR	NM_004357	NS, pretibial bullous skin lesions, neurosensory deafness, bilateral lacrimal

duct stenosis, nail dystrophy, and thalassemia minor CD2AP ADAR NM_012120 FSGS/SRNS COL4A3 AR NM_000091 Alport's disease COL4A4 AR NM_000092 Alport's disease COL4A5 X-linked AR NM_000495 Alport's disease COQ2 AR NM_015697 Mitochondrial disease/isolated nephropathy COQ6 AR NM_182476 NS $\pm$ sensorineural deafness; DMS CRB2 AR NM_173689 SRNS CUBN AR NM_001081 Intermittent nephrotic range proteinuria $\pm$ epilepsy DGKE AR NM_003647 Haemolytic uraemic syndrome + SRNS E2F3 AD NM_001949 FSGS + intellectual disability (whole gene deletion) EMP2 AR NM_001424 Childhood-onset SRNS and SSNS INF2 AD NM_022489 Familial and sporadic SRNS, FSGS-associated Charcot-Marie-Tooth neuropathy ITGA3 AR NM_005501 Congenital interstitial lung disease, nephrotic syndrome, and mild epidermolysis bullosa ITGB4 AR NM_000213 Epidermolysis bullosa and pyloric atresia + FSGS KANK1 AR NM_015158 SSNS KANK2 AR NM_015393 SSNS/SDNS $\pm$ haematuria KANK4 AR NM_0181712 SRNS + haematuria LAMB2 AR NM_002292 Pierson syndrome LMNA AD NM_170707 Familial partial lipodystrophy + FSGS LMX1B AD NM_002316 Nail patella syndrome; also FSGS without extrarenal involvement MYO1E AR NM_004998 Familial SRNS NPHS1 AR NM_004646 Congenital nephrotic syndrome/SRNS NPHS2 AR NM_014625 CNS, SRNS NXF5 X-linked recessive NM_032946 FSGS with cosegregating heart block disorder OCRL X-linked recessive NM_000276 Dent's disease 2, Lowe's syndrome, $\pm$ FSGS, $\pm$ nephrotic range proteinuria PAX2 AD NM_003987 Adult-onset FSGS without extrarenal manifestations PDSS2 AR NM_020381 Leigh syndrome PLCE1 AR NM_016341 Congenital nephrotic syndrome/SRNS PMM2 AR NM_000303 Congenital disorder of glycosylation PODXL AD NM_005397 FSGS PTPRO AR NM_030667 NS SCARB2 AR NM_005506 Action myoclonus renal failure syndrome $\pm$ hearing loss SMARCAL1 AR NM_014140 Schimke's immuno-osseous dysplasia SYNPO AD NM_007286 Sporadic FSGS (promoter mutations) TRPC6 AD NM_004621 Familial and sporadic SRNS (mainly adult) TTC21B AR NM_024753 FSGS with tubulointerstitial involvement WDR73 AR NM_032856 Galloway-Mowat syndrome (microcephaly and SRNS) WT1 AD NM_024426 Sporadic SRNS (children—may be associated with abnormal genitalia); Denys-Drash and Frasier's syndromes

section 21 Disorders of the kidney and urinary tract 4926 although it is estimated that 6 to 10% of adults with primary FSGS have a currently discoverable genetic mutation, rising to at least 17% in those with a positive family history. Currently, genetic screening is not considered cost-effective in adults, but this may change as the cost of sequencing continues to fall. In adults, the genetic contribution to FSGS susceptibility, both primary and secondary, may be polygenic, with the incidence of FSGS increased in family members of patients with FSGS without monogenic inheritance patterns. Much of the increased (four- to fivefold) risk of FSGS seen in African American compared with Caucasian patients has been attributed to a risk allele in the gene encoding apolipoprotein L1 (APOL1), which also contributes to the increased risk of developing HIVAN, diabetic nephropathy, and hypertension-associated arterionephrosclerosis. Clinical features See Chapter 21.3. Treatment General approach FSGS patients without the nephrotic syndrome who have normal kidney function typically have indolent disease that either spontaneously remits or remains stable for years. Patients without nephrotic syndrome who have decreased GFR may have secondary FSGS or else previously severe primary FSGS that went undiagnosed; such patients respond poorly to immunosuppressive therapies. ACE inhibitors/ARBs to reduce proteinuria and reduce the rate of decline of renal function are indicated, as well as close attention to blood pressure control. In nephrotic FSGS patients, supportive treatment with salt restriction and diuretics is required as for MCNS. Immunosuppression—initial strategy Corticosteroid and immunosuppressive therapy should be considered only in idiopathic FSGS associated with clinical features of the

nephrotic syndrome. Studies have reported spontaneous remission in 5 to 25% of patients, particularly in patients with tip lesions, well-preserved renal function, and lower grades of proteinuria. In such patients, immunosuppression could be delayed in case spontaneous remission occurs. Given the lack of an evidence base, there is debate about the optimal glucocorticoid regimen in FSGS: KDIGO recommends that, when appropriate, glucocorticoid treatment is initiated and tapered as in MCNS (see earlier discussion). Data from retrospective studies show response rates for complete remission ranging from 28 to 74%, and partial remission rates from 0 to 50%. The average time to complete remission is 3 to 4 months, with a range up to 8 months. As in MCNS, calcineurin inhibitors should be considered as first-line therapy for patients with relative contraindications or intolerance to high-dose glucocorticoids. Steroid-dependent or steroid-resistant disease For steroid-resistant FSGS (defined as per steroid-refractory MCNS described previously), RCT evidence supports initial treatment with ciclosporin at 3 to 5 mg/kg per day in divided doses for at least 4 to 6 months. If there is a partial or complete remission, this is continued for at least 12 months, followed by a slow taper. Response rates are 60 to 70%, but relapse rates also high at approximately 60%. Tacrolimus may be an acceptable alternative in patients who do not tolerate ciclosporin, but there are no RCTs. Calcineurin inhibitors

Gene Inheritance Accession # Disease ZMPSTE24 AR NM_005857 Mandibuloacral dysplasia with FSGS MYH9 AD/assoc. NM_002473 MYH9-related disease; Epstein's and Fechtner's syndromes APOL1 Risk factor variants NM_003661 Increased susceptibility to FSGS and ESRD seen mostly in African Americans, Hispanic Americans, and in individuals of African descent NUP107 AR NM_020401 Early-onset SRNS AD, autosomal dominant; AR, autosomal recessive; ESRD, endstage renal disease; MYH, myosin heavy chain 9; NS, nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome. Fig. 21.8.3.5 A schematic of the locations in the podocyte that proteins encoded by nephrotic syndrome genes are expressed. GBM, glomerular basement membrane; SD, slit diaphragm. Reproduced with permission from Malaga-Dieguez and Susztak. J Clin Invest. 2013 Dec 2; 123(12):4996–9. Copyright © 2013 American Society for Clinical Investigation. Table 21.8.3.4 Continued

21.8.3 Minimal-change nephropathy and focal segmental glomerulosclerosis 4927 carry a risk of nephrotoxicity, particularly in patients with a reduced GFR, hence many clinicians would not use a calcineurin inhibitor in patients with an eGFR less than 30 to 40 ml/min per 1.73 m². Patients with steroid-resistant FSGS who do not tolerate ciclosporin can be treated with a combination of mycophenolate mofetil and glucocorticoids. In addition, cyclophosphamide may be considered in patients who have shown a partial response to prednisone and have an eGFR less than 30 to 40 ml/min per 1.73 m². If used, cyclophosphamide is added before the prednisone has been discontinued and is administered for 8 to 12 weeks. More prolonged therapy (>12 weeks) is not beneficial. Several case reports have described successful use of rituximab in adult patients with steroid-dependent but not steroid-resistant FSGS; the efficacy of this therapy appears limited to patients with steroid-dependent disease. Patients with FSGS and persistent proteinuria are at increased risk of progressive CKD and its accompanying cardiovascular morbidity and mortality. Risks are dependent on the level of proteinuria and kidney function. The potential benefit of therapy includes disease cure, control, and/or slowing the progression to endstage renal disease. However, the toxicity of the therapies previously outlined is significant, particularly given the prolonged nature of the treatment and the risk of relapse. In addition, some patients, possibly as many as 50%, will not respond to immunosuppression, but can accrue a significant morbidity as a result of prolonged attempts with various treatments. It is questionable whether the benefits of immunosuppression outweigh the risks in those patients who have significantly impaired renal

function (eGFR <30 ml/min per 1.73 m²) and histological evidence of extensive glomerulosclerosis and interstitial fibrosis. In addition, for those patients in whom the disease has proved refractory to multiple prolonged courses of immunosuppression, the persistent nephrosis together with treatment side effects can result in multiple hospital admissions for complications including infection, excessive oedema, and thromboembolic disease. Occasionally, the patient and clinician together may take the decision to allow or even encourage renal failure as the disease burden of the resultant renal replacement therapy may be less than that of ongoing nephrosis. In exceptional cases, nephrectomy may be performed.

Paediatric perspective In children with FSGS without a genetic cause, or where results are awaited, a calcineurin inhibitor is used as initial therapy as per adult therapy. As in adult practice, concurrent treatment with ACE inhibitors or ARBs should be instituted for children with FSGS. In children who fail to achieve complete or partial remission with calcineurin inhibitor therapy, mycophenolate mofetil, high-dose corticosteroids, or a combination of these agents is considered. There is evidence that cyclophosphamide is not beneficial in children with FSGS, although it should be remembered that those trials were done before any genetic testing was available, so stratification of patients into those who have a disease that mechanistically benefits may still be possible. A RCT found that rituximab was not beneficial in childhood FSGS but the same caveats apply.

Prognosis In most cases of idiopathic FSGS, the progress of the disease is prolonged and characterized by a relapsing–remitting pattern, with even complete remitters having a relapse rate of up to 40%. Those with partial remissions have a risk of slowly progressive loss of kidney function. Prognosis in patients with idiopathic FSGS is predicted by the severity and persistence of proteinuria. Patients with non-nephrotic proteinuria have a good prognosis, with kidney survival rates of more than 95% after a mean follow-up of 6.5 to 9.3 years, even in older studies when few patients, if any, were treated with ACE inhibitors. A recent study concluded that even partial remission (reduction to non-nephrotic range proteinuria) was associated with significant improvement in kidney survival (80 vs 40%) compared to no remission. Prognosis of nephrotic FSGS is far worse: in a retrospective analysis of 197 patients with biopsy-proven nephrotic FSGS, at a median follow-up of 1.8 years, 23% were on dialysis. Prognosis and treatment response were predicted by histological subtype. The 17% with the tip lesion had the least tubulointerstitial injury and best renal function, and almost 50% achieved complete remission with glucocorticoid therapy. The 11% of patients with the collapsing variant had the worst outcomes, with lower rates of renal survival at both 1 year (74% vs 86% for the remaining patients) and 3 years (33% vs 67%). Treatment response also predicts survival: patients who achieve a complete remission have a 5-year survival off dialysis of 94%, as compared with 53% of those who do not achieve remission. In children with FSGS, up to 50% will reach established renal failure within 5 years. Following progression to endstage kidney disease, patients are assessed for renal transplantation, although this carries a risk of recurrent disease. As already described, a remarkable phenomenon in FSGS is that of recurrence of massive proteinuria after transplantation, sometimes within minutes or hours of the graft being placed. The reported recurrence rate in adults is 30%, and this leads to graft failure in approximately 50% of cases. After recurrence in a first transplant, the rate of recurrence in a subsequent transplant approaches 75%. Plasma exchange and protein immunoadsorption have resulted in a reduction of proteinuria or a remission of the nephrotic syndrome in some patients. In children, recurrence occurs in 50% who test negative for currently known genetic mutations. Children at highest risk are those with steroid sensitivity early in the course of disease, followed by resistance to steroids with eventual renal failure, where there is a 90% risk of post-transplantation recurrence.

Future developments The podocyte is the target cell of nephrotic syndrome and is damaged by either inherent insults (genetic mutations) or external insults, most prominently by circulating

factor(s) in this disease. Much has been learnt about important cellular pathways in the podocyte that are disrupted in disease states, most involving slit diaphragm- based signalling. As our understanding increases, this will allow much better stratification of disease according to mechanism- based understanding of the pathogenesis. For example, Mendelian monogenic disease can already be identified and treated differently, and the prospect of gene therapy based on constructs that utilize podocyte-specific promoters for targeting is realistic. As our knowledge of podocyte (or immune-related) biomarkers advances, we will be able to stratify nongenetic nephrotic syndrome into groups that will respond to targeted biological therapies that specifically affect those pathways.

Revision #1

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