Case Report

Recurrent Anion Gap Acidosis: An Unusual Presentation of X-Linked Adrenoleukodystrophy in a Five-year-old Male

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Abstract. We are presenting a five-year-old male with recurrent anion gap acidosis. During his last admission, it was detected that he had elevated VLCFA and the evaluation discovered that he had X-linked Adrenoleukodystrophy. He had the Addisonian only phenotype without any clinical or radiographic CNS findings. We were unable to find any other reports of this presentation of ALD. If the work-up of recurrent anion gap acidosis does not uncover an etiology, X-linked ALD should be considered in the differential diagnosis.

Key words: adrenoleukodystrophy, anion gap metabolic acidosis

Introduction

Adrenoleukodystrophy (ALD) is an X-linked metabolic disorder caused by a peroxisomal enzyme deficiency that typically presents with neurodegenerative symptoms or adrenal insufficiency. Young males with X-linked ALD may be asymptomatic. With new preventive and treatment modalities, early diagnosis may be beneficial to prevent the development of disease symptoms. We are presenting a case of a five-year-old male who had recurrent episodes of vomiting, dehydration, normal serum electrolytes, and an anion gap acidosis. On evaluation for his recurrent acidosis, he was found to have elevated very long chain fatty acids (VLCFA) consistent with X-linked ALD.

Case Report

A five-year-old male presented to the Comer Children’s Hospital at the University of Chicago on April 24, 2007 with vomiting, dehydration, and an anion gap acidosis. He had been treated in the emergency department for similar symptoms three times over the past year. These illnesses were associated with mild abdominal pain and responded quickly to intravenous fluids. Radiologic evaluation revealed mesenteric adenitis on one occasion. His development was normal and he was doing well in kindergarten. His height and weight were increasing at the appropriate rate. There were no significant family illnesses.

On this admission, he presented with acute renal failure and mental status changes. On physical examination he was lethargic and significantly dehydrated. His temperature was...
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37.4°C, heart rate 181 beats per minute, respiratory rate 20 breaths per minute, and the blood pressure was 77/35 mm Hg. There were no focal findings and no evidence of hyperpigmentation. Laboratory examination upon admission and previous presentations to the emergency department are presented in Table 1. A complete blood count and serum lactate were normal. A urine screen for toxins was negative.

After aggressive treatment with normal saline boluses of 20 cc/kg/h, the patient’s clinical status and anion gap acidosis improved (Table 1). Because of his recurrent anion gap acidosis, he was evaluated for an inborn error of metabolism. Plasma amino acids were within normal limits. A urine screen for organic acids revealed elevations in excretion of C6-C10 saturated and unsaturated dicarboxylic acids. These results were not indicative of a dietary source such as medium chain triglycerides, but suggested a mitochondrial fatty acid oxidation disorder or an interference with mitochondrial energy metabolism as is seen in peroxisomal disorders. A peroxisomal panel was sent for analysis of very long chain fatty acids (Table 2). These results were indicative of hemizygosity for X-linked-ALD (1).

A comprehensive family history was negative for neurological or endocrinological disease. Magnetic resonance spectroscopy and magnetic resonance imaging (MRI) of the brain were normal. An evaluation for adrenal function revealed a low plasma cortisol level (3.8 umg/dl) and an elevated adrenocorticotropin hormone (ACTH) of 2,180 pg/ml. A Cosyntropin stimulation test revealed an insufficient cortisol response (Table 3). The mineralcorticoid activity remained intact with normal electrolytes, renin, and

### Table 1 Summary of laboratory investigations corrections

| Date       | Emergency Room visit with vomiting and dehydration | Emergency Room visit with vomiting and dehydration | Emergency Room visit with vomiting and dehydration | First Admission with vomiting and dehydration | After fluid resuscitation and first admission | Emergency Room visit with vomiting and dehydration after cortisol treatment | Emergency Room visit with vomiting and dehydration after cortisol treatment | Emergency Room visit with vomiting and dehydration after cortisol treatment |
|------------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|---------------------------------------------|---------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 9/17/06    | 139                                                 | 143                                                 | 139                                                 | 139                                         | 133                                         | 141                                                                      | 138                                                                      |
| 1/30/07    | 4.9                                                 | 5.1                                                 | 4.3                                                 | 5.4                                         | 4.0                                         | 5.2                                                                      | 4.3                                                                      | 3.5                                                                      |
| 3/28/07    | 99                                                  | 104                                                 | 101                                                 | 97                                          | 118                                         | 96                                                                       | 102                                                                      | 99                                                                       |
| 4/24/07    | 10                                                  | 7                                                   | 12                                                  | 6                                           | 10                                          | 21                                                                       | 22                                                                       | 23                                                                       |
| 4/25/07    | 20                                                  | 32                                                  | 26                                                  | 36                                          | 15                                          | 16                                                                       | 17                                                                       | 16                                                                       |
| 7/11/07    | 139                                                 |                                                     | 139                                                 | 143                                         | 133                                         | 141                                                                      | 138                                                                      |
| 11/2/07    |                                                     |                                                     |                                                     | 45                                          | 2.7                                         | 150                                                                      | 122                                                                      |
| 12/6/08    |                                                     |                                                     |                                                     | 550                                         | 7.21                                        | 7.34                                                                      | 18                                                                       | 30                                                                       |
| Sodium (me Q/l) | 139 | 143 | 139 | 139 | 143 | 133 | 141 | 138 |
| Potassium (me Q/l) | 4.9 | 5.1 | 4.3 | 5.4 | 4.0 | 5.2 | 4.3 | 3.5 |
| Chloride (me Q/l)  | 99 | 104 | 101 | 97 | 118 | 96 | 102 | 99 |
| Carbon Dioxide (me Q/l)  | 10 | 7 | 12 | 6 | 10 | 21 | 22 | 23 |
| Anion Gap | 20 | 32 | 26 | 36 | 15 | 16 | 17 | 16 |
| Urea Nitrogen (mg/µl) | 139 | 143 | 139 | 139 | 143 | 133 | 141 | 138 |
| Creatinine (mg/dl) | 298 | 298 | 298 | 298 | 298 | 298 | 298 | 298 |
| Amylase (µ/l) | 550 | 550 | 550 | 550 | 550 | 550 | 550 | 550 |
| Lipase (µ/l) | 7.21 | 7.34 | 7.21 | 7.34 | 7.21 | 7.34 | 7.21 | 7.34 |
| PH | 18 | 30 | 18 | 30 | 18 | 30 | 18 | 30 |
| PLO2 (mmHg) | 120 | 95 | 120 | 95 | 120 | 95 | 120 | 95 |
| PO2 (mmHg) | –20 | –9 | –20 | –9 | –20 | –9 | –20 | –9 |
| Ammonia (mcg/dl) | <20 | <20 | <20 | <20 | <20 | <20 | <20 | <20 |
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aldosterone. These results are consistent with adrenal glucocorticoid insufficiency and he was started on 10 mg oral hydrocortisone daily.

Subsequent genetic testing revealed a nucleotide change of c.293C>T on the ABCD1 gene, thus providing molecular confirmation of a biochemical diagnosis of X linked-ALD.

Two years following diagnosis, the patient remains on hydrocortisone. He has had no further incidents of an anion gap acidosis. He was admitted in December 2008 with vomiting that required stress doses of hydrocortisone. His electrolytes were normal at that time (Table 1). There have been no neurological changes and his MRI has remained normal.

Discussion

Haberfeld and Spieler (2) described the first patient with X-linked ALD in 1910. Their patient was a 6 yr old boy who presented with loss of vision and cognitive function, and later the inability to walk. He died within two years and an older brother died with similar symptoms and progression of disease. The autopsy performed by Schilder on this patient showed diffuse changes and loss of myelin in the brain (3). Siemerling and Creutzfeldt described a patient with a similar course who had adrenal findings at autopsy (4).

The pathophysiologic process in X-linked ALD is secondary to the accumulation of VLCFA in tissues, particularly in the central nervous system and adrenal glands. Patients with X-linked ALD lack a peroxisomal membrane protein that allows transfer of VLCFA into peroxisomes. The VLCFA accumulates as cholesterol esters in the adrenal cortex and this leads to reduction of mitochondrial and microsome function and later cell atrophy. In the brain there is a loss of myelin, accumulation of cholesterol esters, and a perivascular inflammatory response. This leads to the cell changes and the resultant clinical manifestations (5).

There are six phenotypes of X-linked ALD (5). Childhood cerebral ALD has an onset before ten years of age and progresses rapidly. The adolescent cerebral type is similar to the childhood form, but begins between ten and twenty-one years of age. An adult form commences after eighteen years of age. Both have a rapid progression similar to the childhood form. The adrenomyeloneuropathy phenotype begins in the late twenties with peripheral weakness, loss of sphincter function, a slowly progressive sensorimotor polyneuropathy and may involve cerebral manifestations later in the disease course. In the Addison only phenotype, patients have signs of Addison’s disease without neurological findings. There is also an asymptomatic phenotype that has the genetic mutation without endocrine or neurological abnormalities.

In a study of 49 asymptomatic X-linked ALD males identified with elevated VLCFA because they were relatives of known patients, 80% had evidence of adrenal insufficiency after an ACTH stimulation test (6).

Our patient presented numerous times with vomiting, dehydration, and an anion gap acidosis. There were no known precipitators of these events including changes in diet, exercise, and identifiable infectious etiologies. In evaluating him for causes underlying his recurrent acidosis, he was discovered to have an abnormal VLCFA

| Table 2 | Peroxisomal panel |
| --- | --- |
| C22:0 (µmol/l) | 50.2 (<96.3) |
| C24:0 (µmol/l) | 75.7 (<91.4) |
| C26:0 (µmol/l) | 2.96 (<1.30) |
| C24/22 (µmol/l) | 1.51 (<1.39) |
| C26/22 (µmol/l) | 0.059 (<0.023) |

| Table 3 | Cosyntropin test (administered 10 mcg) |
| --- | --- |
| Baseline Cortisol | 7.8 mcg/dl |
| 30 min Cortisol | 8.2 mcg/dl |
| 60 min Cortisol | 6.5 mcg/dl |
profile consistent with X-linked-ALD. His ACTH levels and ACTH stimulation test results were consistent with adrenal insufficiency. Genetic evaluation uncovered a hemizygous missense mutation in the ABCD1 gene: c. 293C>T that results in the amino acid change p.Ser98Leu. This mutation has been previously reported in multiple individuals with ALD and is associated with a variable phenotype and has been seen in patients with late onset disease and patients with adrenomyeleloneuropathy (7).

There are no reported cases of X-linked ALD presenting with pancreatitis, vomiting, and an anion gap acidosis. There is the possibility that the combination of recurrent anion gap acidosis and ALD is coincidental. Despite having glucocorticoid insufficiency, our patient did not present with clinical evidence of an adrenal crisis. An extensive evaluation did not reveal an alternative etiology for his symptoms.

Early diagnosis of X-linked ALD is important because timely intervention can slow down or halt the progression of severe neurological symptoms associated with the disease (8). Clinical signs of adrenal insufficiency often precede neurological symptoms by years or decades and episodes of metabolic acidosis could portend adrenal or neurologic failure and alert physicians to the need for closer monitoring. In addition to adrenal hormone replacement therapy, regular MRIs are indicated to monitor progression of the disease. Bone marrow transplantation (BMT) may be indicated when patients are pre-symptomatic but have MRI findings consistent with early cerebral ALD (8). Because of the possibility of preserving cognitive function with timely therapy, some studies have recommended neonatal screening for X-linked ALD (9). Long-term follow-up of patients receiving BMT have shown that there are beneficial effects when the procedure is done at an early stage of the disease (10).

We believe that peroxisomal disorders should be included in the differential diagnosis of a pediatric patient with an anion gap if the initial workup does not reveal an etiology. Serum VLCFA should be sent and if these are abnormal, further diagnostic tests for X-linked ALD should be performed to confirm the diagnosis.

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