CASE REPORT

Sodium valproate-induced Fanconi type proximal renal tubular acidosis

Mark Knights,[1] Tina Thekkekkara,[2] Alistair Morris,[3] Eric Finlay[1]

[1]University of Leeds Teaching Hospitals, Leeds, UK
[2]Sheffield Children's Hospital, Sheffield, UK
[3]Calderdale and Huddersfield NHS Foundation Trust, Huddersfield, UK

Correspondence to
Dr Mark Knights,
markknights@doctors.org.uk

Accepted 14 January 2016

SUMMARY

We present a case series of three patients with sodium valproate-induced Fanconi's syndrome, with ages ranging from 5 years to 12 years. The most important diagnostic features of this syndrome include hypophosphataemia, glycosuria and proteinuria, which are also noted in our series. Furthermore, also added is that clinical fractures representing an underlying osteopaenia may provide an opportunity for early intervention as it raises the suspicion of Fanconi's syndrome. Previous case reports suggest there is a subpopulation of individuals who are at risk of developing this condition. These individuals share similar characteristics, including being non-ambulatory, developmentally delayed and/or tube fed. Withdrawing sodium valproate therapy is the ultimate treatment for valproate-induced Fanconi's syndrome and from previous case series, normalised renal function occurs in approximately 6 months. Often, supplement support is also required for deranged electrolyte balance.

BACKGROUND

Sodium valproate is one of the commonest antiepileptic medications prescribed. It is used in the treatment of seizure activity as well as for control of bipolar disorder, depression, myoclonus and migraines. Common side effects of valproate include nausea, weight gain, gastric irritation and diarrhoea; it can also cause liver dysfunction.

Currently, there have been 25 reported cases of sodium valproate-induced Fanconi's syndrome,[1 2–15] a disease of the proximal renal tubule in which glucose, amino acids, uric acid and electrolytes are lost in the urine instead of being reabsorbed, which can have a devastating impact on child development and health. We report three cases of valproate-induced Fanconi's syndrome.

CASE PRESENTATION

Case 1

The first case is that of a 6-year-old White British boy. Family history and pregnancy were both uneventful. He was diagnosed with Mowat-Wilson syndrome in the first year of life. At the age of 2 years, he started to develop atypical absent seizures, which were treated with valproate and topiramate. He was fed through a jejunal tube, due to the severity of his gastro-oesophageal reflux.

At the age of 6 years, he was electively admitted for investigation of hypophosphataemia and pathological fractures, which were identified a year earlier. A bone mineral density scan carried out at the same time revealed a Z score of −5.2. At this time, the patient weighed 13.8 kg and was on a valproate dose of 35 mg/kg/day (normal range 20–40 mg/kg/day). His other regular medications included topiramate (25 mg twice daily), ranitidine and erythromycin (as a motility agent). Serum biochemistry and urine dipstick results are reported in table 1.

Case 2

The second case involves a 12-year-old British Asian boy. At week one of life, he started to have tonic seizures and was treated with phenobarbitone, later phenytoin was trialled, before being switched to valproate and topiramate. At 8 months of age, he was recognised to have developmental delay and learning disability, with microcephaly, retinal dystrophy, high myopia and thalassaemia traits. To date, he remains with an undiagnosed neurogenetic condition, is non-ambulatory, and is fed via gastrostomy tube with his seizures remaining difficult to control. At the age of 10 years he had an X-ray where the bones were described as osteopaenic.

At the age of 12 years, weighing 35 kg, he was reviewed as an acute outpatient due to parental concerns that he was generally unwell, lethargic and not his normal active self. His examination was unremarkable. His regular medications at the time were sodium valproate 17 mg/kg/day, topiramate (100 mg twice daily), Becotide inhaler and Abidec. His blood gas showed that he had a mild compensated metabolic acidosis with a pH 7.36, pCO_2 4.4 and base excess −6.3. Serum biochemistry and urine dipstick results can be seen in table 1.

Case 3

The final case is that of a British Asian boy. Within the first year of life, he was diagnosed with severe developmental delay with microcephaly and gastro-oesophageal reflux. At the age of 2 years, he was started on valproate for generalised tonic clonic seizures. To date he remains with an undiagnosed neurological condition, and is tube fed and non-ambulatory.

When he was 5 years of age, his parents brought him to the Paediatric Assessment Unit because of a 1-month history of puffiness and swelling of his face and lower limbs. Examination was unremarkable. An X-ray of his left wrist was also carried out at the time, which was suggestive of underlying rickets. At admission, his sodium valproate dose was 35 mg/kg/day. His regular medications were baclofen, ranitidine, erythromycin (used as a motility agent) and Gaviscon. Serum biochemistry and urine dipstick results can be seen in table 1.

To cite: Knights M, Thekkekkara T, Morris A, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2015-213418

Table 1 Serum biochemistry and urine dipstick results of the three cases

	Case 1	Case 2	Case 3	Normal range
Serum biochemistry				
Alkaline Phosphatase	3726	Not recorded	2602	40–150 iu/L
Bicarbonate	19	20	Not recorded	22–30 mmol/L
(Adjusted) calcium	2.11	2.65	2.16	2.20–2.60 mmol/L
Parathyroid hormone	4.7	2.8	5.3	1.5–7.6 mmol/L
Phosphate	0.38	0.47	0.51	1.05–1.80 mmol/L
Potassium	3.7	3.1	3.3	3.5–5.0 mmol/L
Sodium	147	136	135	135–145 mmol/L
Urea	8.0	6.6	5.6	2.5–7.0 mmol/L
Urine dipstick				
pH	6.0	8.0	Not recorded	4.5–8.0
Blood	Negative	+	++	Negative
Glucose	+++	++	++	Negative
Ketoacids	++	Negative	Negative	Negative
Leucocytes	Negative	+	Negative	Negative
Protein	++	++	+++	Negative

DIFFERENTIAL DIAGNOSIS

- Proximal renal tubular acidosis induced by drugs other than sodium valproate (eg, ifosfamide, antiretrovirals, expired tetracyclines).
- Lead poisoning—may be accompanied by a history of pica.
- Lowe syndrome—associated with bilateral cataracts and very rare in females.
- Glycogen storage diseases—variable presentation depending on type.Nephropathic cystinosis—becomes apparent in children older than 6 months, often with eye involvement and reduced skin pigmentation, and progresses to renal failure often by the age of 10 years.
- Wilson's disease—usually appears in children older than 10 years of age, with neuropsychiatric symptoms, cardiomyopathy and Kayser-Fleischer rings.

TREATMENT

Case 1

Based on the results, Fanconi's syndrome was confirmed. The patient was initially put on a weaning dose of valproate, which was eventually stopped altogether. Topiramate was also stopped and levetiracetam slowly introduced at 300 mg twice daily. Electrolyte abnormalities were corrected with calcium Sandoz, phosphate supplement, alfacalcidol, colecalciferol, potassium citrate and sodium bicarbonate. This case was complicated by the lack of large bowel removed at surgery for Hirschsprung's disease. The electrolyte load required to normalise the plasma abnormalities caused huge fluid problems. The patient eventually required a prolonged period of parenteral feeding to gain electrolyte control. Following 3 months of therapy, his tubular acidosis returned to normal with no abnormalities in his serum or urine biochemistry. Two years post event he remains off all supplements and has a negative urinalysis; his epilepsy, however, has become very difficult to control.

Case 2

Based on the findings, a diagnosis of renal Fanconi's syndrome was performed. In the absence of other predisposing factors, it was concluded that long-term valproate therapy was the most likely cause of the proximal renal tubulopathy in this patient. He was screened for other causes of proximal renal tubular acidosis, which were all negative. Consequently, his valproate medication was gradually discontinued over 3 months with topiramate remaining unchanged. Lamotrigine (30 mg twice daily) was added as topiramate alone was not controlling his seizures. Phosphate-Sandoz (6 tablets per day) and potassium chloride (10 mL twice daily) were also added to correct his electrolyte imbalance. Three months after complete valproate discontinuation, his urinalysis had returned to normal, and he was off all electrolyte supplementation, with normal plasma levels.

Case 3

Based on the serum and urine biochemistry results, a diagnosis of Fanconi's syndrome secondary to valproate use was made. The patient was put on a reducing dose of valproate and levetiracetam was slowly introduced (eventually to 450 mg twice daily). He was also started on various supplements including phosphate (13 mmol three times a day), alfacalcidol (1 µg once daily) and calcium gluconate, to correct his electrolyte abnormalities. Three months following his admission all his serum and urine biochemistry had returned to normal and he was off all oral supplements.

DISCUSSION

Fanconi's syndrome is an impairment of the proximal renal tubules where they become ineffective in reabsorbing electrolytes, glucose, amino acids and low molecular weight proteins, leading to acidosis, electrolyte imbalance, osteomalacia and growth failure. In our report, a review of all three patients' medical history showed normal laboratory findings during previous years so that a congenital form of Fanconi's syndrome could be excluded. Furthermore, Fanconi syndrome can be caused by heavy metals, antibiotics and cytotoxic agents.[16] None of these substances had been administered to the patients at any time. Finally, the relatively quick recovery of electrolyte balance and clear urine samples following the cessation of valproate therapy (improvement seen within the first few weeks) in itself is highly indicative of a proximal tubulopathy induced by this medication.

The mechanism of action of valproate includes sodium channel blockade, increased γ-aminobutyric acid function and modulation of *N*-methyl-D-aspartate receptors.[17] In terms of the difference in absorption, one paper compared it between the nasogastric route, per rectal route and intravenous route among neonates. Among the six neonates who had valproate through the nasogastric tube, significant differences were noted in the volume of distribution, oral clearance and rate of elimination.[18] This may explain why the subpopulation of patients who were tube fed in this series have a higher predisposition to develop Fanconi's syndrome.

It is not uncommon for individuals who develop Fanconi's syndrome to also present with osteopaenia, as occurred with these cases. In each case, parathyroid hormone levels were within normal range, ruling out hyperparathyroidism as a cause of the osteopaenia. Adjusted calcium levels were below normal range in two of the cases but above normal in the other case. Low calcium would be an unlikely cause of the reduced bone density because of the lack of associative symptoms and a normal parathyroid hormone. Vitamin D deficiency could be a possible cause for the osteopaenia in these cases and it is a recognised side effect of antiepileptic drugs, although this is rarely observed in the newer, non-enzyme-inducing drugs.

Ultimately, the authors suspect the osteopaenia may indicate an early stage of valproate-induced Fanconi's syndrome, which could provide an opportunity for early intervention, and therefore any child taking valproate who presents with reduced bone density should be regarded with a high degree of suspicion as to the cause and investigated accordingly. Vitamin D deficiency has also been known to cause proximal renal tubular acidosis directly, although a rise in parathyroid hormone levels would be expected, which was not seen in any of the cases.

Valproate is thought to cause an exacerbation of underlying mitochondrial cytopathy[18–21] and is considered to be the antiepileptic drug with the highest potential to do so.[17] However, none of our patients had confirmed mitochondrial disorders and, unlike the features described in the various publications, this case series does not demonstrate features consistent with mitochondrial toxicity, which include stroke-like episodes, lactic acidosis, myopathy and features suggestive of encephalopathy.

All three cases also share a number of similarities that are notable in case studies previously reported including being tube fed, developmentally delayed and severely disabled or bedridden. It appears that these features, due to their commonality in being reported, indicate a subpopulation of individuals who may be more likely to develop Fanconi's syndrome, than those who suffer from epilepsy and take valproate, and are otherwise well. Furthermore, the range in the duration of valproate therapy from beginning medication to developing Fanconi's syndrome, is between 3 and 11 years according to our case series, suggesting that the progress is not quick nor does it develop in a predictable time frame, although an infection has been suggested as a trigger mechanism for developing the syndrome.

In conclusion, since the first case we discovered, we have raised awareness and, as a result, have identified an increasing number of valproate-induced Fanconi's syndrome cases. We suggest from our experience that this condition goes undetected and as a result remains under-reported. Indeed, Altunbaşak *et al*[22] found significantly increased levels of N-acetyl-β-D-glucosamine:creatinine ratio in children on valproate compared to those who were not taking it, indicating that subclinical proximal tubular toxicity could be significantly more common than simply those cases who present clinically. To reiterate, the authors report a further three clinical cases that also have a striking number of features in common with those previously reported. It would appear that there is a subpopulation of individuals particularly at risk of developing Fanconi's, who share one or a number of features including being non-ambulatory, tube fed and/or developmentally delayed. The reasons for these associations and the pathophysiology of Fanconi syndrome as a valproate-induced complication are not yet understood. The authors advise physicians to be vigilant of all epileptic children taking valproate, especially those who fit within the subpopulation and those who develop osteopaenia or present with fractures. Hypophosphataemia, glycosuria and proteinuria are the commonest presenting manifestations of Fanconi's, but there is variability in the presenting electrolyte derangement. Regular urine and serum analysis is therefore advised for individuals taking valproate, especially high-risk individuals.

Learning points

- There are increasing numbers of valproate-induced Fanconi's syndrome cases that often go undetected or that are under-reported.
- There appears to be a subpopulation of individuals who are particularly at risk of developing Fanconi's syndrome who are non-ambulatory, tube fed and/or developmentally delayed.
- High vigilance is needed for those who fit within the subpopulation and develop osteomalacia or who present with fractures.
- Hypophosphataemia, glycosuria and proteinuria are the commonest presenting manifestations of Fanconi's syndrome but there is variability.

Contributors MK and TT authors; AM and EF editing and data supply.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Knights M, Thekkekkara T, Morris A. Finlay E. Abstracts—48th ESPN Meeting, Brussels, September 2015. *Pediatr Nephrol* 2015;30:1543–730.
2 Dhillon N, Högler W, Fractures and Fanconi syndrome due to prolonged sodium valproate use. *Neuropediatrics* 2011;42:119–21.
3 Fukuda Y, Watanabe H, Ohtomo Y, *et al*. Immunologically mediated chronic tubulo-interstitial nephritis caused by valproate therapy. *Nephron* 1996;72:328–9.
4 Endo A, Fujita Y, Fuchigami T, *et al*. Fanconi syndrome caused by valproic acid. *Pediatr Neurol* 2010;42:287–90.
5 Hawkins E, Brewer E. Renal toxicity induced by valproic acid (Depakene). *Pediatr Pathol* 1993;13:863–8.
6 Inoue T, Tanaka Y, Otani R, *et al*. [Three cases of Fanconi syndrome associated with valproate sodium treatment]. *No To Hattatsu* 2011;43:233–7.
7 Knorr M, Schaper J, Harjes M, *et al*. Fanconi syndrome caused by antiepileptic therapy with valproic Acid. *Epilepsia* 2004;45:868–71.
8 Lande MB, Kim MS, Bartlett C, *et al*. Reversible Fanconi syndrome associated with valproate therapy. *J Pediatr* 1993;123:320–2.
9 Lenoir GR, Perignon JL, Gubler MC, *et al*. Valproic acid: a possible cause of proximal tubular renal syndrome. *J Pediatr* 1981;98:503–4.
10 Shiari R, Bagherzade L, Alaei MR. Fanconi syndrome associated with valporic acid: a case report. *Iran Red Crescent Med J* 2011;13:844–5.
11 Smith GC, Balfe JW, Kooh SW. Anticonvulsants as a cause of Fanconi syndrome. *Nephrol Dial Transplant* 1995;10:543–5.
12 Watanabe T, Yoshikawa H, Yamazaki S, *et al*. Secondary renal Fanconi syndrome caused by valproate therapy. *Pediatr Nephrol* 2005;20:814–17.
13 Yoshikawa H, Watanabe T, Abe T. Fanconi syndrome caused by sodium valproate: report of three severely disabled children. *Eur J Paediatr Neurol* 2002;6:165–7.
14 Zaki EL, Springate JE. Renal injury from valproic acid: case report and literature review. *Pediatr Neurol* 2002;27:318–9.
15 Watanabe T, Nakayasu K, Nagayama Y. Autoimmune haemolytic anaemia and renal Fanconi syndrome caused by valproate therapy. *Eur J Pediatr* 2005;164:186–7.
16 Izzedine H, Launay-Vacher V, Isnard-Bagnis C, *et al*. Drug-induced Fanconi's syndrome. *Am J Kidney Dis* 2003;41:292–309.
17 Nanau RM, Neuman MG. Adverse drug reactions induced by valproic acid. *Clin Biochem* 2013;46:1323–38.
18 Chaudhry N, Patidar Y, Puri V. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes unveiled by valproate. *J Pediatr Neurosci* 2013;8:135–7.
19 Krähenbühl S, Brandner S, Kleinle S, *et al*. Mitochondrial diseases represent a risk factor for valproate-induced fulminant liver failure. *Liver* 2000;20:346–8.
20 Lam CW, Lau CH, Williams JC, *et al*. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) triggered by valproate therapy. *Eur J Pediatr* 1997;156:562–4.
21 Lin CM, Thajeb P, Valproic acid aggravates epilepsy due to MELAS in a patient with an A3243G mutation of mitochondrial DNA. *Metab Brain Dis* 2007;22:105–9.
22 Altunbaşak S, Yildizaş D, Anarat A, *et al*. Renal tubular dysfunction in epileptic children on valproic acid therapy. *Pediatr Nephrol* 2001;16:256–9.