Pancreatitis in Children

Bharani Pandrangi MD
Clinical Assistant Professor
Pediatric Gastroenterology
University of Texas Health Science Center San Antonio

Outline

- Case Presentation
- Differential Diagnosis
- Pertinent background information to understanding complex case
- Overview of chronic pancreatitis
- Answer some questions related to case with EBM

Case Presentation - HPI

J.M. is an almost 5 year old male with a history of propionic acidemia, pancreatitis, and eosinophilic gastroenteritis, with recurrent vomiting and presumed abdominal pain.

Past Surgical History

- Gastrostomy tube
- Port-A-Cath X 3
- Circumcision 02/2010

FMH

- Waldenstrom's macroglobulinemia
- No pancreatitis or GI related disorders

Relevant Financial Relationships

- "Within the past 12 months, I have had no financial relationships with proprietary entities that produce health care goods and services."
Social History

- Lives with mother and father in San Antonio; no siblings
- Father is in Army based in San Antonio
- Attends kindergarten
- Developmental delay – does not speak

PMH

- Full term baby, C-section due to failure to progress, born in Germany
- NICU for 2 months prior to discharge
- Diagnosed with propionic acidemia on DOL#2
- Hospitalized many times for pancreatitis (6 episodes 2008 – elevated lipase)
- Immunizations up to date

PMH continued

- Hospitalized for fever, atypical pneumonia Nov. 2008
- Hospitalized for hemolytic uremic syndrome in 2008, required dialysis
- Genetic tests sent to Ambry lab for hereditary pancreatitis 12/2008 (results = normal CFTR, PRSS1, and SPINK1)
- Hospitalized for left femur fracture 02/2009

PMH continued

- Hospitalized 08/2009 for pancreatitis and MSSA bacteremia
- CT abdomen and pelvis 09/08/2009: stable free fluid around pancreas, mild enlargement of pancreatic head, no gallstones

PMH continued

- Hospitalized 09/2009 pneumonia, fever, lethargy, neutropenia
- UTI with *Klebsiella pneumoniae* 09/2009
- Normal ECHO 11/02/2009

PMH continued

- MRCP 10/29/09 = minimal dilation of the pancreatic duct
- Possible ocular myasthenia gravis 11/2009 “droopy eyelids”
- EGD on 11/23/2009 – visually linear furrowing, white nummular lesions
Pathology – 11/23/09

- Duodenum = focal Brunner’s gland hyperplasia and increased mucosal eosinophils (35 eosinophils/hpf)
- Stomach = mild chronic gastritis, increased eosinophils (60 eosinophils/hpf); no H.pylori or metaplasia/dysplasia, etc.

Pathology – 11/23/09

- Esophagus, distal = mild chronic esophagitis – acanthosis, parabasal edema, chronic inflammation including eosinophils
- Esophagus, proximal – same as distal, increased eosinophils 15/hpf

Eosinophilic esophagitis

- Esinophilic esophagitis and eosinophilic gastroenteritis
- Treatment - formula changed to Neocate
PMH continued

- Re-fracture of left femur 12/2009
- Hospitalized for pancreatitis 12/2009 (elevated lipase)
- Hospitalized in March 2010 for central line infection – *Klebsiella pneumoniae* and *Citrobacter braakii*

PMH continued

- GI consult 05/2010 for recurrent vomiting and constipation, started on Reglan
- MRI brain secondary to dizziness and emesis in 05/2010 negative
- Hospitalized in August 2010 for emesis, abdominal pain, slight rise in lipase

PMH continued

- Hospitalized 09/11/2010, GI consulted for intractable emesis – started on steroids
- UGI contrast study 09/22/10 = normal, no malrotation

Pertinent Labs

- Fecal elastase [normal 201-500]:
  - 88 on 11/20/09
  - 35 on 11/27/09
  - 91 on 09/29/10
  - 79 on 09/30/10
- Ammonia
- Lipase
- Amylase

See Graphs

Ammonia levels for J.M. (2 years)

Lipase for J.M. (2 years)
Impression – recurrent vomiting and abdominal pain

- Exacerbation of metabolic disorder
- Pancreatitis – due to propionic acidemia or other causes
- GI motility disorder secondary to eosinophilic disorder or other
- Gastroesophageal reflux
- Infection – H. pylori, rotavirus, etc.

Impression – recurrent vomiting and abdominal pain continued

- Malrotation with intermittent volvulus
- Cyclic vomiting syndrome
- Intracranial mass
- Recurrent UTI's
- UPJ obstruction

Pathology 09/24/10

- Repeat EGD 09/23/2010 – visually normal
- Duodenum – expanded Brunner’s glands with likely secondary distortion of mucosal villous architecture
- Gastric antrum – mild focal chronic inactive gastritis
- Distal and mid esophagus – normal; comment regarding significant congestion and dilatation of papillary vessels
- NO INCREASED EOSINOPHILS!

Hospital Course

- MRCP = irregular beaded appearance to pancreatic duct
- ERCP 10/05/10 = normal cholangiogram; high-grade stricture at the head of the pancreas, papillary stenosis at biliary orifice – therefore biliary sphincterotomy with immediate drainage of contrast and bile

Follow-up

- ERCP 10/12/10 - markedly ectatic tortuous pancreatic duct with side branch dilation consistent with chronic pancreatitis, unable to pass guidewire all the way to the tail due to tortuosity of pancreatic duct, s/p minor papillotomy, s/p pancreatic stent placement
- New diagnosis = pancreas divisum
Pediatrics Grand Rounds
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University of Texas Health Science Center at San Antonio

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**ERCP**

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**GI clinic visit 10/29/10**

- Doing well with no nausea or vomiting
- Diet remains all G-tube with “well” and “sick” formulas per metabolic specialist
  - Well consists of combination of Polycose, Neocate Jr and Benefiber 53 oz/24hrs
    (17 ml/hr X 10 hrs at night, 300 ml bolus X 3 during day)
  - Sick formula ProFree and Polycose

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**GI clinic visit 10/29/10**

- Severe oral aversion and has not been able to make progress with speech therapy. Family currently not interested in addressing this issue.

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**Physical Exam**

- VSS: wt=20.3 kg(75%), ht=107.3 cm(25-50%)
- GEN: active, well-nourished, non-verbal
- Abd: several small well healed scars. normal bowel sounds. soft, NT/ND, MIG-Key 14 Fr 1.7 cm g-tube with no granulation tissue or discharge
- Port-A-Cath

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**Follow-up**

- F/U ERCP 01/14/2011 pancreatic duct stent not present; high grade stricture; pancreatic duct dilated, stricture transversed with cannula with difficulty, new stent placed
- Patient required hospitalization until 01/27/11 due to feeding intolerance but is now home

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**GI clinic visit 10/29/10**

- Continues on Bicitra, Biotene and Carnitor
- Interested in toilet training
- Enjoying kindergarten
- No constipation, Miralax on hold due to slightly loose stools
- Check labs – anemia, risk for vitamin deficiencies (esp. fat soluble - normal)
- Started pancreatic enzyme supplementation Creon 12,000 units TID

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Differential Diagnosis for Pancreatitis

- Cystic Fibrosis-pancreatic sufficient
- Hereditary Pancreatitis
- Gallstone Pancreatitis
- Drug/Toxin induced Pancreatitis (alcohol)
- Anatomical anomalies—pancreas divisum, ansa pancreatica

Differential Diagnosis for Pancreatitis

- Other – metabolic disorders
- Autoimmune (adults)
- Idiopathic
- Tropical

What is propionic acidemia?

- Deficiency in enzyme propionyl-CoA carboxylase – made of 2 subunits on chromosome 13 and 3
- Occurs in approximately 1 in 100,000 newborns

What is propionic acidemia?

- Typically present in newborn period
- Some patients have hepatomegaly and seizures
- Vomiting, lethargy, FTT, protein intolerance, hypotonia
- Can have cardiac conduction abnormalities
- Some with dysmorphic features

Propionic Acidemia

- Diagnose by obtaining UOA and high levels of metabolites of propionyl-CoA
- High ammonia levels
- Low plasma carnitine
- Acylcarnitine profiles with high levels of propionylcarnitine

Propionic Acidemia

- Definitive diagnosis by measuring deficient activity of propionyl-CoA carboxylase in skin fibroblasts or peripheral blood leukocytes
Propionic Acidemia

- Propionyl-CoA produced through the catabolism of certain a.a. and cholesterol as well as produced by gut bacteria.
- Treatment consists of low protein diet, also restriction on fat intake (odd chain f.a. and polyunsaturated fat), start Biotin, may use carglumic acid which may reduce ammonia by direct activation of carbamoyl phosphate synthetase 1.

Chronic Pancreatitis – Clinical Manifestations

- Recurrent episodes of acute pancreatitis
- Abdominal pain – epigastric, radiate to back, relieved by sitting up/leaning forward, worse post-prandial and after fatty meals
- Nausea and vomiting
- Malabsorption - protein maldigestion occurs before fat

Chronic Pancreatitis – Clinical Manifestations

- Obstructive jaundice
- Abnormal liver tests
- Growth failure/malnutrition
- Glucose intolerance
- Pancreatic pseudocysts
- Asymptomatic

Imaging studies

- Plain films
- Ultrasound
- CT
- MRCP
- ERCP
- Possible EUS

Labs

- Routine CMP with Direct bilirubin, GGT
- Amylase, lipase
- Fecal elastase more sensitive than fecal chymotrypsin
- Fecal fat
- Direct studies – Secretin and CCK stimulation not commonly used in pediatrics

Genetic Markers

- PRSS1
  - mutations in the cationic trypsinogen, present in 52-81% patients with hereditary pancreatitis
  - mapped to long arm of chromosome 7
  - autosomal dominant, over 20 mutations
  - interferes with trypsinogen inactivation or enhances its activation to trypsin, therefore permitting autodigestion of the pancreas
**Genetic Markers**

- **SPINK1**
  - mutations in serine protease inhibitor Kazal type 1 gene
  - impairs the ability of pancreatic acinar cells to inhibit and counteract the damaging effects of activated intracellular trypsin
  - complex mode of inheritance — likely AR

- **CFTR mutations**
  - homozygous versus heterozygous
  - mild versus severe mutations
  - Over 1500 different genetic polymorphisms have been identified

**Treatment of pancreatitis**

- NPO, gut rest, eventually low fat diet
- Pain control
- May need TPN/NJ feeds temporarily
- Consider pancreatic enzymes
- PPI
- Consider antioxidants such as:
  - Vitamin E 400 units TID,
  - Vitamin C 250 mg TID,
  - Selenium 75 mcg PO Qday

- Consider MCT supplementation
- May need ADEK, oral hypoglycemics, insulin
- Follow-up imaging
- Endoscopic therapy
- Surgery — decompression (lateral pancreaticojejunostomy = Puestow), resection (Whipple), denervation
- Cholecystectomy if gallstone pancreatitis

**Does constipation contribute to propionic acidemia?**

- Children’s Hospital of Boston did study evaluating correlation between gut motility and metabolic status in patient’s with PA over 7 days
- Only 4 patients
- Gave Senokot laxative after 4 days of regular diet and measure intestinal transit time
- Oro-cecal transit time measured by lactulose breath test
Does constipation contribute to propionic acidemia?

- No significant change in symptoms of gagging, vomiting, tachypnea, lethargy
- Decreased ammonia levels after Senokot, reduction in propionylglycine levels and increase in free carnitine and total carnitine
- Bicarb and plasma glycine remained the same

What is pancreatic divisum?

- Ventral and dorsal ducts of the embryonic pancreas fail to fuse
- Dorsal and ventral pancreatic buds fuse during 2nd month of fetal development
- Most common congenital variant of pancreatic ductal development
- Occurs in ~10% of individuals

Ammonia levels during study

Development of the Pancreas

Pancreatic ductal variations

- Theory stenotic minor papilla cause of pancreatitis (or intermittent plugging of minor papilla)
- ERCP diagnostic – ventral duct short (1-4 cm) and does not cross midline
Is ERCP safe in children?

- Age 3-17, average age 10.3 years
- 26 patients had one procedure, 2 patients had 2 procedures, 1 patient had 8 procedures due to papillary stenosis with stents
- All patients that had more than one ERCP had chronic pancreatitis
- 8 ERCP’s due to suspected CBD obstruction

- Complication rate 10.5% per procedure and 13.8% per patient since 4 patients had pancreatitis after procedure with resolution within 4 days
- 79% of patients had long-term follow-up at center for average of 43 months and no long term complications from ERCP

- Recent study from Montreal, Canada from January 2010
- ERCP first described in 1970 as useful tool in pancreaticobiliary diseases
- Smaller caliber fiberoptic duodenoscopes have increased use in pediatric population
- Data collection between 09/1990 – 07/2007
- 38 ERCP’s on 29 children

- Of the 20 recurrent or chronic pancreatitis 14 had anatomical cause: 6 pancreas divisum, 6 papillary stenosis, 1 sclerosing cholangitis, 1 choledochocele
- Success rate defined as completion of the procedure with adequate imaging of the pancreaticobiliary ducts anatomy = 97%.
- ERCP success in children in general reported 89.5-100%; no difference base on age of child

- Adult data ERCP morbidity 1-15% (mild pancreatitis), mortality ranges 0.4-1.2%
- 1 published pediatric death 30 years ago, infection of pancreatic pseudocyst after ERCP
- Complications (adult data) can include pancreatitis (3-7%), hemorrhage, perforation, infection
Is ERCP safe in children?

- Ultrasound sensitivity to detecting CBD stone = 46-82%
- MRCP with secretin may have sensitivity and specificity as high as 98 to 100% for CBD obstruction and pancreatic divisum. May be as low as 38% sensitivity alone
- No data on possible long-term complications of sphincterotomy or the use of stents in pediatric patients

Summary

- Patients can have more than one diagnosis, keep the full differential in mind!
- Propionic acidemia – metabolic disorder associated with pancreatitis
- Constipation may make propionic acidemia worse
- Pancreatic divisum diagnosed by MRCP or ERCP and it is associated with chronic pancreatitis
- Many causes of chronic pancreatitis in children, important to remember hereditary pancreatitis

Summary

- Important to identify underlying cause of chronic pancreatitis if possible
- Reviewed treatment of chronic pancreatitis in children
- ERCP is becoming a more common procedure in children and is relatively safe

References

- Prasad et al. J Pediatr 2004;144;532-5. The Importance of Gut Motility in the Metabolic Control of Propionic Acidemia