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A rare case of genetically linked primary distal renal tubular acidosis and Southeast Asian Ovalocytosis

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A 23-year-old Malaysian female presented to the emergency department with fever and left loin pain on a background of established dRTA of unknown aetiology.

CT imaging demonstrated nephrocalcinosis and left-sided ureteric obstruction (Fig 1A). Both blood and urine cultures were positive for *Abiotrophia defectiva*. Blood pH was 7.13 (7.35-7.45); serum bicarbonate was 9 mmol/L (21-28) and creatinine elevated at 146 μ mol/L(49-90). White cell count was elevated and mild macrocytic anaemia noted. LDH was elevated (409 U/L (<250)) and haptoglobin reduced (<0.1L g/L (0.3-2.0)). Blood film revealed erythrocytes with transverse bands of pallor known as stomatocytes (Fig 1B).

A diagnosis of urosepsis secondary to ureteric obstruction on a background of dRTA combined with SAO and haemaolytic anaemia was established. The patient received intravenous antibiotics, sodium bicarbonate and ureteric stenting, with rapid recovery and discharge to home for outpatient LASER stone disintegration. Genetic testing confirmed the diagnosis of SAO with concomitant dRTA.

[Insert Figure 1 (A,B) here]

SAO is a hereditary haematological condition common in Southeast Asia and Melanesia with a prevalence as high as 30% in some areas.¹⁻³ It presents as

macrocytosis with stomatocytes on blood film and may confer some protection against *Plasmodium falciparum*, but is otherwise clinically benign.²

Genetically, SAO is an autosomal dominant variant of the *SLC4A1/AE1* gene on chromosome 17: a *p.Ala400_Ala408* deletion variant (a deletion of codons 400-408 known as B3SAO).¹ This gene codes for a protein known as “Band 3” that is found in both the membrane of red blood cells and the basolateral membrane of renal α -intercalated cells in the nephron collecting duct. In the red cell it acts as a component of the membrane cytoskeleton and in both locations acts as a chloride-bicarbonate anion exchanger.² This genetic variant results in SAO, but despite its effects on the nephron, does not on its own result in a dRTA phenotype.²

dRTA is rare, with incidence estimated to be <1:100 000.⁴ It is characterised by the inability of α -intercalated cells of the collecting duct to secrete H⁺ ions into urine and an associated metabolic acidosis caused by a non-functional chloride-bicarbonate anion exchanger in α -intercalated cells.²⁻⁴ Familial dRTA may result from a simple autosomal recessive variant on the *SLC4A1/AE1* gene of chromosome 17 in which a p.G701D loss-of function mutation occurs.¹ This may either occur in homozygosity, or due to compound heterozygosity with SAO gene mutations.²

These genetic abnormalities are relatively uncommon. The *p.Ala400-Ala408del* and *p.G701D* genetic variants present in very low numbers, with overall minor allele frequency of 0.00005 and 0.00004 in the total data set of the Genome Aggregation Database.⁶ Our patient represents one such rare case where genetic sequencing revealed that on chromosome 17, the *SLC4A1/AE1* gene contained one allele with the classic SAO *p.Ala400-Ala408* deletion mutation (B3SAO) and the other allele a *p.G701D* substitution. Therefore, they may be recognised as one such compound heterozygote ('or pseudodominant' case) for the *G701D/SAO SLC4A1* gene mutation linked with both autosomal recessive dRTA and SAO.^{1,2,5}

As in this patient, it appears that it is when a SAO mutation occurs alongside another Band 3 mutation on the opposite allele (such as the *G701D* mutation here) complete dRTA can also occur.²⁻³

dRTA often presents with nephrocalcinosis and nephrolithiasis.⁴ If inadequately recognised and treated, it may severely impact on childhood growth and lead to a 3-fold risk of developing chronic kidney disease.⁴ Current research suggests long-term management of dRTA should focus on maintaining urine calcium and serum bicarbonate in the normal range.⁴

(ii) References

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(iii) Figure 1: (A) CT imaging demonstrating nephrocalcinosis and left sided urinary tract obstruction and (B) Patient blood film containing stomatocytes