Lesch-Nyhan Syndrome associated with chronic kidney disease due to renal hypoplasia: a case study

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INTRODUCTION:
Deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) causes a broad spectrum of disorders. The more severe form, Lesch-Nyhan Syndrome (LNS), is associated with minimal residual enzyme activity, causing neurological dysfunction and other consequences of uric acid overproduction (gouty arthritis and nephrolithiasis)1.

We report a two-year-old boy with LNS, who presented with stable chronic kidney disease (CKD) on a background of developmental delay. Renal biopsy demonstrated renal hypoplasia, rather than uric acid nephropathy, as the cause of his kidney disease. This is the first case report of renal hypoplasia in a patient with Lesch-Nyhan Syndrome.

DIAGNOSTIC TESTS:
Whole exome sequencing:
HPRT1 (NM_000194.2): c. 568G>T | p.G190X
Enzyme activity:
HPRT activity 0.1U/g Hb (normal range 3.7-7.5)

CASE REPORT:
History:
• The patient initially presented at four months of age with mild developmental delay and failure to thrive, and was noted to have raised creatinine (78umol/L, upper limit of normal 36).
• Renal ultrasound showed a 13mm shadowing non-obstructive calculus in the interpolar region of the normally-sized left kidney. There was bilateral echogenicity and loss of corticomedullary differentiation, with a small right kidney (<5th centile).
• A left renal biopsy demonstrated cortical maldevelopment, with persisting subcortical metanephric blastema and nephrogenic rests, and up to 30% focal tubular volume loss (see pictures below)
• Molecular testing for developmental delay identified a hemizygous likely pathogenic variant in HPRT1 (see ‘Diagnostic Tests’); serum uric acid was elevated (0.33mmol/L; reference range 0.07-0.33), and enzyme activity was also supportive of a diagnosis of LNS.
• Allopurinol was commenced, with improvement in the uric acid level to within the reference range (0.28mmol/L)
• The patient has ongoing mild-moderate developmental delay.
• Follow-up ultrasounds have demonstrated persistent parenchymal echogenicity, with minimal increase in size of the kidneys over two years; the renal function has stabilized (most recent creatinine 44umol/L)

DISCUSSION:
Lesch-Nyhan Syndrome (LNS) is an X-linked disorder of purine metabolism. It reflects the severe end of a spectrum of conditions associated with hemizygous pathogenic variants in HPRT1: in LNS the residual enzyme activity encoded by these molecular changes is generally less than 2% of normal controls2.

Aside from the characteristic neurological phenotype (mild-to-moderate developmental delay, hypotonia and behavioural disturbances including self-injury), patients with LNS also manifest with other signs of uric acid overproduction, including nephrolithiasis and gouty arthritis3. The nephrolithiasis that is classically described occurs due to uric acid stones, and is one of the major causes of death in the second or third decade of life4.

We report renal hypoplasia in a patient that was diagnosed with chronic renal failure of unclear aetiology, who was subsequently noted to have LNS. There was no evidence of uric acid stones on serial renal ultrasonography.

Renal hypoplasia is a relatively common condition in children, with an estimated incidence of 1 in 4004. It is often contributed to by environmental factors, such as uroplacental insufficiency and maternal undernutrition5. However there are also numerous genetic syndromes associated with renal hypoplasia, indicating that in some circumstances molecular factors also are implicated6.

Given renal hypoplasia has not been reported previously in LNS, this could be an unrelated finding. However it is also possible that it is part of an expanded LNS phenotype, or that it may co-exist with uric acid nephropathy (given biopsies are rarely performed if the likely cause of renal failure is already known).

CONCLUSION:
LNS has been associated with uric acid nephropathy and nephrolithiasis previously; however, this is the first report of renal hypoplasia. Investigation of further cases of CKD in LNS will help ascertain whether this is part of an expanded renal phenotype. If renal hypoplasia is indeed part of the renal phenotype, allopurinol is unlikely to halt disease progression.

References:

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