Recent Recommendations for Diagnosis and Management of Autoimmune Pancreatitis in Childhood: Consensus From INSPPIRE

JPGN 2018;67: 232–236

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Autoimmune pancreatitis (AIP) is a distinct, infrequent form of pancreatitis in children. In recent years, the disease of pediatric AIP (P-AIP) has been increasingly recognized but many questions remain regarding its physiopathology, diagnosis, and treatment.

International **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE** (INSPPIRE) is the first and largest international multicenter effort studying children with acute recurrent and chronic pancreatitis. INSPPIRE has enrolled more than 400 patients with acute recurrent and chronic pancreatitis since 2012, from 22 different sites worldwide with the goal to study the risk factors, natural history, and outcome of the disorders in children.

The INSPPIRE P-AIP working group recently drafted 15 statements including definition, diagnosis, and management of P-AIP following the review and appraisal of collected data. In contrast to adult AIP (A-AIP), there are no established guidelines directing a common diagnostic and therapeutic approach for P-AIP. In fact, most previous published case series have relied on adult criteria for P-AIP management decisions. INSPPIRE P-AIP working group has made use of the expertise of a large panel of pediatric pancreatologists to develop pediatric-focused clinical recommendations for the definition, diagnosis, and treatment approach of P-AIP.

Working Definition of Autoimmune Pancreatitis

- AIP in children is a distinct subtype of pancreatitis associated with pancreatic parenchymal changes including lymphoplasmacytic and/or neutrophilic infiltrates and/or parenchymal fibrosis. A feature of the disease is the prompt clinical response to steroids.

Clinical Presentation

- Children with AIP may present with acute onset of abdominal or back pain, jaundice, fatigue, and/or weight loss.

Diagnosis

- As a form of pancreatitis, P-AIP is associated with elevated amylase and lipase. However, due to a common subacute presentation, these may have already normalized at the time of diagnosis.There is lack of data to associate a diagnosis of P-AIP with increased gammaglobulin levels or autoantibodies such as antinuclear antibody (ANA), rheumatoid factor, or anti– Saccharomyces cerevisiae antibody (ASCA).
- Transabdominal ultrasound serves as an important first line imaging technique in children presenting with symptoms suggestive of pancreatitis and/or obstructive jaundice. However, high suspicion for AIP, a hypoechoic parenchyma, diffuse or focal enlargement of the pancreas, a pancreatic mass lesion with/or without a dilated common bile duct in absence of choledocholithiasis, should prompt a magnetic resonance imaging (MRI)/MRCP.
- MRI/MRCP findings seen in P-AIP include focal, segmental, or global pancreas enlargement; hypointense pancreas on T1-weighted images; hypointense capsule-like rim on T2-weighted images; main pancreatic duct irregularities or stricture; common bile duct stricture or dilatation of the common bile duct which tapers toward an enlarged pancreatic head. Although most of these features are not specific for P-AIP, the presence of more than one should raise the suspicion for P-AIP.
- Histological findings of acute and/or chronic inflammatory cell infiltration around pancreas acinar periductular and/or presence of IgG4-positive plasma cells with or without pancreas fibrosis is suggestive for the diagnosis of P-AIP.
- A tissue diagnosis should ideally be obtained before initiating therapy. Barriers, however, exist to recommend routine EUS-guided biopsies for all children (eg, limited number of EUS-skilled pediatric endoscopists and pediatric pathologists, inadequate biopsy needles). If these barriers cannot be overcome, we suggest that the diagnosis of P-AIP can be made based on the clinical and imaging findings, because the risk for pancreatic cancer in children is extremely low.
- More data are needed to determine the utility of major papilla biopsies for the diagnosis of P-AIP

Therapeutic Options and Response to Therapy

- Some P-AIP patients may have symptom resolution without any therapy. There are, however, no long term data comparing complication or recurrence rate with and without treatment. Thus, as per adult literature and reports of P-AIP, treatment with oral prednisone is recommended for symptomatic patients after establishing the AIP diagnosis.
- Oral prednisone, 1 to 1.5mg /kg/day to a maximum of 40 to 60 mg given in 1 or 2 divided daily doses for 2 to 4 weeks is recommended as first-line treatment in PAIP. Prednisone should then be tapered.
- Treatment response to corticosteroid therapy should be assessed as clinical response within 2 weeks after starting corticosteroid therapy, imaging response by imaging such as transabdominal US, MRI/MRCP, or EUS about 3 months after starting corticosteroid therapy. In case of AIP relapse, a new course of prednisone may be tried.
- The introduction of an immunomodulator such as 6- mercaptopurine, azathioprine, mycophenolate mofetil, or infliximab (in patients with a concomitant diagnosis of inflammatory bowel disease) can be an alternative to prednisone in biopsy-proven P-AIP patients if maintenance therapy is required. There is insufficient data to suggest one immunomodulator over another.

Other Organ Involvement

- Children with a diagnosis of AIP are at greater risk to develop other autoimmune or inflammatory diseases.

Mid- and Long-term Outcome

- There is currently insufficient data about the long term risk of complications such as EPI and diabetes. Hence, patients with P-AIP should be monitored regularly by pediatric gastroenterologists, and when reaching adulthood, by adult gastroenterologists.

In this article, a working definition of the disease and recommendations for the diagnosis and therapy of P-AIP is provided. The goal is to provide a standardized approach to diagnose, treat, and follow patients with P-AIP, bring uniformity to patient care and facilitate future research.

Commentary

AIP is the only form of CP for which targeted (anti-inflammatory) treatment is available hence its identification is vital. At the present time, pediatric gastroenterologists rely on the adult AIP guidelines to diagnose and manage AIP in children and that exclusive use of adult criteria may lead to underdiagnosis of AIP in children. AIP in adults is classified into two subgroups, AIP type 1 (lymphoplasmacytic sclerosing pancreatitis) & AIP type 2 (idiopathic duct-centric pancreatitis). A definitive diagnosis of idiopathic duct-centric pancreatitis requires histologic examination (predominant type seen in children), whereas lymphoplasmacytic sclerosing pancreatitis can be diagnosed without it. Diagnosis of AIP in children can be established based on the combination of specific clinical symptoms at presentation and distinct findings on cross-sectional imaging, and ideally with histology. Clinical presentation of AIP is different in children compared with adults. In literature, majority of children had symptoms of abdominal pain and/or obstructive jaundice in combination with focal pancreas enlargement, main pancreatic duct irregularities, and distal CBD narrowing on cross-sectional imaging. Infact abdominal pain, weight loss, and fatigue are more consistently reported in children than in adult AIP patients who present with painless jaundice.A time-limited corticosteroid treatment course to treat the acute symptoms of pancreatitis, which may also prevent long-term complications of pancreatic insufficiency, is justified. However, further studies are needed to determine whether the advantages of steroid therapy outbalance the potential side effects of this therapy, particularly in children. In this regard, it will be helpful to obtain control imaging about 3 months after starting corticosteroids to evaluate for normalization of the pancreatic imaging findings, confirming the diagnosis of AIP.