21.10.7 Sickle cell disease and the kidney 5032 Cl

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section 21 Disorders of the kidney and urinary tract 5032 Renal transplantation in HUS STEC-HUS Patients with STEC-HUS normally recover renal function, although a few individuals will progress to endstage renal failure. Renal trans- plantation following STEC-HUS is associated with a low recurrence rate, less than 1%, and the 10-year graft survival is similar to those transplanted for dysplasia/uropathies and significantly better than those transplanted for other renal conditions. Renal transplantation is therefore possible in these individuals, but it is advisable to under- take genetic screening first. There have been very occasional reports of individuals with confirmed STEC-HUS having recurrent HUS following renal transplantation due to a coexistent genetic mutation. Atypical HUS In comparison, the transplant outcome for patients with aHUS was historically very poor, largely because of recurrence in the allograft. This outcome is predicted largely by the underlying genetic abnor- mality, with highest risk associated with CFH, CFB, and C3 muta- tions, and the lowest with CD46 mutations. Unlike the plasmas proteins FH, FI, C3, and FB, CD46 is mem- brane bound. As such, a renal allograft would be predicted to correct the underlying complement defect and protect against aHUS. It is because of this that the outcome is better with a recurrence rate of only approximately 20%. In those individuals with CD46 mutations in whom recurrence has occurred, additional genetic risk factors or endothelial microchimerism have been suggested to be the cause. It is perhaps not surprising that individuals with underlying gen- etic defects have a high recurrence rate because the post-transplant milieu provides the necessary disease triggers (e.g. viral diseases, ischaemia reperfusion injury, donor-specific antibodies, and im- munosuppressive drugs) to cause endothelial cell damage and acti- vation of the complement cascade. Although plasma exchange has a low success rate in rescuing recur- rent aHUS after renal transplantation, pre-emptive plasma exchange has been associated with a trend to decrease recurrence. Rescue therapy or pre-emptive treatment with eculizumab is successful and is now the treatment of choice in transplantation for aHUS. FURTHER READING Hanna RM, et al. (2019).

Atypical hemolytic uremic syndrome and complement blockade: established and emerging uses of comple- ment inhibition. Curr Opin Nephrol Hypertens, 28, 278–87. Kavanagh D, Goodship TH, Richards A (2013). Atypical hemolytic uremic syndrome. Semin Nephrol, 33, 508–30. Kavanagh D, Raman S, Sheerin NS (2014). Management of hemolytic uremic syndrome. F1000Prime Rep, 6, 119. Legendre CM, et al. (2013). Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med, 368, 2169–81. Lemaire M, et al. (2013). Recessive mutations in DGKE cause atypical hemolytic-uremic syndrome. Nat Genet, 45, 531–6. Menne J, et al. (2012). Validation of treatment strategies for enterohaemorrhagic Escherichia coli O104:H4 induced haemolytic uraemic syndrome: case-control study. BMJ, 345, e4565. Sheerin N, et al. (2016). A national specialised service in England for atypical haemolytic uraemic syndrome—the first year's experience. QJM, 109, 27–33. Spinale JM, et al. (2013). Update on Streptococcus pneumoniae associated hemolytic uremic syndrome. Curr Opin Pediatr, 25, 203–8. 21.10.7 Sickle cell disease and the kidney Claire C. Sharpe ESSENTIALS About 60% of patients with sickle cell disease have sickle cell neph- ropathy. Clinical symptoms reflect medullary compromise, with polyuria, troublesome nocturia, enuresis, and dehydration being typical early manifestations. Haematuria, nonvisible and visible, is common. The prevalence of albuminuria rises with age, and those in whom this progresses rapidly are at greatest risk of developing endstage kidney disease, which eventually affects 10 to 15% of pa- tients with sickle cell nephropathy. Management of chronic kidney disease due to sickle cell nephrop- athy is along standard lines: no specific treatment has been shown to prevent the condition or retard its progression. Introduction Sickle cell disease (SCD) is endemic in malaria-prevalent (or pre- viously prevalent) regions due to the protective nature of the car- rier state. It is most commonly found in sub-Saharan Africa, India, Saudi Arabia, and the Mediterranean (Turkey, Greece, and Italy). The prevalence of the sickle cell trait (heterozygous carriers) ranges between 10 and 40% across equatorial Africa and decreases to be- tween 1 and 2% on the north African coast and less than 1% in South Africa. Renal involvement (sickle cell nephropathy (SCN)) affects approximately 60% of patients with SCD (homozygous haemo- globin S (HbSS) and HbSβ0 thalassaemia) at some point during their life, although only 10 to 15% of these patients develop endstage kidney disease. These figures are halved in individuals with the HbSC form of the disease, which is generally less se- vere. Heterozygous patients (HbSA) may develop some tubular defects later in life, but there is no evidence that they are at a greater risk of developing progressive chronic kidney disease. It is important to remember, however, that not all renal disease in patients with SCD is due to SCN. These patients may have other conditions, for example, lupus nephritis or glomerulo- nephritis secondary to blood-borne viruses, and so microscopic

 haematuria, proteinuria, and renal dysfunction should always be investigated with this in mind. Pathophysiology A single point mutation on the β-globin gene on the short arm of chromosome 11 results in the substitution of a valine residue for the usual glutamic acid at the seventh amino acid position (including the initial methionine) and is responsible for the formation of sickle haemoglobin (HbS). This substitution renders the haemoglobin molecule much less soluble under hypoxic and acidotic conditions and prone to polymerization. This process leads to the formation of rope-like structures that span the cell and cause it to become mis- shapen and rigid. Although in health the kidneys receive approximately 25% of the cardiac output, the vessels (vasa recta) that supply the medulla of the kidney branch off early from the efferent arteriole, taking only a fraction of the total renal blood flow with them. Much of the blood that enters the renal cortex is therefore delivered back to the venous circulation without entering the medulla at all. The relatively sluggish but intricate circulation of the inner

medulla is critical to maintaining the countercurrent multiplier system of the loop of Henle, which drives water and solute reabsorption and allows for effective urinary concentration. However, the resulting hypoxia (partial pressure of oxygen 10–35 mmHg), acidosis, and hyperosmolarity make the inner medulla an ideal environment for the polymerization of deoxygenated HbS and subsequent sickling of red blood cells. Ultimately, this results in loss of vasa recta, im- paired renal medullary blood flow, microinfarcts, papillary ne- crosis, and loss of normal medullary function (Fig. 21.10.7.1). Alongside this, the persistent anaemia and a high cardiac output lead to a paradoxically increased blood flow to the renal cortex and raised glomerular filtration rate in children and young adults, resulting in glomerular hypertrophy and hyperfiltration. Over time, the persistent high pressure in the glomeruli can cause proteinuria and eventually glomerulosclerosis and renal impair- ment. Association studies have suggested that those patients who have the highest degrees of haemolysis are more likely to have a raised glomerular filtration rate and to develop the early manifest- ations of SCN. Clinical manifestations Tubular dysfunction Hyperfiltration alongside poor medullary perfusion causes hyposthenuria (inability to concentrate urine under water-deprived conditions) in early childhood. Up to the age of 10 this is reversible with blood transfusions, but later in life this is irreversible, frequently leading to polyuria, troublesome nocturia, enuresis, and dehydra- tion. In addition, tubular dysfunction can be demonstrated in patients with SCN who often have a partial form of distal renal tubular acid- osis and a primary defect in the tubular secretion of potassium re- sulting in a hyperchloraemic metabolic acidosis and hyperkalaemia (Table 21.10.7.1). In contrast, proximal tubular function appears to be supranormal, associated with increased reabsorption of phosphate and β-microglobulins and increased secretion of creatinine, making this molecule a poor surrogate marker of glomerular filtration rate. Haematuria Haematuria is common, both in SCD and sickle cell trait. It can range from nonvisible and painless, through visible and painless, to visible and painful. It is usually self-limiting but can be severe enough to require transfusion. Small microinfarcts are often the cause of minor bleeding but full-blown renal papillary necrosis with sloughing of the ischaemic papilla can cause severe haemorrhage and obstruction and may be complicated by superadded infection. Although most cases of haematuria are self-limiting, it is important that they are in- vestigated to exclude more sinister underlying causes. One rare but devastating complication of both SCD and, more commonly, sickle cell trait is medullary carcinoma, a cancer specific to patients with (a) (b) (c) Fig. 21.10.7.1 Microangiograph of a pyramid from (a) a normal kidney (72 years); (b) a sickle cell haemoglobin C disease kidney (HbSC) (5 years); and (c) a homozygote sickle cell disease kidney (3 years). Reprinted from The Lancet, Vol. 295, Statius van Eps LW, Pinedo-Veels C, de Vries GH, de Koning J, Nature of concentrating defect in sickle cell nephropathy microangiopathic studies, 450–452, Copyright © 1970, with permission from Elsevier.

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