CLINICAL PRACTICE

Clinical Vignettes

Valproate-induced Fanconi Syndrome in a 27-Year-old Woman

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Valproate-induced Fanconi Syndrome (VFS) is a rare complication of this therapy that has been previously described only in children with epilepsy. We report the first known case of an adult with VFS. Metabolic derangements lead patients to present with fatigue, confusion, weakness, and even bone fractures. Identification and discontinuation of the offending agent is the treatment of choice and helps confirm the diagnosis. This case highlights the importance of surveillance for metabolic derangements among patients on long term therapy with this commonly prescribed medication.

KEY WORDS: valproic acid; valproate; Fanconi syndrome; adult.

J Gen Intern Med 26(9):1072-4

DOI: 10.1007/s11606-011-1708-7

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INTRODUCTION

Fanconi syndrome or proximal tubular dysfunction is characterized by urinary losses of amino acids, low-molecular weight protein, bicarbonate, glucose, phosphate, and sodium resulting in dehydration, electrolyte abnormalities, altered mental status, and in severe cases, osteomalacia and fractures. Fanconi syndrome may be caused by inborn errors of metabolism (primary), by acquired conditions or exposure to toxic agents (secondary), or rarely, it can be idiopathic. Fanconi syndrome is a rare but well-described complication of valproate therapy among a subset of children¹⁻¹¹. Previous reports of this phenomenon are among severely disabled and bedridden children on long term valproate therapy. Here we describe, to our knowledge, the first reported case of valproate-induced Fanconi syndrome (VFS) in an adult, review the literature, and discuss diagnosis, pathogenesis, and management of VFS.

CASE REPORT

A 27-year-old Caucasian female with history of epilepsy characterized by generalized tonic-clonic seizures presented three and a half weeks after sustaining a fall during a seizure which lasted less than 30 seconds and resulted in an ankle injury. The patient's husband noted that she was extremely fatigued, confused, and bedridden for an unusually long time after the

event. Upon evaluation, she was complaining of increasing swelling, redness, and tenderness of the left lower extremity. Her review of systems revealed polyuria, polydipsia, but no constitutional symptoms or changes in appetite, diet, or abnormal ingestions (e.g., pica). Her past medical history was most notable for epilepsy requiring a vagal nerve stimulator implantation and was otherwise unremarkable for any kidney, liver, neurologic, or psychologic diseases. Review of her medications included oxycodone/acetaminophen, valproate, pregabalin, and alprazolam. She denied any family history for malignancies, diabetes, or metabolic disorders. She denied any alcohol intake in the last 2 years, as well as any tobacco or illicit drug use.

Physical exam demonstrated a temperature of 36.6 C, blood pressure 121/76 mm Hg, pulse 97 beats per minute, and respiratory rate 16 breaths per minute. She was extremely disoriented. Fundoscopic exam revealed no signs of hemorrhages or papilledema. Integument exam did not show any evidence of alopecia or nail bed abnormalities. Musculoskeletal exam was significant for ecchymoses and significant left ankle edema along with bimalleolar tenderness, decreased range of motion of the ankle, and a decreased Achilles tendon reflex. Cardiac, respiratory, and abdominal exams were benign. There was no hepatomegaly or splenomegaly. Neurologic exam showed normal cranial nerves, motor, strength, sensation, and reflexes. Pertinent laboratory findings included hypokalemia (2.4 mmol/L [3.6-5.2]), hypocalcemia (8.6 [8.9-10.1 mg/dL]), hypophosphatemia (1.2 mg/dL [2.5-4.5]), hypouricemia (1.6 mg/dL [2.7-6.1]), normoglycemia (91 mg/dL [70-100]), and hypovitaminosis D (<6.0 ng/ml [>20]). Her complete blood count was unremarkable. Her fasting lipid profile showed no abnormalities. Urinalysis revealed glucosuria of 137 mg/dL (<25) and uric aciduria of 755 mg/spec (<750) (Table 1). Urine protein in a 24-hour analysis was significantly elevated at 4.7 grams. A left lower extremity x-ray revealed trimalleolar fracture with lateral displacement of a distal fibular fragment.

The patient's altered mental status, glycosuria without hyperglycemia, and suggestive constellation of electrolyte abnormalities (Table 1) raised the clinical suspicion for a proximal tubule defect (type 2) as the unifying mechanism of illness. Furthermore, the patient's low impact ankle fracture and hypovitaminosis D was consistent with the known causal association between proximal tubule dysfunction and osteomalacia in adults¹². This suspicion prompted measurement of urine electrolytes, which were likewise suggestive (Table 1). A nephrology consult was obtained, and their recommendations prompted measurement of renal proximal tubule function using a 24-hour urinary retinol binding protein (RBP) assay, a low-molecular weight protein, and showed a level of 212,112 ug/24 hours (<163 ug/24 hours), thereby confirming the diagnosis of proximal tubule dysfunction.

Attention was then directed to the identification of potential secondary causes for proximal tubular dysfunction. A thorough

Received October 28, 2010

Revised January 12, 2011

Accepted March 9, 2011

Published online April 23, 2011

Table 1. Admission Serum and Urine Studies

	Serum	Urine
Na+	136 mmol/dL (135-140)	85 mmol/L (41-227)
K+	↓ 2.4 mmol/L (3.6-5.2)	49 mmol/L (17-77)
HCO ₃ ⁻	↓ 21 mmol/L (22-29)	-
Cl ⁻	108 mmol/L (100-108)	50 mmol/L (40-224)
Urea nitrogen	6 mg/dL (6-21)	-
Cr	1 mg/dL (0.6-1.1)	159 mg/dL (2-610)
Mg 2+	2.4 mg/dL (1.7-2.3)	-
Ca 2+	↓ 8.6 mg/dL (8.9-10.1)	-
Phos	↓ 1.2 mg/dL (2.5-4.5)	101 mg/dL (2-285)
Glucose	91 mg/dL (70-100)	↑ 137 mg/dL (<25)
Protein	6.7 g/dL (6.3-7.9)	↑ 440 mg/dL (2-10)
Uric Acid	↓ 1.6 mg/dL (2.7-6.1)	↑ 755 mg/dL (2-275)
Anion Gap	7	84

Note normoglycemic glycosuria, with hypouricemia, hypophosphatemia, non-anion gap metabolic acidosis, and a positive urine anion gap, all indicative of a proximal tubule dysfunction

family history for inherited renal disorders was unremarkable and the patient's past medical history revealed no evidence of congenital renal disorders or nephrolithiasis. She was unemployed and lived primarily at home without any unusual occupational or environmental exposures (e.g., heavy metals). She did not take herbal products. The patient denied any exposures to lead, aminoglycosides, chemotherapeutic agents, or expired tetracyclines. HIV testing was negative. Serum and urine protein electrophoresis with immunofixation were within normal limits. Heavy metal evaluation was negative.

Literature review revealed that valproate has been shown to cause Fanconi syndrome in children. Although our patient was an adult, her presentation was consistent with these previous case reports and further medication history revealed that she has been using valproate for roughly 5 years. Valproate levels revealed elevated free (25 ug/mL [4-15]) and total (136 ug/mL [40-100]) values. Valproate was immediately discontinued and her seizures were controlled with lamotrigine. She was started on calcium,

phosphate, potassium, vitamin D supplementation, and intravenous normal saline. Within one week, serum electrolytes, uric acid, urinalysis, and urinary electrolytes all normalized. Her mental status improved and she was stable for orthopedic surgical intervention.

DISCUSSION

Our patient demonstrated findings consistent with valproate-induced Fanconi syndrome. Valproate therapy in children is a known cause of Fanconi syndrome, with reports describing severe mental status changes, electrolyte disturbances, and osteomalacia; however, many of these cases have been previously reported among bedridden children with epilepsy. To our knowledge, this is the first case documenting valproate-induced Fanconi syndrome in an adult, thereby extending the demographic spectrum of this side effect beyond the pediatric population. Internists should be aware of the potential for this serious side effect of this commonly prescribed medication.

Fanconi syndrome is predominantly a proximal tubule defect that is usually acquired in the adult population, but can be inherited as well (Table 2). Previous case reports among children have shown that VFS can develop as early as 10 months after initiation of valproate or as late as 8 years^{2,8}. Patients present with insidious onset of fatigue, polyuria, polydipsia, and dehydration. Prolonged bedrest has been implicated as potential risk factor for developing VFS, however, no epidemiologic studies have done to assess this assumption^{5,6,8,10}. If the condition is not diagnosed early, patients may present with metabolic bone disease leading to pathologic fractures. Typical electrolyte disturbances include hypokalemia, hyperchloremia, hypophosphatemia, hypocalcemia, hypouricemia, and a non-anion gap metabolic acidosis all consistent with a type II renal tubular acidosis. Urinalysis reveals severe electrolyte wasting, positive urine anion gap, and inappropriate loss of low-molecular weight proteins, amino acids, and glucose. The finding of a normoglycemic patient with glucosuria should be the first sign that the proximal tubule filtration/resorption system is impaired and that asymptomatic, inappropriate loss of electrolytes may be occurring.

Depending on the clinical picture, confirmatory testing for proximal tubule dysfunction is not mandatory. Nevertheless, multiple low-molecular weight proteins that are typically transported from the proximal tubule lumen back into the circulation can be used to confirm a defect in transportation. While our institution utilizes a RBP urine assay, urinary β 2-microglobulin, N-acetyl- β -glucosaminidase, β -galactosidase, and RBP can all be sensitive markers of renal tubule damage and can show abnormalities in urinary levels, even when patients are not symptomatic⁶. Furthermore, an elevated urinary lactate to creatinine ratio has been postulated as a sensitive marker of proximal tubule dysfunction in children¹³.

When a diagnosis of Fanconi syndrome is made, secondary causes should be considered, as appropriate. These include evaluation for toxic exposures or heavy metal ingestion, reviewing the medication history, performing serum and urine protein electrophoresis with immunofixation, and measuring serum ceruloplasmin levels. When considering a diagnosis of VFS, serum valproate levels do not necessarily correspond to the risk of developing VFS, nor do they confirm a diagnosis of VFS.

The pathogenic mechanism of VFS remains unknown. In previous experimental studies, valproate has been shown to

Table 2. Etiologies of Fanconi syndrome

Etiologies of Fanconi Syndrome
Acquired
Drugs
Expired Tetracyclines
Valproate
HAART
Aminoglycosides
Ifosfamide
Heavy Metals
Lead
Mercury
Cadmium
Copper
Paraproteinemias
Multiple Myeloma
Amyloidosis
MGUS
Inherited
Cystinosis
Galactosemia
Fructose Intolerance
Glycogen Storage Diseases
Wilson's Disease
Lowe' Disease
Dent's Disease
Idiopathic

inhibit mitochondrial beta-oxidation¹⁴, leading to hypocarnitine-mia^{15,16}. The loss of adequate fatty acid oxidation combined with the lack of carnitine, prevents fatty-acid transport and leads to lipid accumulation in the proximal tubule cells of the kidney causing a failure of transport mechanisms². Further, there is speculation that valproate may concentrate within the intracellular compartments of tubule cells causing mitochondrial dysfunction before its secretion into the tubular lumen¹⁷. Finally, valproate therapy has been hypothesized to cause oxidative stress which may result in a loss of protective mechanisms (glutathione) resulting in nephrotoxicity¹⁸. Electron microscopy of tissue from children with VFS has shown lipid droplets, swollen mitochondria, or increases in auto-lysosomes in proximal tubular segments^{2,10}; however, the exact mechanisms of these findings and their predisposition for the proximal tubule has yet to be elucidated.

The treatment of all acquired etiologies of Fanconi syndrome begins with identifying and reversing the underlying cause. In the case of VFS, once valproate is discontinued, patients can be provided supportive care with intravenous fluids and electrolyte replacement, as appropriate. Discontinuation of the drug may cause remission of symptoms within week, but can take up to months, and even years^{6,8,10}. Periodic analysis of serum electrolytes (including phosphate), serum uric acid, and urine electrolytes should be conducted to ensure resolution of kidney dysfunction. Furthermore, periodic surveillance of serum electrolytes and urinalysis of all adults on long-term valproate therapy should be considered to screen for VFS.

CONCLUSION

Acquired Fanconi syndrome in adults is rare and requires a high index of suspicion among providers. Typical metabolic derangements in the blood and urine are usually sufficient for diagnosis, though elevated urinary low molecular weight protein specific to the proximal tubule can confirm the diagnosis. A detailed review of medications is critical in establishing the cause of Fanconi syndrome, and we report what is to our knowledge the first case of VFS in an adult. Removal of this medication is both therapeutic and diagnostic. Internists should be aware of this potential side effect among all of their patients on valproate therapy.

Key Points

- Fanconi Syndrome is a proximal tubule dysfunction manifested by hypokalemia, hyperchloremia, hypophosphatemia, hypocalcemia, hypouricemia and eventual metabolic bone disease.
- In adults, Fanconi Syndrome is usually acquired, and a detailed medication review is essential.
- Removal of the offending agent can be diagnostic and therapeutic.
- Valproate can cause Fanconi Syndrome in adults.
- Monitor serum and urine electrolytes when prescribing valproate.

Acknowledgements: All authors have read the policies as outlined by the journal.

Contributors: None.

Funders: None.

Prior Presentation: None.

Conflict of Interest: None Disclosed.

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