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P332 -A Novel SGPL-1 gene mutation causing a congenital nephrotic syndrome with associated primary adrenal insufficiency

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A 5-month-old male infant, born to consanguineous first-cousin Bengali parents, presented with a gastrointestinal illness and persistent metabolic acidosis. The past history included gastro-oesophageal reflux disease (GORD), failure to thrive and prolonged neonatal jaundice.

Systemic examination revealed mild peripheral oedema, bilateral cryptorchidism, under-virilised male genitalia, ichthyosis, and generalized motor developmental delay. Initial investigations demonstrated hypoalbuminaemia, nephrotic range albuminuria, hypothyroidism, persistent raised anion gap metabolic acidosis, lymphopenia and transient glycosuria and hypokalaemia. The raised anion gap, hypokalemia and glycosuria subsequently normalised with rehydration. He was diagnosed with congenital/infantile nephrotic syndrome (CNS) and additionally diagnosed with primary adrenal insufficiency (PAI) and gonadal failure.

Initial genetic screening (Bristol steroid resistant nephrotic syndrome genetic panel) for congenital and infantile nephrotic syndromes revealed the patient to be 46 X,Y karyotype with a heterozygous missense mutation in COL4A4 (NM_000092.4); Intron 41, c.3974-4dupT which did not explain the clinical phenotype.

Medical therapy was initiated with ACE inhibition (captopril), levothyroxine, hydrocortisone, fludrocortisone, sodium bicarbonate, sodium feredetate, 1-alfacalcidol and ranitidine.

ACE inhibition was terminated following a rising trend in plasma creatinine which heralded a rapid deterioration in renal function.

The patient died at 9 months of age with acute pulmonary oedema and oligo-anuric renal failure precipitated by a volume-depleting diarrhoeal illness. The family declined renal replacement therapy because of the high burden of morbidity to date.

Based on clinical suspicion, specific Sanger sequencing identified a rare homozygous missense mutation in SGPL1 (chr10:72619152, c.511A>G; p.N171D) and heterozygosity was confirmed subsequently in his parents and two sisters. Renal biopsy was deferred initially due to small size, ongoing nephrosis and risk of bleeding. A later opportunity did not present itself.

SGPL1 encodes the intracellular enzyme sphingosine-1-phosphate lyase (SGPL1). This enzyme is found in the endoplasmic reticulum of renal podocytes, mesangial and endothelial cells¹. Immunofluorescence studies have also found co-localization in the renal proximal tubules, which may explain the initial biochemical picture of some proximal tubular leak in our patient¹. The enzyme is also found in the adrenal cortex, testes and thyroid gland, justifying the phenotype of this genetic mutation².

Here, we report a case with a newly described variant of the mutation in the sphingosine-1-phosphate lyase (SGLP1) gene which links CNS and PAI. SGPL1 deficiency has also been associated with other endocrinopathies and neurological impairment. The management of patients with SGPL1 deficiency is

complex and requires a multidisciplinary approach. Awareness that the syndrome exists will prompt screening for associated conditions and genetic counselling for the family.

The identification of the SGPL1 mutation finally provides a diagnostic link for patients presenting with CNS and PAI. It has also led to the identification of co-morbidities associated with this syndrome, resulting in the possibility of earlier screening and treatment. This could reduce the rate of CKD progression and perhaps minimise the long-term incidence of associated complications.