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Reminder of important clinical lesson

Anticonvulsant-induced rickets and nephrocalcinosis

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Summary

Reported here is the case of a severely disabled young girl who developed Fanconi syndrome secondary to long-term valproic acid administration, ultimately leading to hypophosphatemic rickets. Although nephrocalcinosis is not a common feature in patients with proximal tubulopathy, the patient presented also with this condition, and the concomitant use of another anticonvulsant might have potentiated this condition. The purpose of this report is to increase awareness among healthcare providers of such rare but significant complications associated with anticonvulsants.

BACKGROUND

Valproic acid is a commonly used antiepileptic medication with remarkable activities against a wide range of seizure disorders. While it is commonly known for adverse effects such as elevation of hepatic enzymes, hyperammonemia, pancreatitis, gastrointestinal disturbances, thrombocytopenia, alopecia and weight gain, there have been rare reports of patients acquiring Fanconi syndrome after consumption of valproic acid.[1] Although Fanconi syndrome is characterised by generalised defects in the proximal tubules, secondary to defective reabsorption of the glomerular filtrate, nephrocalcinosis is not a common feature due to the coexisting renal wasting of citrate.[1] The excessive urinary loss of small solutes, if uncorrected, leads to acidosis, rickets, growth failure and hypokalemic myopathy.[2] Topiramate, on the other hand, has been demonstrated to predispose patients to calculi formation.[3]

CASE PRESENTATION

A 10-year-old Caucasian female was referred to the nephrology service for hypophosphatemia. She was born at 40 weeks gestation with a birth weight of 2040 g. She was diagnosed postnatally with a complex syndrome secondary to partial deletion of chromosome 4p. She suffered from severe developmental delay and poor oral intake that required gastrointestinal tube supplemental feeding soon after birth. Valproic acid was initially started at the age of one for recurrent seizures. Topiramate was also added to the regimen soon after, due to inadequate control of her seizures by valproic acid alone. The current doses of her antiepileptics and other medications are: valproic acid: 125 mg a.m, 62.5 mg p.m and 125 mg nocte; topiramate: 25 mg a.m, 12.5 mg pm and 25 mg nocte; carnitine 50 mg twice daily; lansoprazole 15 mg twice daily and calcium carbonate 125 mg daily. Her valproic acid levels had been within therapeutic ranges. Her family history was insignificant for any renal or metabolic disease. The patient experienced a distal fracture of her left femur secondary to a road traffic accident. Her laboratory investigations 6 months before this incident were within normal limits, except for a mild elevation of alkaline phosphatase at 414 U/l (normal range: 40 to 360 U/l). On physical examination, both body weight (11.4 kg) and length (102 cm) were below the 5th percentile of standards. Her pulse was 96 beats per min and her blood pressure was 86/42 mm Hg. The physical examination was generally unremarkable aside from dysmorphic facial features and small body size.

Tables 1 and 2 depict the results of her initial laboratory investigations. She had non-anion gap metabolic acidosis and renal hypophosphatemia with a fractional excretion of phosphate of 66%. Otherwise, her serum electrolytes were within normal limits. Urinalysis revealed generalised proximal tubulopathy with presence of glucose, protein,

Table 1 Results of initial laboratory investigations (blood)

Blood			
Test	**Results**	**Reference ranges**	
Sodium	137	135–145	mmol/l
Potassium	3.7	3.5–5.0	mmol/l
Chloride	108	98–107	mmol/l
CO2	16	22–30	mmol/l
Urea	2.5	3.0–6.5	mmol/l
Creatinine	53	50–100	μmol/l
Total calcium	2.22	2.15–2.55	mmol/l
Phosphate	0.57	1.20–1.80	mmol/l
Magnesium	1.02	0.60–1.10	mmol/l
Total protein	63	60–80	g/l
Albumin	37	35–50	g/l
Glucose	3.8	<11.1	mmol/l
Anion gap	13	5–17	mmol/l
Ionised calcium	1.32	1.16–1.29	mmol/l
Aspartate transaminase	34	<35	U/l
Alanine transaminase	18	0–28	U/l
Alkaline phosphatase	414	40–360	U/l
Creatine kinase	30	<150	U/l
Intact PTH	3.9	1.6–6.9	pmol/l
25 (OH) Vit D	127.5	>80	nmol/l
1,25 (OH) Vit D	37	39–193	pmol/l
White blood cell count	8	4.5–13.5	$\times 10^9$/l
Haemoglobin	126	115–155	g/l
Platelet count	173	150–400	$\times 10^9$/l

25 (OH) Vit D, 25-hydroxy vitamin D; 1,25 (OH) Vit D, 1, 25 dihydroxy vitamin D; PTH, parathyroid hormone.

Table 2 Results of initial laboratory investigations (urine)

Urine		
Test	**Results**	**Reference ranges**
Osmolality	272	50–1200 mmol/kg
Creatinine	1.7	mmol/l
Sodium	34	mmol/l
Potassium	38	mmol/l
Chloride	49	mmol/l
Calcium	3	mmol/l
Phosphate	12	mmol/l
Protein	0.23	g/l
Glucose	1+	Negative
Specific gravity	1.01	
Blood	Negative	Negative
pH	6.5	5.0–8.0
Nitrites	Negative	Negative
Leucocyte esterase	Negative	Negative
Reducing sub	0.25%	Negative
β2-microglobulin	74540	0–212 μg/l
B2M/UCR ratio	21297.1	0–29
Phosphoserine	193	70–138 μmol/gCr
Taurine	570	639–1866 μmol/gCr
Threonine	4893	121–389 μmol/gCr
Serine	6983	362–1100 μmol/gCr
Asparagine	1332	72–332 μmol/gCr
Glutamine	7772	369–1014 μmol/gCr
Glycine	37716	897–4500 μmol/gCr
Alanine	6054	231–915 μmol/gCr
Citruline	1009	Oct-99 μmol/gCr
-butyric	116	0–77 μmol/gCr
Valine	263	58–143 μmol/gCr
Cystine	1002	25-125-μmol/gCr
Cystathionine	86	0–26 μmol/gCr
Ornithine	524	31–91 μmol/gCr
Lysine	3427	153–634 μmol/gCr
Histidine	3983	644–2430 μmol/gCr
Arginine	126	31–109 μmol/gCr

B2M/UCR, β-2-microglobulin to urine creatinine; Reducing sub, reducing substances.

amino acids, β2-microglobulin and phosphate in her urine (table 2). Her intact parathyroid hormone and vitamin D levels were within acceptable limits. X-rays of the fractured limb revealed generalised osteopenia compatible with rickets. Her alkaline phosphatase was abnormally high at presentation. Renal ultrasound showed bilateral nephrocalcinosis, and her urine calcium creatinine ratio was 1.8 (normal is less than 0.2).

DIFFERENTIAL DIAGNOSIS

The clinical presentation was suggestive of Fanconi syndrome with rickets and nephrocalcinosis. Although renal loss of calcium is part of the proximal tubulopathy of Fanconi syndrome, nephrocalcinosis is not a usual feature due to the co-existing excessive loss of citrate in urine. However, mixed types of proximal and distal tubular acidosis complicated by nephrocalcinosis have been reported in patients treated with valproic acid.[4 5] On the other hand, topiramate, a weak carbonic anhydrase inhibitor, has led to nephrolithiasis secondary to tubular acidosis and reduction of citrate excretion in urine.[3] Although there has not been any report of nephrocalcinosis in patients treated with topiramate, it may potentiate the calcium deposition in renal tissue by reducing the citrate excretion.

TREATMENT

The approach to the management of secondary Fanconi syndrome should include elimination or minimisation of further exposure to the offending drug, in addition to replacing the electrolyte deficiencies.[6] As valproic acid was the likely cause of Fanconi syndrome in our patient, the medication was stopped and replaced by levetiracetam. On the other hand, as topiramate can cause renal tubular acidosis and might worsen the calcium deposition in the kidney, the dose of topiramate was reduced initially and was subsequently discontinued. The patient was also treated with vitamin D and phosphorous supplementations for her hypophosphatemic rickets, as well as potassium citrate for her renal tubular acidosis.

OUTCOME AND FOLLOW-UP

Her hypophosphatemia and acidosis, as well as her proteinuria and glucosuria, improved over the next few months. Subsequent x-rays showed resolution of her rickets. Her vitamin D, phosphorus and potassium citrate supplementation were discontinued after 12 months. At her follow-up 6 months after the termination of all supplementation, her serum phosphate level was normal at 1.36 mmol/l and her bicarbonate level was 22 mmol/l. Her alkaline phosphatase level also returned to normal at 135 U/l. The urinalysis was negative for glucose and protein. A repeat renal ultrasound showed only minimal nephrocalcinosis.

DISCUSSION

While the exact causative mechanism remains unclear, Fanconi syndrome typically occurs with some inborn errors of metabolism such as cystinosis, as well as with some acquired diseases. Certain heavy metals and pharmacological agents have been reported to cause secondary Fanconi syndrome, including antibiotics, various cytotoxic agents and anticonvulsants.[7] Among anticonvulsants, valproic acid has been reported to be associated with Fanconi syndrome in a number of cases.[7–13] A study performed by Watanabe *et al*, which sought to clarify the clinical characteristics of patients with Fanconi syndrome secondary to valproic acid use, indicated that young age, being severely disabled with tube feeding, and polypharmacological therapy for seizures are all contributing factors, and our patient had all of these clinical characteristics.[12]

The mechanism by which valproic acid causes Fanconi syndrome remains to be elucidated. In some previously reported cases, observed giant mitochondrial abnormalities in the proximal tubules were thought to represent a direct effect of valproic acid on these mitochondria.[13 14] It is also possible for drug-induced interstitial nephritis, caused by hypersensitivity to drugs, to result in Fanconi syndrome.[15] This is generally associated with systemic manifestations of hypersensitivity, including skin rash and fever. Thus, it is currently believed that valproic acid-induced Fanconi syndrome may be caused by a direct nephrotoxic effect or hypersensitivity as major mechanisms.[7 16] In the case reported here, drug-induced hypersensitivity was not likely, as there were neither signs of interstitial nephritis nor any extra-renal manifestations of hypersensitivity.

Although most of the paediatric cases of Fanconi syndrome complicated by valproic acid consumption have

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reported from Asia,[2 7 12 17 18] children from other continents have also been reported.[8–11 19–21] It is not known whether or not geographical or ethnical background plays any role in the pathogenesis.

Anand *et al* have described a child who presented with Fanconi syndrome secondary to chronic valproic acid use.[5] The child also suffered from nephrogenic diabetes insipidus secondary to the long-term acidosis and hypokalemia, and the resulting hypernatremia was the focus of their case. The presence of nephrocalcinosis is not common in patients with proximal tubular defects, as the co-existing wasting of citrate in urine usually prevents the formation of nephrocalcinosis. On the other hand, topiramate is a commonly prescribed medication for the treatment of resistant partial seizures and has been known for the associated risk of renal calculi in adults, only a few cases have been reported in children.[22–27] Topiramate is a weak inhibitor of carbonic anhydrase that leads to an increased loss of bicarbonate and increased pH in the urine, as well as hypocitraturia, thus facilitating the intrarenal calcium deposition and nephrocalcinosis.[23 28–30] We attributed the nephrocalcinosis in our patient to the chronic use of valproic acid, and the concomitant use of topiramate might have also worsened the situation by inducing hypocitraturia.[31 32] However, whether or not supplementation of citrate may mitigate the problem has not yet been systemically tested.

As levetiracetam is excreted in urine, its use has been restricted in patients with renal dysfunction.[33] Our patient has normal renal function and her dose needed to be adjusted only according to her body weight. Caregivers need to balance the risks and benefits when considering altering any treatment plan. In our patient, despite the fact that her Fanconi syndrome resolved after the discontinuation of valproic acid and topiramate, her seizure control deteriorated. Lacosamide has recently been added to her regimen. The team is currently monitoring the efficacy of this new combination.

CONCLUSION

Based on the small number of cases that have been reported thus far, the risks for valproic acid-induced Fanconi syndrome and topiramate-induced nephrolithiasis in children are still low. However, as the clinical uses of these medications are common and the resultant morbidities are profound, children who are being treated with these medications should be routinely screened for complications.

Learning points

- Children with disabilities maybe more at risk to develop complications secondary to valproic acid treatment.
- Patients on valproic acid need to be monitored routinely for potential risks of developing Fanconi syndrome.
- Topiramate is another commonly used anticonvulsant that can lead to significant morbidity.

Competing interests None.

Patient consent Obtained.

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