Failure to Thrive: An Expanded Differential Diagnosis

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Abstract

The patient is a term 6-month-old male, who presented with failure to thrive since birth. History was remarkable for suspected milk and soy protein allergy, gastroesophageal reflux, constipation, and abdominal distension that was present since birth. He was losing weight despite oral intake of over 100 kcal/kg per day. Prior workup including laboratory studies, abdominal X-ray, upper gastrointestinal series with fluoroscopy, barium enema, and abdominal ultrasound were all within normal limits. The patient's history, diagnostic evaluation, and final diagnosis are revealed. This case highlights a rare condition presenting as failure to thrive, a common problem with a wide differential diagnosis.

Keywords

- Wolman's disease
- failure to thrive

Case History by Dr. Aprile

The patient is a 6-month-old male, presenting with failure to thrive (FTT) since birth. He had been followed closely by his primary pediatrician with frequent weight checks, revealing progressive weight loss in the 4 weeks prior to presentation.

On presentation, he was taking ranitidine and omeprazole for gastroesophageal reflux as well as polyethylene glycol for constipation. He had a history of bloody stools; following multiple formula trials, he was ultimately placed on Alfamino (a hypoallergenic free amino acid-based formula) 24 kcal/oz due to suspected milk and soy protein allergy. Formula was temporarily fortified to 27 kcal/oz, but this was discontinued due to worsening constipation. Diet history revealed intake of 3.5 to 6 ounces of formula every 3 hours, while awake, with a total intake of approximately 28 oz/day. He was also being introduced to solid foods and at time of admission, was consuming approximately 1/8 cup pureed vegetables and 1/2 cup of pureed fruit per day. Developmental milestones were being appropriately achieved, and he was able to hold his head up, sit in a tripod position, cross midline with objects, transfer items between his hands, babble, laugh, and roll from front to back. A review of systems on admission also revealed frequent sweating that had been present since birth.

Several outpatient evaluations had been undertaken, including a normal abdominal radiograph, normal upper gastrointestinal series with fluoroscopy, normal barium enema, and normal abdominal ultrasound. Labs, including a complete metabolic panel, total IgA (immunoglobulin A), tissue transglutaminase-IgA, thyroid stimulating hormone, free T4, and sweat chloride test were all unrevealing.

Weight was 5.41 kg (0.02 th percentile) and length was 61 cm (0.06th percentile). Vitals revealed an afebrile infant with a heart rate of 125, a respiratory rate of 30, and a blood pressure of 64/41. He appeared small for age and pale, with no dysmorphic features. Mucous membranes were moist, and his anterior fontanelle was soft and flat. Conjunctivae were pale. His palate was intact and he displayed a good suck. He had a soft systolic murmur with a mildly hyperdynamic precordium. His abdomen was soft but protuberant, and his ribs were clearly visible. His liver was palpated 3 to 4 cm below the costal margin with a possibly palpable spleen tip. No other abdominal masses were appreciated, and his hepatomegaly did not seem large enough to explain his abdominal distension. His capillary refill was difficult to assess due to pallor. He had shotty, diffuse lymphadenopathy (cervical, occipital, axillary, and inguinal). He spontaneously moved all of his extremities. He was awake and alert with no deficits on neurologic exam.

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Case History by Dr. Daymont

Failure to thrive is the clinical sign of inadequate weight gain or weight loss in a child. There are no universally accepted growth criteria to define, when weight gain is inadequate.¹ One common definition, a weight below the 5th percentile for age, may over-identify children, who are healthy but have a growth potential at the low end of the typical range. Another common definition is a weight-for-age percentile that crosses two decreasing major percentile lines on a growth chart. This definition has the potential advantage of identifying children, who develop inadequate weight gain even if they had previously grown well. However, a large proportion of healthy children will have a weight-for-age percentile that crosses two decreasing major percentile lines, including almost 20% of children 0 to 6 months in the prospective Child Health and Development Study.² The lack of accepted criteria notwithstanding, this child's weight gain, with a weight-for-age percentile of 0.02% (3.5 standard deviations, below the mean) and minimal weight gain in 6 months, was clearly inadequate.

The causes of FTT have sometimes been referred to as existing in one of two categories: (1) organic, due to an identifiable medical condition in the child, or (2) nonorganic, also referred to as psychosocial causes. However, there has been recognition that FTT is often multifactorial.^{3–5} There may be interaction between ongoing or resolved medical problems and the behavior or relationships of children and caregivers, and there may be subtle abnormalities in feeding skills or neurologic status in children with FTT that are not found to stem from a specific diagnosis.^{3,4} Regardless of the etiology, the underlying cause of FTT is undernutrition relative to the child's needs.

There is a lack of evidence to support any specific evaluation strategy for FTT. Sometimes, the ability to gain weight during a brief hospitalization is seen as evidence that FTT is "nonorganic." In a retrospective evaluation of 122 children in-hospital, weight gain was not found to be a reliable indicator of the presence or absence of an identified medical cause of FTT, although details of this analysis were not presented.⁶ There are hundreds, if not thousands, of conditions that can cause FTT; a search for the term in the Online Mendelian Inheritance in Man database alone identifies 676 records.⁷ Clearly, evaluation for all or even a substantial proportion of these conditions is not possible or appropriate. Two retrospective analyses (combined $n = 307$) from 1978 to 1982 found a low yield (0.8–1.4%) from any individual diagnostic test. However, a substantial proportion (18–30%) of children were diagnosed with "nonorganic" FTT.^{6,8} In one of these publications, it is reported that "no (diagnostic) study was of positive value without a specific indication from the clinical evaluation." However, "specific indication" is not described further, and it is not clear from this retrospective assessment how to prospectively determine whether a diagnostic test is indicated.⁸ It is also not clear whether poor growth alone is an indication for certain evaluations, such as an evaluation for celiac disease, which may present with poor growth as the sole symptom,⁹ in children whose growth

failure began after exposure to gluten. More prospective research is needed to provide further guidance about appropriate medical evaluation in children with FTT.

When performing a history and physical examination, it may be useful to consider three primary categories of the causes of undernutrition: low caloric intake, decreased caloric absorption, and increased caloric need, which may occur alone, or in combination.¹⁰ In this child, several signs and symptoms raised concern about the presence of a medical condition, affecting each of these three causes including the severity and persistence of his difficulty with weight gain despite report of adequate intake of calories; severe and persistent constipation from a very young age that limited efforts to increase caloric intake; diaphoresis; pallor; and abdominal distension. His liver and possibly spleen were apparently large on examination, although a recent ultrasound showed a liver (9.2 cm) and spleen (5 cm) within normal limits for age. Additionally, although none of his individual lymph nodes were particularly large, the number and wide distribution of palpable lymph nodes was unusual, especially in the absence of symptoms of acute viral illness. Given these concerning signs, we pursued diagnostic testing in parallel with observation of his feeding, with a plan to consider nasogastric feeding for supplemental calories if weight gain was not observed. Initial evaluations, with specific indications beyond inadequate growth in parentheses, included (1) a complete blood count (pallor, hepatomegaly, lymphadenopathy); (2) comprehensive metabolic panel (hepatomegaly); (3) iron profile (pallor); (4) lactate dehydrogenase (pallor, hepatomegaly, lymphadenopathy); (5) echocardiogram/electrocardiogram (diaphoresis and murmur); (6) chest X-ray (diaphoresis); and (7) abdominal X-ray (constipation).

Case Presentation Continued

Adrenal calcifications were incidentally found on abdominal X-ray (→Fig. 1). We obtained a random cortisol level that was 3.1 µg/dL (reference range: 1.7–22.7). Glucose checks overnight were 68 to 109 mg/dL, and additional laboratory studies were unrevealing. As the primary team, our differential diagnosis at that time was prior adrenal hemorrhage versus neuroblastoma, and an abdominal CT (computed tomography) was ordered.

Laboratory studies showed a hemoglobin of 10.5 g/dL (reference range: 10.5–13.5), hematocrit of 31.9% (33–39), white blood cell count of 10.64 K/µL (6–17.5), platelets of 380 K/µL (158–470), ALT (alanine transaminase) of 60 unit/L (13–45), total bilirubin of 0.4 mg/dL (0.2–1.3), alkaline phosphatase of 189 unit/L (95–380), AST (aspartate transaminase) of 100 unit/L (9–80), albumin of 4.2 g/dL (3.5–5.0), protein of 6.8 g/dL (6.3–8.2), pre-albumin of 21 mg/dL (17–36), vitamin D of 48 ng/mL (30–100), LDH (lactate dehydrogenase) of 1,187 unit/L (313–618), 8 a.m. cortisol of 5.9 µg/dL (1.7–22.7), insulin-like growth factor binding protein-1 of 22 ng/mL (no local reference range for age group, for 5–9 years, 15–95 ng/mL), aldosterone of 24.1 ng/dL (7–99), thyroid stimulating hormone of 4.72 µIU/mL (0.7–6.4), free T4 of 0.8 ng/dL (0.8–2),

Fig. 1 Abdominal X-ray is shown below. Abdominal X-ray was read as “bilateral adrenal calcifications, marked by arrows.”

uric acid of 3.1 mg/dL (3.5–8.5), ferritin of 66.4 ng/mL (17.9–464), iron saturation of 12% (20–55), iron of 41 µg/dL (49–181), total iron binding capacity of 344 µg/dL (261–462), total cholesterol of 157 mg/dL (125–200), low density lipoprotein of 102 mg/dL (50–130), high density lipoprotein of 21 mg/dL (> 35), and triglycerides of 170 mg/dL (< 200).

Case History by Dr. Ladda (Geneticist)

In an infant, who presents with abdominal distention (bloating) with hepatosplenomegaly, the first concern would be for possible storage disease or tumor. An abdominal radiograph

showing bilateral adrenal calcification would narrow the differential diagnosis to include at the top of the list Wolman's Disease.¹¹ Adrenal calcification in infancy may be the result of hemorrhage associated with neonatal asphyxia, sepsis, blunt trauma, or coagulopathy. Adrenal tumors such as neuroblastoma, adenoma, or pheochromocytoma are usually unilateral, whereas bilateral adrenal calcification is the hallmark of Wolman's disease.

In Wolman's disease, the accumulation of cholesteryl esters in cells throughout the body, but especially in the liver and spleen, leads to the organomegaly (fatty liver), and in the intestine to malabsorption and foul-smelling stools. Adrenal calcification appears to be due to high levels of oxidized cholesteryl esters in tissues.¹² The underlying mechanism unique to adrenal cells may be either high levels of innate lipid peroxidation in adrenal cells, or increased uptake of oxidized low-density lipoproteins.¹³ Accumulation of these esters leads to cellular necrosis and accumulation of calcium.¹⁴

Case Presentation Continued (Which Reveals the Diagnosis)

An abdominal CT was ordered showing hepatosplenomegaly, hepatic steatosis, and bilateral adreniform enlargement with stippled calcification of the adrenal glands, most consistent with Wolman's disease (► Fig. 2). Echocardiogram showed no abnormalities. Genetics was consulted for further assessment.

While hospitalized, the patient remained on his home feeding regimen. In-hospital calorie counts showed an average intake of 119 kcal/kg/day. The patient gained 120 g during the 3-day hospitalization and was discharged home with definitive testing for Wolman's disease pending and close follow-up.

Dr. Ladda (Geneticist)

Review of the radiographic studies, showing the bilateral adrenal calcifications strongly supported Wolman's disease

Fig. 2 (A–C) An abdominal computed tomography was then obtained, which showed hepatosplenomegaly (A) and hepatic steatosis in association with bilateral adreniform enlargement and stippled calcification of the adrenal glands (B) without focal adrenal mass to suggest neoplasm.

(lysosomal acid lipase deficiency). The first level of screening was a lysosomal panel through the Jefferson University Lysosomal laboratory, which revealed an acid lipase level of 20.8 units, compared with a control β -galactosidase level of 77.9 units. This laboratory reported the unaffected acid lipase range as 50 to 100 units and the affected range as 5 to 25 units. The lysosomal acid lipase level was confirmed through Baylor Genetics laboratory with an acid lipase of 3.1 pmol/min/mg protein compared with control levels 1:63.2 and control 2:69.1 pmol/min/mg protein with normal control range of 20 to 300 pmol/min/mg protein compared with the affected control value 1.5 pmol/min/mg protein. These findings were diagnostic of Wolman's disease (cholesteryl ester storage disease). A blood sample was then forwarded to Baylor Genetics laboratory for *LIPA* gene sequence analysis. This patient was found to have two deleterious mutations: nucleotide change c.531-2A > G in exon 6 (amino acid change not available) and nucleotide change c.684del in exon 7, amino acid change p.F228Lfs*13. There were also seven benign variants identified with no clinical significance. The diagnosis of Wolman's disease was confirmed by these studies, and the patient was referred for enzyme replacement therapy.

Case History by Drs. Ficicioglu and Cohen (Metabolic Experts)

Wolman's disease is an autosomal recessive disorder first described in 1956 and has been the term used to describe an infantile-onset, severe form of lysosomal acid lipase deficiency. The spectrum of diseases this disorder belongs to has also been referred to as cholesteryl ester storage disorders, with Wolman's disease on the severe end of the spectrum.¹¹

Lysosomal acid lipase is a key enzyme in lipid metabolism and trafficking. In healthy individuals, low density lipoprotein (LDL) cholesterol is taken up by the LDL receptor and transported to the lysosome. In the lysosome, the lysosomal acid lipase (LAL) breaks up the cholesteryl esters and triglycerides into free fatty acids and free cholesterol, which are then released into the cell for use. In LAL deficiency, mutations in *LIPA* cause a deficient enzyme. The LDL cholesterol is still taken up by the LDL receptor and transported to the lysosome; however, the lack of LAL enzyme prevents the cholesterol esters and triglycerides from being appropriately broken down into free fatty acids and free cholesterol. As a result, the lysosomes swell with excess cholesteryl esters and triglycerides, and feedback signals note a shortage of intracellular free fatty acids and free cholesterol. This leads to an upregulation of LDL receptors, which therefore leads to increased cholesterol uptake. The result is that hepatocytes release more very low-density lipoprotein (VLDL) cholesterol and less high-density lipoprotein (HDL) cholesterol into circulation, leading to the abnormal laboratory results seen in a patient with Wolman's disease.¹⁵⁻¹⁸

Infants with Wolman's disease present with symptoms and signs of malabsorption, which leads to malnutrition and FTT. The storage of cholesteryl esters and triglycerides in hepatic macrophages leads to hepatomegaly and liver disease. The clinical presentation includes persistent vomiting and diar-

rrhea, abdominal distension, profound growth failure, and hepatosplenomegaly. Lipid accumulation in these patients also impacts the spleen, adrenal glands, lymph nodes, intestinal mucosa, vascular endothelium, and skeletal muscle. A finding common in Wolman's disease is adrenal gland calcification, which can lead to adrenal cortical insufficiency.¹⁵⁻¹⁷

Without enzyme replacement therapy, the disease is rapidly progressive and typically fatal by 6 to 12 months of age from multiorgan failure. Previously, patients had been trialed with hematopoietic stem cell transplantation, which was unsuccessful. With the recent advent of enzyme replacement therapy, FDA approved in 2015, the prognosis has improved significantly. The enzyme, known as sebelipase alfa, binds to a mannose-6-phosphate receptor, travels intracellularly to the lysosome, where it acts on sterol regulatory element-binding proteins (SREBPs) and downregulates the SREBPs in the nucleus. The downstream effect is a lowering of the VLDLs.¹⁹

The published phase III clinical trial was a multicenter, randomized, double blind, placebo-controlled study of 66 patients, the youngest of which was 4 years old, which reported reductions in hepatic fat content by magnetic resonance imaging (MRI), reductions in LDL level, decrease in triglycerides, and increase in HDL.¹⁹ In 2017, Jones et al studied 9 infant patients, less than 6 months of age in an open-label multicenter, dose-escalation study of sebelipase alfa, during which 67% survived to 12 months old, with improvements in weight-for-age, reduced markers of liver dysfunction and hepatosplenomegaly, improved anemia and improved gastrointestinal symptoms.²⁰ In this study, a transition to high medium chain triglyceride (MCT)-content pediatric formula, and low-fat oral diet led to improved weight-for-age growth.²⁰ As with many enzyme replacement therapies, patients have developed anti-drug antibodies to sebelipase alfa; however, an association between these antibodies and reductions in efficacy, or increased occurrence of adverse events has not yet been determined. Of note, most patients required dose escalation from 1 mg/kg to 3 to 5 mg/kg, depending on the severity of their disease. The Jones et al trial published in 2017 found reductions in ALT, AST, LDL, triglycerides, total bilirubin, and ferritin, and an increase in HDL, albumin, platelets, and hemoglobin. Symptomatically, these patients showed decreased diarrhea, vomiting, abdominal distension, and liver, and spleen size, as well as decreased need for blood transfusions and for total parenteral nutrition. Most patients had normal developmental screening test scores and the oldest patient in the trial entered preschool at 3 years of age and was performing in a comparable manner to peers.²⁰

On the spectrum of lysosomal acid lipase deficiency, a less severe form can present in children and adults, leading to liver disease (specifically, fibrosis and cirrhosis) and dyslipidemia, which can lead to accelerated atherosclerosis.¹⁶

Case Presentation Continued

Permanent intravenous access was obtained for the initiation of weekly enzyme replacement, and his diet was changed to Monogen (a low fat, high MCT formula) 27 kcal/oz ad lib on demand (approximately 22 oz/day) with 1 teaspoon of

Fig. 3 (A–C) Growth charts for the patient for weight, head circumference, and length. Open diamonds represent the values on admission; x represents all other measurements.

MCT oil, 8 grams of fat from table foods, 1 whole milk yogurt per day, and free water throughout the day. He has developed some oral aversion and is currently receiving feeding therapy. He continues to achieve developmental milestones appropriately for his age, and his liver enzymes, total cholesterol, HDL, and LDL have continued to improve. He no

longer has any hepatosplenomegaly on physical exam and was weaned off ranitidine and polyethylene glycol. He developed partial adrenal insufficiency and requires supplementation during times of physiologic stress; however, he does not require daily maintenance therapy. He was also noted to have hypothyroidism on laboratory evaluation and was started on thyroid replacement therapy. His mild anemia has remained stable, and the eosinophilia that was noted on a complete blood count was attributed to his hypothyroidism. He has shown substantial catch-up growth on his new feeding regimen. His length-for-age z-score increased from -3.52 to -2.87 , and his weight-for-length z-score increased from -2.92 to -0.28^{21} (**Fig. 3**).

Conclusion

Our case represents a true diagnostic dilemma for a common pediatric complaint with an uncommon etiology. Despite normal imaging and laboratory findings prior to presentation, we continued an evaluation of the cause of failure to thrive based on a constellation of signs and symptoms, including the severity and persistence of poor weight gain, which pointed to an organic etiology. The discrepancy between the normal ultrasound, including normal liver size-for-age, and the hepatomegaly apparent on CT may indicate that reference ranges for organ size-for-age are not appropriate for children, who are much smaller than their age-matched peers.²² Our patient's significant weight gain on oral feeds during his short initial hospitalization despite an underlying metabolic condition, causing poor weight gain underscores the need for caution, when interpreting weight changes over short periods of time. Inborn errors of metabolism are a rare cause of FTT, but should be considered in patients with organomegaly, among other conditions.²³ Coupled with his presenting symptoms and evolving findings, additional workup, ultimately led to our diagnosis of a serious and treatable underlying condition.

Conflict of Interest

None declared.

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