Case Reports

Fanconi syndrome in a child on anticonvulsant therapy

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Case report

A 10 year old girl was referred to the psychiatric unit at the Lady Ridgeway Hospital (LRH) for management of progressively worsening symptoms thought to be of psychosomatic origin, of 9 months duration. She was the first born to unrelated parents. Her developmental milestones except for speech were normal. She had been treated for a generalized seizure disorder since two and a half years of age with sodium valproate at a dose of 30mg/kg/day (recommended dose: 10–50mg/kg/day). Although she was seizure free for two years and three months, she was still on anticonvulsant therapy.

9 months prior to presentation to LRH she developed pain in the lower limbs with difficulty in walking. She received symptomatic treatment at the local hospital where the investigations done were normal. She was irritable and depressed and almost confined to her bed as she found it extremely difficult to walk and she could no longer go to school where she was a year 5 student with poor academic performance. Seven months after onset of symptoms she was re-investigated and found to have osteoporosis involving the lower limbs which was attributed to 'disuse'. The birth of the second child coincided with the onset of these symptoms and as an organic reason apart from the 'disuse osteoporosis' could not be identified; she was referred to LRH for psychiatric assessment.

At LRH, fluoxetine was started for the depressive symptoms and a DEXA scan confirmed severe osteoporosis and as the serum phosphate was found to be very low, she was referred to us for further evaluation. Polyuria and polydipsia of one month duration was also noted.

On examination in January 2008, her growth parameters were well below the 3rd percentile. She was in pain and refused to walk. There was generalized muscle wasting and weakness mostly involving the proximal muscles of the lower limbs with a power of grade 4. Rest of the examination was normal.

A differential diagnosis of a renal tubular disorder or a metabolic bone disease was entertained. Although there were no clinical features, there was radiological evidence of rickets with a fracture of the shaft of the left ulna (Figure 1) and a very high alkaline phosphatase of 2319 u/l (80-480 u/l) and marginally low calcium of 2.14mmol/l (2.2-2.7mmol/l).

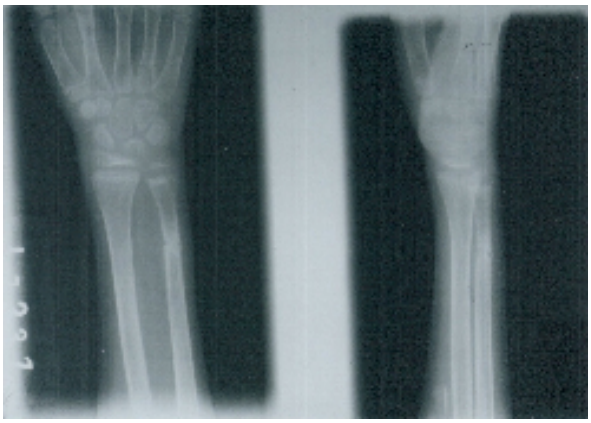

Figure 1: *Active rickets with fracture of shaft of left ulna*

The persistently low serum potassium values of 2.2 to 2.6mmol/l (3.5-5.5mmol/l) and the very low serum phosphate value of 0.6mmol/l (1.45-2.16mmol/l) indicated a probable proximal renal tubular defect. This was confirmed by generalized aminoaciduria, glycosuria, phosphaturia of 22 mg/kg/day (15-20mg/kg/day) and an arterial blood gas analysis showing hyperchloraemic normal anion gap mild metabolic acidosis with pH of 7.35 and bicarbonate of 17mmol/l. Serum creatinine was normal and there was no nephrocalcinosis on ultrasonography and an acid loading test excluded distal renal tubular acidosis (DRTA).

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The most likely diagnosis was hypophosphataemic rickets resulting from proximal renal tubular acidosis (PRTA) as a very rare complication of sodium valproate therapy.

She was started on polycitra (sodium citrate and potassium citrate) and phosphate buffer or Joulie solution (dibasic sodium phosphate and phosphoric acid) and 1, 25 dihydroxy cholecalciferol in March 2008. Two weeks later her serum potassium had normalized and she no longer had polyuria. The sodium valproate was tailed off and stopped over 8 weeks. At review, after four months of treatment, she was no longer depressed and she could now walk without any pain. Her appetite had improved and weight had increased by 1 kg. Her biochemistry had significantly improved with alkaline phosphatase of 881 u/l, serum phosphate of 1.20mmol/l, normal calcium, electrolytes and blood gas values. Radiological changes of osteomalacia and rickets had improved and the fracture had healed (Figure 2).

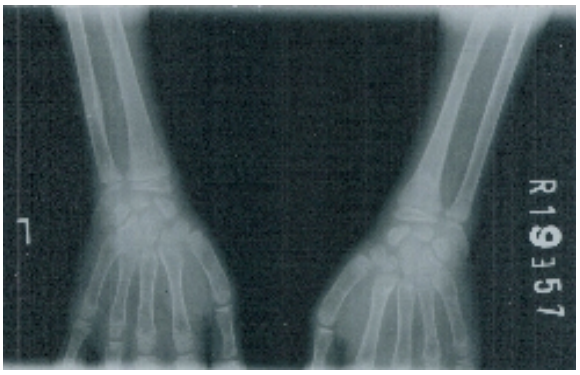

Figure 2 *After treatment*

We gradually tailed off sodium valproate over 8 weeks and she was started on phosphate buffer for the phosphate supplementation, 1,25 dihydroxy cholecalciferol for rickets and polycitra to supply potassium and bicarbonate. Renal losses of glucose and amino acids are not usually symptomatic and do not require replacement.

We screened this child for cystinosis and Wilson disease. Other hereditary diseases were unlikely from the history and examination and there was no history suggestive of exposure to heavy metals. Therefore, the most likely cause for FS in this child was treatment with sodium valproate.

We reviewed her in October 2009 at the age of 12 years. She was asymptomatic except for an elevated alkaline phosphatase level of 1049 u/l. This was after one and a half years of stopping sodium valproate and six months of being on tailing off doses of the supplements. We will continue to monitor her clinically and biochemically once the supplements are discontinued.

Discussion

Renal tubular disorders are relatively rare in children. However considering the spectrum of renal tubular functions, these disorders result in varied manifestations emphasizing the need for their consideration in many clinical conditions. Tubular dysfunction should be considered in all children with failure to thrive, polyuria, refractory rickets, hypokalaemia and metabolic acidosis[1].

Generalized muscle weakness, bone tenderness, and recent onset polyuria and polydipsia were the initial clues to investigate our patient for a possible renal tubular disorder associated with metabolic bone disease.

The initial assessment of a child with a suspected tubular disorder includes estimating blood levels of sodium, potassium, phosphate, pH and bicarbonate. Urine should be examined for pH and osmolality, and excretion of electrolytes, proteins, sugar and calcium. These tests provide information on renal tubular handling of these ions, and ability to concentrate and acidify urine. Depending on the clinical profile, abnormal screening tests are followed up with tests for specific tubular functions and evaluation for a possible underlying condition.

Our patient had RTA confirmed by hyperchloraemic, normal serum anion gap metabolic acidosis and biochemical and radiological evidence of rickets which favoured proximal renal tubular acidosis (PRTA). However, as she had a positive urine anion gap and alkaline urine (pH 7) an ammonium chloride acid loading test was performed. This confirmed intact acidification at the distal renal tubule excluding DRTA[2]. Definitive diagnosis of PRTA is by assessing the fractional excretion of bicarbonate which cannot be done in Sri Lanka.

Patients with proximal RTA generally have a plasma bicarbonate concentration more than 15 meq/L and severe metabolic acidosis is uncommon as was seen in our patient[3].

Once the diagnosis is confirmed, children with PRTA should undergo evaluation for other proximal tubule functions (phosphate, proteins, glucose, and amino acid excretion) and screening for an underlying aetiology[3].

Phosphaturia was confirmed by 24 hour urine collection for phosphate excretion and a proline amino acid band which is characteristic of generalized aminoaciduria was detected in urine for aminoacid chromatography. Urine for glucose, which was negative initially, became positive in subsequent urine analysis with normal fasting blood sugar level and evidence of proteinuria further confirmed proximal tubular defect. These findings were compatible with Fanconi syndrome (FS).

In children, the commonest cause of FS is cystinosis. Other causes of FS in children include galactosaemia, hereditary fructose intolerance, glycogen storage diseases, Lowe syndrome, medullary cystic disease, tyrosinaemia, familial idiopathic FS, Wilson disease and exposure to heavy metals such as lead, cadmium and mercury.

Although among the adverse effects of sodium valproate, renal involvement is uncommon, FS due to valproate therapy has been reported in several studies[4,5,6].

Prognosis of FS depends on the underlying aetiology. Patients with FS due to valproate therapy reported in the literature have improved after discontinuation of the drug within a period of 2 to 12 months[4].

This case demonstrates the vigilance that is required when managing a child on long term drug therapy.

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