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Autosomal dominant polycystic kidney disease and sickle cell trait

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Macroscopic haematuria due to the rupture of renal cysts is a common manifestation of autosomal dominant polycystic kidney disease (ADPKD). Many patients with ADPKD have frequent episodes of haematuria or evidence of intracystic haemorrhage throughout the progression of the disease.[1] The presence of sickle cell trait (Hb AS) is also accompanied by manifestations in the kidney, particularly haematuria, and papillary necrosis is the most frequent cause of macroscopic haematuria in heterozygous carriers of this haemoglobinopathy.[2-6] In one study, macroscopic haematuria was the cause for 4% of all hospital admissions of Afro-Americans with sickle cell trait.[7] As such, it is not surprising that the simultaneous inheritance of both genetic diseases can create a synergy with regard to the appearance of these haemorrhagic complications. Despite the fact that the association of these two hereditary diseases, ADPKD and sickle cell trait, was first recorded in the 1990's, when a study suggested that Afro-American patients with ADPKD and sickle cell trait could develop chronic renal failure (CRF) early in life,[8,9] only recently was it pointed out that sickle cell trait is a risk factor for the development of chronic kidney disease in a population of Afro-Americans with CRF.[10,11]

Haemoglobin S is the result of glutamic acid being replaced by valine as the sixth amino acid in the beta globin chain, which produces a haemoglobin tetramer (alpha2/beta S2) that is poorly soluble when deoxygenated.[4] Polymerisation of this type of deoxyhaemoglobin (HB S) is essential to vaso-occlusive phenomena.[4,7,12,13] The polymer assumes the form of an elongated fibre that becomes aligned with other fibres, resulting in the distortion of the erythrocyte into the classic crescent-moon or sickle shape, and a drastic reduction in the flexibility of the cell. The common renal manifestations of this disease in homozygous individuals (Hb SS) include defects in urine concentrations (altered counter current mechanism), distal renal tubular acidosis, abnormal proximal tubular function, and in early stages, increased glomerular filtration rate.[14,15] The primary cause of these symptoms appears to be the deformation of erythrocytes (which adopt the sickle shape) in the *vasa recta* capillaries of the renal medulla. It is well established that dehydration, acidosis, decreased oxygen pressure, and high osmolarity are the primary triggers for erythrocytes to adopt the sickle shape. The normal medullary medium plays an important role in this process, as it has a low oxygen pressure and high osmolarity. Furthermore, blood flow in *vasa recta* capillaries is much slower than in cortical vessels, leading to a longer transit time. Congestion and stasis in *vasa recta* capillaries can cause focal haemorrhage and necrosis. Finally, these processes can lead to interstitial inflammation and fibrosis, tubular atrophy, and papillary infarctions due to vascular lesions. These lesions are more severe in patients with Hb SS genotypes than in Hb AS carriers. In very early stages, the physiopathology of hyperfiltration is believed to be attributed to the vasculopathy associated with haemolysis more than vaso-occlusive processes related to viscosity.[14,15] In order to control haematuria resulting from papillary necrosis, several different medical treatments have been used, such as administering vasopressin, tranexamic acid, and oral urea, or direct haemostasis over the affected papillae, which includes the use of laser treatment.[4,16-19]

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Sickle cell disease (Hb SS) affects approximately 300 000 live births per year.[4,7] The prevalence of sickle cell trait is approximately 8%-10% in Afro-Americans,[4] and can be as high as 25%-30% in certain areas of western Africa.[4,7] Roughly 2.5 million people in the USA and 30 million people in the world are heterozygous for the gene that causes sickle cell disease. The presence of sickle cell trait (Hb AS), the most common haemoglobinopathy in the United States, is estimated to be 40 to 50 times more common than sickle cell anaemia (Hb SS), and is particularly prevalent among individuals that descend from Sub-Saharan Africa, India, Saudi Arabia and Mediterranean countries.[4,7] With the current patterns of global migration, the number of carriers of the sickle cell haemoglobin gene is increasing in Europe, and is estimated to be around 1% of the total population. As such, many European countries have introduced early detection programmes for haemoglobinopathies in newborn infants.

Sickle cell trait is a benign disorder with no haematological manifestations in the heterozygous carrier, since the morphology of the erythrocytes, red blood cell indices, reticulocyte count, and peripheral blood smears are normal. In spite of the generally benign nature of Hb AS, several different potentially severe complications have been described. For instance, Hb AS carriers can develop rhabdomyolysis, heat stroke, acute renal failure, papillary necrosis, splenic infarction, and sudden death.[4,7,12,13,20] Some of these events can occur during conditions of extreme physical stress, and are occasionally attributed to vaso-occlusive crises, suggesting that, although sickle cell trait is usually quiescent, it is not always benign. Sickle cell trait is associated with health deterioration in terms of urine concentration, haematuria, and renal papillary necrosis.[21] A less common cause of haematuria in these cases is renal medullary carcinoma, which is a tumour that is almost exclusively found in Hb AS patients.[22]

Although sickle cell trait alone may not be sufficient for the development of chronic kidney disease, it could contribute to the progression of CRF in the presence of additional factors such as ADPKD, diabetes, and hypertension. Since patients with sickle cell trait and diabetes mellitus are prone to suffering from papillary necrosis and episodes of haematuria,[23,24] it is possible that the pathophysiological factors induced by sickle cell trait could exacerbate the microvascular complications that arise from diabetes mellitus. Meanwhile, it is unknown if sickle cell trait patients have an increased risk of developing microvascular complications associated with diabetes mellitus. Recently, association with sickle cell trait has been recognised as an indicator of poor prognosis in diabetic patients, and patients with African heritage develop renal failure on average 10 years earlier than Caucasian patients.

KEY CONCEPTS

1. Sickle cell trait (Hb AS) is a benign disorder carried by heterozygous individuals, with no haematological manifestations. The morphology of erythrocytes, red blood cell indices, reticulocyte counts, and peripheral blood smears are all normal.
2. Dehydration, acidosis, reduced O2 pressure, and high osmolarity are the primary triggers for the sickle shape taken by erythrocytes in the vasa recta capillaries.
3. Hb AS is associated with deteriorating urine concentrations, haematuria, and renal papillary necrosis.
4. Simultaneous inheritance of sickle cell trait and ADPKD can create a synergy, causing recurrent haematuria.
5. In Afro-American patients with ADPKD, sickle cell trait must be ruled out.
6. Although the existence of sickle cell trait alone may not be enough for developing chronic kidney disease, it could contribute to the progression of CRF in the presence of other factors such as ADPKD, diabetes, and arterial hypertension.

REFERENCES

1. Masoumi A, Reed-Gitomer B, Kelleher C, Bekheirnia MR, Schrier RW. Developments in the management of autosomal dominant polycystic kidney disease. Ther Clin Risk Manag 2008;4:393-407.
2. De Jong PE, Statius Van Eps LW. Sickle cell nephropathy: new insights into its pathophysiology. Kidney Int 1985;27:711-7.
3. Allon M. Renal abnormalities in sickle cell disease. Arch Intern Med 1990;150:501-4.
4. Kiryluk K, Jadoon A, Gupta M, Radhakrishnan J. Sickle cell trait and gross hematuria. Kideny Int 2007;1:706-10.
5. Niang A, Diouf B, Ndiaye/Sene FS, Fall S, Moreira/Diop T. Sickle cell disease and the kidney. Saudi J Kidney Dis Transpl 2004;15:180-4.
6. WHO. Sickle-cell Anaemia. Report by the Secretariat. Fifty-ninth World Health Assembly. 2 April, 2006.
7. Shaw C, Sharpe CC. Could sickle cell trait be a predisposing risk factor for CKD? Nephrol Dial Transplant 2010;25:2403-5.
8. Yium J, Gabow P, Johnson A, Kimberling W, Martínez-Maldonado M. Autosomal dominant polycystic kidney disease in blacks: clinical course and effects of sickle-cell hemoglobin. J Am Soc Nephrol 1994;4:1670-4.
9. Kimberling WJ, Yium JJ, Johnson AM, Gabow PA, Martínez-Maldonado M. Genetic studies in a black family with autosomal dominant polycystic kidney disease and sickle-cell trait. Nephron 1996;-72:595-8.
10. Derebail VK, Nachman PH, Key NS, Ansede H, Falk RJ, Kshirsagar AV. High prevalence of sickle cell trait in african americans with ESRD. J Am Soc Nephrol 2010;21:413-7.
11. Cavanaugh KL, Lanzkron S. Time to recognize an overlooked trait. J Am Soc Nephrol 2010;21:385-6.
12. Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong Y. Complications associated with sickle cell trait: a brief narrative review. Am J Med 2009;122:507-12.
13. Funakoshi H, Takada T, Miyahara M, Tsukamoto T, Noda K, Ohira Y, et al. Sickle cell trait as a cause of splenic infarction climbing mt. Fuji. Intern Med 2010;49:1827-9.
14. Haymann JP, Stankovic K, Levy P, et al. Glomerular hyperfiltration in adult sickle cellanemia: a frequent hemolysis associated feature. Clin J Am Soc Nephrol 2010;5:756-61.
15. Hirschberg R. Glomerular hyperfiltration in sickle cell disease. Clin J Am Soc Nephrol 2010;5:748-9.
16. Baldree LA, Ault BH, Chesney CM, Stapleton FB. Intravenous desmopressin acetate in children with sickle trait and persistent macroscopic hematuria. Pediatrics 1990;86:238-43.
17. Moudgil A, Kamil ES. Protracted, gross hematuria in sickle cell trait: response to multiple doses of 1-desamino-8-D-arginine vasopressin. Pediatr Nephrol 1996;10:210-2.
18. Pariser S, Katz A. Treatment of sickle cell trait hematuria with oral urea. J Urol 1994;151:401-3.
19. Herard A, Colin J, Youinou Y, et al. Massive gross hematuria in a sickle cell trait patient with renal papillary necrosis. Conservative approach using a balloon ureteral catheter to tamponade the papilla bleeding. Eur Urol 1998;34:161-2.
20. Scheinman JI. Sickle cell disease and the kidney. Nat Clin Pract Nephrol 2009;5:78-88.
21. Connes P, Hardy-Dessources MD, Hue O. Counterpoint: sickle cell trait should not be considered asymptomatic and as a benign condition during physical activity. J Appl Physiol 2007;103:2138-40.
22. Dimashkieh H, Choe J, Mutema G. Renal medullary carcinoma: a report of 2 cases and review of the literature. Arch Pathol Lab Med 2003;127:e135–e138.
23. Ajayi AA, Kolawole BA. Sickle cell trait and gender influence type 2 diabetic complications in African patients. Eur J Intern Med 2004;15:312-5.
24. Bleyer AJ, Reddy SV, Sujata L, et al. Sickle cell trait and development of microvascular complications in diabetes mellitus. Clin J Am Soc Nephrol 2010;5:1015-20.

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