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Autoimmune pancreatitis in children: A single centre experience in diagnosis, management and long term follow up

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ABSTRACT

Objectives: Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis and data is limited in the paediatric population. We aim to describe in detail a cohort of paediatric patients with AIP including their presentation, investigations that led to their diagnosis, management and long-term follow up.
Methods: We retrospectively reviewed the data of 6 patients diagnosed with AIP over an 10-year period. Data including demographics, clinical information, laboratory parameters, serological markers, radiological and histological findings as well as longitudinal follow up were collected.
Results: Out of the six patients, one was diagnosed with definitive Type 1 AIP, two with definitive Type 2 AIP, two with probable Type 2 AIP and one with suspected Type 2 AIP. Median time of follow up was 3.9 years (range 2.6–10.1). 4 patients had pancreatic biopsies with 2 of these patients showing granulocytic epithelial lesions (GELs). 4 patients received steroids and two of them developed ulcerative colitis. Azathioprine was commenced on the patient with Type 1 AIP to help her wean off steroids that caused significant side effects on her. Only two patients developed exocrine insufficiency.
Conclusions: The long term follow up of our cohort of paediatric AIP shows good prognosis. More follow up data on patients with AIP is needed to help further characterize and define the disease.

Introduction

Autoimmune pancreatitis (AIP) was first described in 1961 by Sarles et al. as a form of chronic pancreatitis that was associated with hypergammaglobulinaemia [1]. Since then several definitions have been suggested and diagnostic criteria have been proposed. Currently, the diagnosis of AIP can be either definitive or probable, based on adult diagnostic criteria with no specific criteria for children. The International Consensus Diagnostic Criteria (ICDC) for AIP was developed in 2011 to help clinicians in the diagnosis of AIP [2]. ICDC classified AIP to types 1 and 2 based on five cardinal features which include pancreatic histology, imaging of pancreatic parenchymal and ductal changes, serological markers, other organ involvement (OOI) and response to steroid therapy [2].

Type 1 AIP, also known as lymphoplasmacytic sclerosing pancreatitis (LPSP) is characterised histologically by dense periductal infiltration of plasma cells and lymphocytes, obliterative phlebitis, storiform fibrosis and abundant immunoglobulin G-subclass 4 (IgG4) positive plasma cells. Type 1 AIP is associated with elevated serum IgG4 levels and extrapancreatic manifestations including sclerosing cholangitis, sclerosing sialadenitis and retroperitoneal fibrosis associated with infiltration by abundant IgG4-positive plasma cells. Type 1 AIP occurs predominantly in older male population [2].

Type 2 AIP, or idiopathic duct-centric pancreatitis (IDCP), is characterised by intraluminal and intraepithelial neutrophilic infiltrate in the medium- and small-sized ducts as well as in acini, which may result in the destruction and obliteration of the ductal lumen. Although type 2 AIP shares some histological features with AIP 1 such as periductal lymphoplasmacytic infiltrate and storiform fibrosis, IgG4-positive plasma cells are not a diagnostic feature. Type 2 AIP is not typically associated with either serum IgG4

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List of abbreviations

AIP	Autoimmune pancreatitis
EUS	Endoscopic ultrasound
LPSP	lymphoplasmacytic sclerosing pancreatitis
IgG4	Immunoglobulin G-subclass 4
IDCP	idiopathic duct-centric pancreatitis
UC	Ulcerative colitis
N/a	Nil available
CBD	Common bile duct
OOT	Other organ involvement
CT	Computed Tomography scan
P	Parenchymal imaging
S	Serology
Rt	Response to steroids
NAFLD	Non-alcoholic fatty liver disease
Type 2 DM	Type 2 diabetes mellitus
PD	Pancreatic duct
BD	Bile duct
USS	Ultrasound scan
MRCP	Magnetic resonance cholangiopancreatography
D	Ductal imaging
H	Histology

elevation or with OOI. Approximately 30% of Type 2 AIP patients have associated inflammatory bowel disease, such as ulcerative colitis. Type 2 AIP shows no sex predilection and presents in younger people compared to type 1 AIP. The diagnosis of type 2 AIP requires pancreatic tissue histological confirmation due to its lack of serological marker or other organ involvement [2].

The diagnosis and management of paediatric AIP has always been based on adult criteria and experience. However, the distinction of two AIP subgroups as described in adults is difficult to achieve in children. This is due to limitations in endoscopic ultrasound (EUS)-guided pancreatic tru-cut biopsies in children, the poor diagnostic sensitivity of fine needle aspiration samples compared to tru-cut biopsies and the overall risks in obtaining pancreatic biopsy specimens [3,4]. In addition, pancreatic tissue histology in children has not yet been validated in relation to the disease phenotype and there is a possibility that AIP in children may follow a distinct disease pattern [2,5]. Data on paediatric AIP remains limited with a recent extensive review by Scheers et al. summarising 30 previously published cases and 18 new patients [6].

We describe here our centre's experience in diagnosis, management and outcome of paediatric AIP.

Methods

Data were retrospectively collected in all children who were diagnosed with AIP in our centre from September 2006 to July 2017 as part of a service audit. Children with non-traumatic pancreatitis would undergo biochemical [serum amylase, lipase, liver function tests, calcium, lipid profile, autoimmune (immunoglobulins G, A, M, immunoglobulins G subclasses, complement component 3 &4, autoantibodies (SMA, LKM, ANA, GPC, AMA and extractable nuclear antigens), exocrine and endocrine pancreatic function, viral serology and subsequently genetic screening. Data including demographics, clinical information, laboratory parameters, serological markers, radiological and histological findings as well as longitudinal follow up were collected. Genetic testing including *PRSS1*, *SPINK1, CPA1* and *CFTR* were negative for these patients. All patients were tested at presentation for mutations in *PRSS1*, *SPINK1* and *CFTR* but for *CPA1* patients 1, 4 and 5 were screened retrospectively. Pancreatic biopsies were obtained in 4/6 patients with pancreatic enlargement (head or generalised) to exclude pancreatic neoplasm and obtain further diagnostic evidence prior to committing these children to immunomodulatory medications. In patients with pancreatic atrophy on imaging the role of biopsy was deemed not helpful.

Results

Over the study period, six Caucasian patients (5 female) were diagnosed with AIP, with female to male ratio of 5:1. The median age at presentation was 12 years (range, 7–13 years). Median time of follow up was 3.9 years (range 2.6–10.1 years). Patients 4 & 5 were previously reported [7] and we are focusing on their further follow up and disease evolution (see Table 1).

Table 1
Summary of demographic, clinical and histopathologic features of patients with autoimmune pancreatitis.

Patients	1	2	3	4	5	6
Age (gender)	9yr (F)	13yr (F)	12yr (F)	13yr (F)	11yr (M)	12yr (F)
Jaundice/ abdominal pain	+/+	−/+	+/+	+/+	+/+	−/+
Family history	+	+	+	−	−	−
OOI	Nil	BD dilatation	BD dilatation	UC	UC	BD dilatation
Autoantibodies IIF/ELISA IgG	Negative	ANA 1/40	ANA 1/160	Negative	SMA 1/20	ANA 1/40
IgG/IgG4 (g/L)	12.1/3.3	12.4/0.1	9.9/0.3	14.1/1.9	8.7/0.38	10.2/0.8
Amylase (Local)	412	989	227	39	N/a	481
Amylase (KCH)	52	59	66	38	33	62
Lipase	N/a	56	N/a	N/a	N/a	19
USS/MRCP/CT	+/ ±	+/ ±	+/ ±	+/+/+	+/+/+	+/ ±

Table 1 (*continued*)

Patients	1	2	3	4	5	6
USS findings	Moderate liver fatty changes	BD dilatation	CBD, R and L duct dilatation	BD dilatation Bulky pancreatic head	CBD, R and L duct dilatation Pancreatic head mass	Right BD dilatation
MRCP Findings	Parenchymal atrophy (body & tail) Mild PD dilatation (body & tail)	Uncinate process enhancement Smooth stricturing and dilatation of PD Smooth inflammatory stricture of distal BD within pancreatic head. Intra-and extra hepatic BD dilatation	Focal enlargement of pancreatic head and uncinate process Mild distal pancreatic atrophy Irregular PD with proximal duct stricture BD obstruction with distal CBD stricture and upstream BD dilatation	Pancreatic head enlargement PD dilatation Distal CBD stricture with biliary dilatation	Diffusely swollen pancreas/ focal enlargement of the head Intra-and extra hepatic PD dilatation	Atrophic pancreas Selective BD dilatation
ERCP/stent insertion	−	±	+/+	+/+	+/+	−
Endoscopic USS/FNA	−	−	+	−	+	-
Parenchymal/ Ductal disease	±	+/+	+/+	+/+	+/+	No
Biopsy	−	+	+	+	+	−
Inflammation	N/a	+	+	+	+	N/a
IgG4/GEL	±	−/−	−/−	−/+	−/+	N/a
Steroid treatment	+	+	+	−	+	−
Classification	Definitive AIP 1 Level 1 S Level 2 D	Probable AIP 2 Level 2 H Level 2 D OOI 1	Probable AIP 2 Level 2 H Level 2 P/D Rt	Definitive AIP 2 Level 1 H Level 2 P/D	Definitive AIP 2 Level 1 H Level 1 P Rt	Suspected AIP 2 OOI Level 1b
Comorbidities	NAFLD Type 2 DM			UC	UC NAFLD Type 2 DM	

F; Female, M; Male, NAFLD; non-alcoholic fatty liver disease, UC; ulcerative colitis, Type 2 DM; Type 2 diabetes mellitus, IgG; immunoglobulin G, AIP; autoimmune pancreatitis, n/a; nil available, PD; pancreatic duct, CBD; common bile duct, BD; bile duct, OOI; Other organ involvement, USS; Ultrasound scan, CT; Computed Tomography scan, MRCP; Magnetic resonance cholangiopancreatography, P; Parenchymal imaging, D; Ductal imaging, S; Serology, H; Histology, Rt; Response to steroids.

Clinical presentation

Presenting features were jaundice in 3 (50%), abdominal pain similar to that of acute pancreatitis in 5 (83%), weight loss in 2 (33%), vomiting in 1 (17%) and pale stools in 1 (17%). Two (33%) patients were subsequently diagnosed with ulcerative colitis (UC) based on endoscopic and histological features. Non-alcoholic fatty liver disease was additionally diagnosed in 2 (33%) patients, with one (17%) diagnosed 4 months after initial presentation to our centre and the other 2 months after initial presentation. Both these patients also developed diabetes mellitus; the first around the time of steroid introduction, and the latter 4 years from presentation.

Below is a summary of each patient's clinical presentation and clinical course.

Patient 1

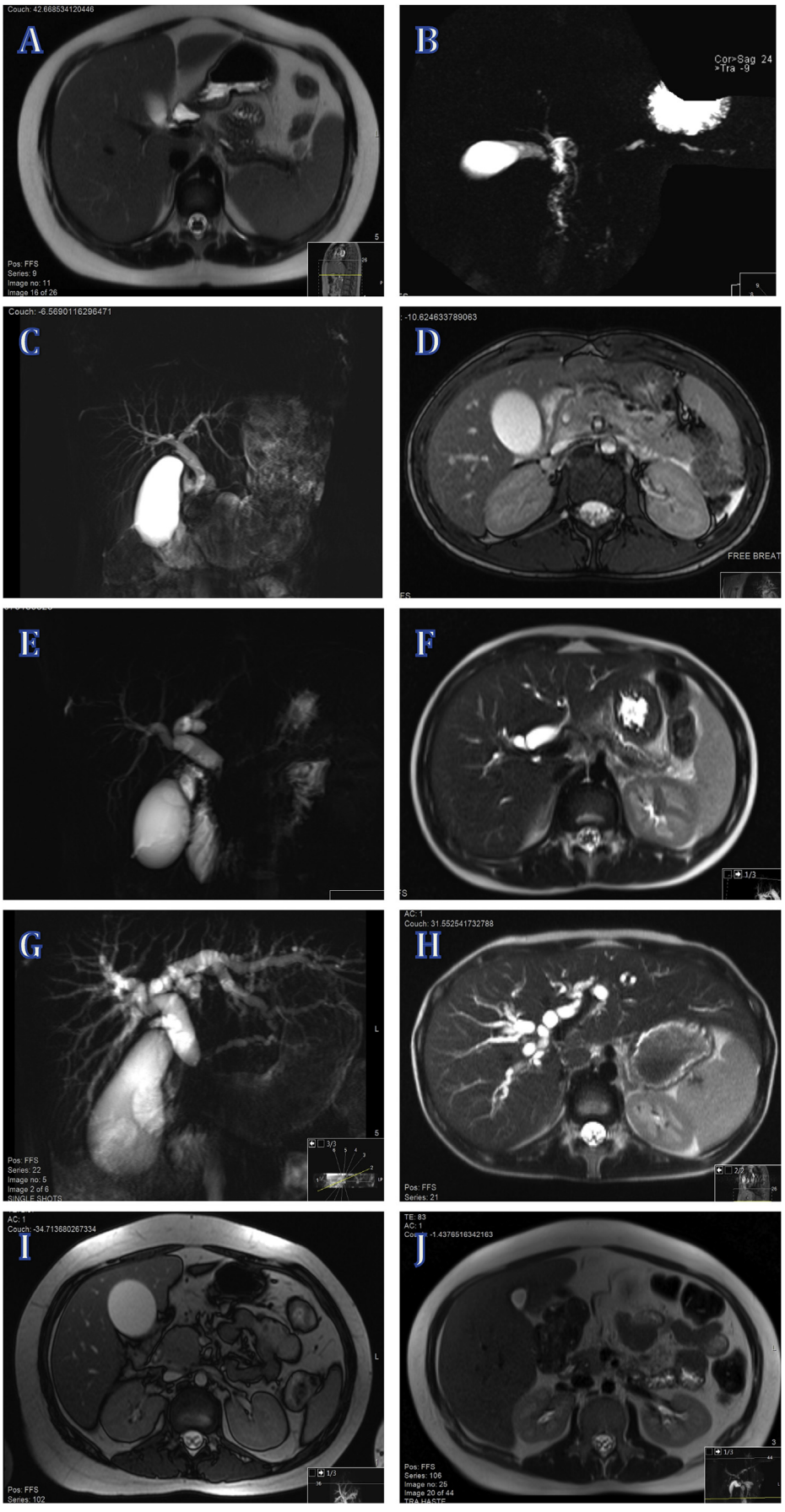
Patient 1 had an 18-month history of non-specific recurrent abdominal pain prior to her trip to India at the age of 7 years during which she was hospitalised for acute pancreatitis and was treated with intravenous fluids and antibiotics. Her recurrent abdominal pain continued on her return to the United Kingdom. At 9 years of age, she presented to her local hospital with severe abdominal pain and raised serum amylase 412 IU/L (nv < 100 IU/L), alanine transaminase (ALT) 92 IU/L (nv, 5–55 IU/L), C-reactive protein (CRP) 22 mg/L (nv < 5 mg/L). Six months later she represented to her local hospital with abdominal pain and serum amylase 155 IU/L, ALT 104 IU/L and CRP 15.9 mg/L.

Following the last episode of pancreatitis she was referred to our centre. Her aspartate transaminase (AST) was raised at 97 IU/L (nv, 7–36 IU/L) but by then her serum amylase had normalised. Her autoimmune profile showed raised IgG4 levels at 3.30 g/L (nv 0.14–0.89) and IgG2 4.66 (nv 0.6–4). Complement component 3 (C3) was high at 1.89 g/L (nv 0.7–1.65) with normal C4 0.47 g/L (nv 0.16–0.54). Her antinuclear antibodies (ANA), anti-soluble liver antigen (SLA) and anti-mitochondrial M2 antibodies were negative.

Liver USS at presentation showed moderate fatty changes in the parenchyma. Magnetic resonance cholangiopancreatography (MRCP) showed pancreatic body and tail parenchymal atrophy in association with mild dilatation of the pancreatic duct at the body and tail (Fig. 1A, B). Liver biopsy confirmed severe steatosis (>80%) with hepatocyte ballooning, mild steatohepatitis and moderate portal and perivenular fibrosis. Immunostaining for IgG4 was present, but did not reach diagnostic criteria (>10 cells/HPF). Upper gastrointestinal endoscopy showed only mild oesophagitis and gastritis.

On the basis of level 2 radiological [Parenchymal (P) & ductal (D)] and level 1 serological criteria type 1 AIP was suspected. She was commenced on prednisolone 1 mg/kg once daily (OD) and steroids were gradually weaned and stopped after 2 years with good radiological and clinical response. Unfortunately, she developed hyperglycaemia, requiring insulin shortly after introduction of steroids. In addition, she also suffered from other side-effects steroid therapy including weight gain and hirsutism. Therefore, azathioprine was introduced a few weeks later to minimise the dose of steroids and was discontinued at the same time of steroid treatment cessation. Faecal elastase at presentation was reduced at 15 (nv > 200 μg/g). She was commenced on pancreatic enzyme replacement for two years and subsequently stopped due to normalisation of exocrine function.

On follow up MRCP, nine years from diagnosis, there was diffusely steatotic liver and a 6 × 5 mm isolated cyst in the uncinate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process of the pancreas with no complex features and thus unlikely of clinical significance. At her latest review at 19 years of age, 10 years following her initial presentation she had mild epigastric tenderness with no other symptoms but insulin dependant. Amylase level was normal at 57 IU/L. IgG subclasses were all normal.

Patient 2

Patient 2 presented locally at the age of 13 years with her first episode of acute pancreatitis with raised serum amylase of 989 IU/L. She had right-sided upper abdominal pain for 1 week prior to her presentation. A month before, she had an episode of alopecia which self-resolved. She has a family history of hyperthyroidism. The episode of pancreatitis resolved within a few days but she re-presented to her local hospital one month later with right upper quadrant and generalised abdominal pain with raised amylase at 424 IU/L.

She was referred to our centre for further investigations. She had ongoing epigastric pain, loss of appetite and weight loss. Her total IgG (12.44 g/L) and IgG subclasses (IgG1 6.35 g/L, IgG2 2.88 g/L, IgG3 0.7 g/L and IgG4 0.11 g/L) were within normal range. Autoantibodies were negative apart from ANA titre of 1/40.

Liver ultrasound scan on presentation showed dilated extrahepatic bile ducts and pancreatic duct changes at the level of the pancreatic head. MRCP confirmed marked intra-and extrahepatic cholangiopathy with smooth inflammatory stricture of the distal bile duct within the pancreatic head (Fig. 1C). There was rim-like enhancement around the uncinate process of the pancreas as well as smooth stricturing and dilatation of the pancreatic duct suggestive of AIP as a potential aetiology (Fig. 1D).

Endoscopic retrograde cholangiopancreatography (ERCP) was performed to assess patency of pancreaticobiliary system and ampullary endoscopic biopsies were obtained. Histology showed inflammation with lymphocytic, plasma cell and eosinophilic infiltrate in the lamina propria. The epithelium had evidence of focal regeneration. Immunostaining for IgG4 showed only a small number of IgG-4 positive cells (<10 cells/HPF) and no fibrosis.

Based on P1, D2 and OOI (biliary involvement) AIP type 1 was diagnosed. The patient was commenced on prednisolone 1 mg/kg OD. Her steroids were gradually weaned and were stopped 19 months later after a good clinical response. Pancreatic exocrine function was suboptimal 2 months later with faecal elastase levels at 15 and she was started on pancreatic enzyme replacement.

At her last follow up, 5 years from initial presentation, she remained asymptomatic while off all medications apart from oral contraceptive pill. Her autoimmune profile remains unchanged with persistent ANA at 1/40. Repeated MRCP showed evidence of further pancreatic atrophy and mild prominence of the proximal aspect of the pancreatic duct compared to the previous imaging.

Patient 3

Patient 3 initially presented to her local hospital at the age of 12 years with left sided abdominal pain, vomiting and raised serum amylase at 227 IU/L. She was subsequently referred to our centre with one month's history of worsening left-sided abdominal pain, jaundice, dark urine, pale stools and deranged liver function tests: AST 163 IU/L, ALT 234 IU/L, total bilirubin 74 μmol/L (nv 3–20 μmol/L), conjugated bilirubin 60 μmol/L (nv < 4 μmol/L), GGT 315 IU/L and ALP 440 IU/L (nv 93–386 IU/L) and serum amylase 66 IU/L. Her IgG subclasses were all within normal range. Her autoantibody profile was negative except from elevated ANA titre of 1/160.

Her liver ultrasound scan demonstrated intra- and extrahepatic duct dilatation. The more peripheral ducts were also mildly dilated. MRCP showed evidence of biliary obstruction with a stricture in the distal common bile duct and proximal dilatation of the biliary system but no intrinsic cholangiopathy. There was irregular pancreatic duct with focal enlargement and diffuse increased signal within the pancreatic head and uncinate process reflecting focal inflammatory change. There was also relative stricturing of the proximal pancreatic duct with mild distal pancreatic atrophy (Fig. 1E, F).

Therapeutic ERCP demonstrated irregular, dilated pancreatic duct and a 2 cm low common bile duct stricture through which a biliary stent was placed. Pancreatic tissue histology obtained via EUS and 22G FNA showed parenchymal inflammation with lymphoplasmacytic cell infiltration, acinar atrophy, and fibrosis. The inflammatory infiltrate was neutrophilic with infiltrated ductules as well as acini (Fig. 2). Due to sample limitations no evidence of obliterative phlebitis was observed. However, classic features of granulocytic epithelial lesion were not identified. Immunostaining for IgG4+ plasma cells was negative.

Based on radiological (P1, D1) and histological (1/2 criteria) criteria type 2 AIP was confirmed and she was commenced on prednisolone 1 mg/kg OD, which was gradually weaned down to 5 mg/day and stopped one year later. Her biliary stent was removed 7 weeks after the insertion. Repeated ERCP showed improvement of the pancreatic duct calibre compared to the previous cholangiographies.

On her latest follow up, 3.5 years following her initial presentation, she remained clinically well. Her anti-nuclear antibodies titre remained raised (1/640) with speckled pattern. Her IgG subclasses, liver function tests, faecal elastase and serum amylase remained normal. Her liver ultrasound scan showed homogenous parenchyma with mildly dilated bile ducts and normal pancreatic duct. All medication had been stopped apart from ursodeoxycholic acid.

Patient 4

Patient 4 previously described by Zen Y et al. [7] presented at the age of 14 years with a 2-week history of jaundice and pale stools. Blood tests showed bilirubin 82 μmol/L, GGT 452 IU/L, ALP 672 IU/L, AST 261 IU/L and amylase 39 IU/L. Apart from myeloperoxidase-anti-neutrophilic cytoplasmic antibody at 8 U/mL (normal range <5), serum autoantibodies were negative. Abdominal CT revealed a mass-like enlargement of the pancreatic head with a tight stricture of the lower bile duct and calibre irregularity of the pancreatic duct. She had papillotomy and biliary stent insertion with ERCP to optimise biliary drainage. A CT guided biopsy of her pancreas using a 20G Tru Cut technique demonstrated lymphoplasmacytic infiltration, periductal and lobular neutrophilic infiltration with GELs, and no IgG4 plasma cells on immunostaining. The features were consistent with Type 2 AIP. Despite the level 1 histological evidence of type 2 AIP, the decision was made not to treat with steroids as her biochemistry improved rapidly following the stent insertion.

Two months following the initial presentation, she had a

Fig. 1. Radiological appearances in patients with autoimmune pancreatitis. (A) Patient 1: MRCP demonstrating pancreatic atrophy (A), MRCP showing pancreatic body and tail duct dilatation (B), Patient 2: MRCP demonstrating smooth duct dilatation (C), MRCP demonstrating signal change in a rim around uncinate process of pancreas (D), Patient 3: slightly dilated pancreatic duct and biliary tree dilatation (E), MRCP demonstrating biliary tree dilatation (F), Patient 4: MRCP showing duct dilatation (G), MRCP demonstrating biliary tree and pancreatic duct dilatation (H), Patient 5: MRCP demonstrating swollen uncinate processus (I) and post-treatment MRCP demonstrating reduction in uncinate processus' swelling (J).

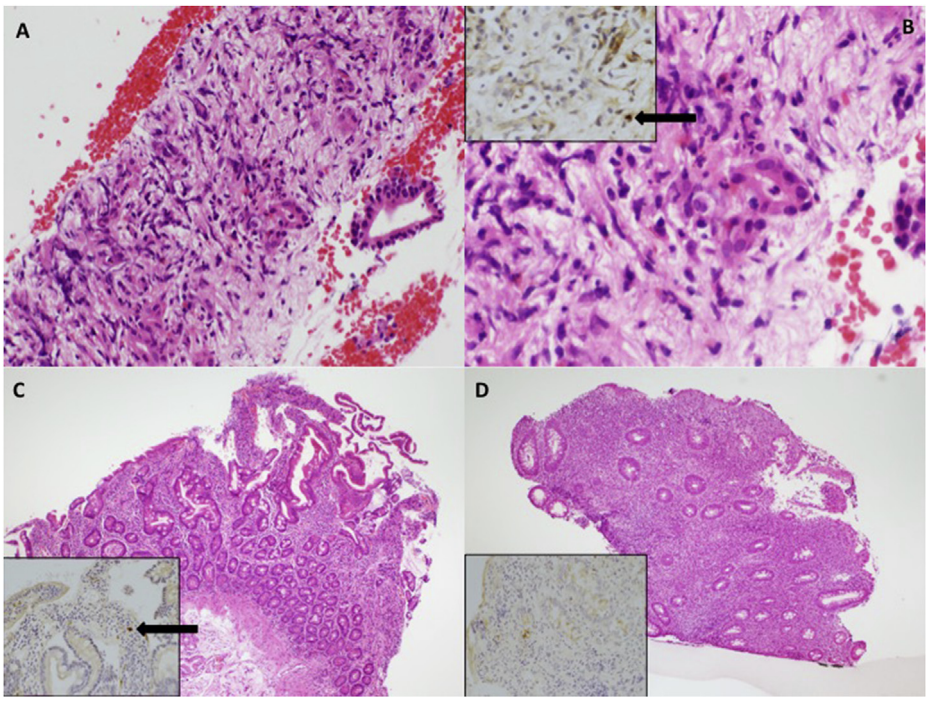

Fig. 2. Patient 3 at twelve years of age underwent pancreatic and ampullary biopsies. The pancreatic biopsy (**A**: H&E x100 magnification and main image **B**: H&E x200 magnification) showed acinar atrophy and inflammation featuring lymphocytes, neutrophils and very occasional eosinophils and plasma cells. Occasional ductal intra-epithelial neutrophils were identified, falling short for Granulocytic Epithelial lesions (GEL). There were only very occasional IgG4 positive plasma cells, amounting to 1 per high power field (**B:**inset, IgG4 immunostain x200 magnification, arrow indicating IgG4 expressing plasma cell). No significant pathological features were seen in the ampulla biopsy (**C:**H&E x100 magnification) and only very occasional IgG4 expressing plasma cells were identified (upto 1 per high power field, image **C**inset IgG4 immunostain x200 magnification, arrow indicating an IgG4 expressing plasma cell). Patient 4 developed ulcerative colitis (**D**: rectal biopsy, H&E x100 magnification) without significant expression of IgG4 positive plasma cells within the inflammatory infiltrate (**D:**inset, IgG4 immunostain, x200 magnification).

repeated ERCP where the old stent was removed. The lower CBD stricture had resolved. There was only a minor residual cholangiopathy in the left duct.

Her autoimmune profile showed raised C3 at 3.27 g/L at presentation and normal C4. Her p-ANCA levels were mildly raised at 8 (<5 U/ml). IgG4 levels measured 2 years following presentation were raised at 1.9 g/L (normal range 0.23–1.11 g/L) and subsequently peaked at 3.51 g/L three years after presentation. Total IgG levels were persistently normal. Her IgG1 levels were also high at 9.55 g/L (normal range 4.8–9.5 g/L) at 2.5 years following presentation and peaked at 13.7 g/L 18 months later.

Subsequently she developed rectal bleeding 1.5 years from presentation and was diagnosed with ulcerative colitis (UC) based on endoscopic and histological findings (Fig. 2). She was treated initially with prednisolone followed by mesalazine and azathioprine for her UC and eventually infliximab but these failed to control her symptoms. She required adalimumab at 19 months from diagnosis of UC to induce remission.

She was last reviewed 4 years after her initial presentation when her amylase was 350 IU/L but with no abdominal symptoms and normal pancreatic exocrine function. Her azathioprine was stopped 5 months prior to last follow up appointment as it was suspected that it was contributing to her raised serum amylase. She was on adalimumab weekly injections.

Patient 5

Patient 5, also previously described by Zen Y et al. [7], was an 11 year-old boy who presented with epigastric pain, jaundice, and weight loss. Blood investigations showed bilirubin 225 μmoL/L, GGT 120 IU/L, ALP 597 IU/L, AST 78 IU/L, normal amylase at 33 IU/L and normal serum IgG4 at 37.6 mg/dL. On MRI, the pancreas appeared diffusely enlarged with loss of the cobblestone architecture of the pancreatic surface. Combined endoscopic biliary stenting was carried out following confirmation of a tight long distal bile duct stricture within the head of pancreas by percutaneous cholangiogram and ERCP. To exclude malignancy histology of a CT-guided biopsy using a 22G Tru Cut needle showed severe pancreatitis with lymphoplasmacytic and neutrophilic infiltration, with infiltration of the lining epithelium of the pancreatic duct/ductules consistent with granulocytic epithelial lesions (GEL).

Based on the level 1 histological and radiological criteria for Type 2 AIP, he was treated with prednisolone 1 mg/kg OD, tapered down to 5 mg/day that was weaned off 2 years later.

Repeat MRCP 6 weeks after initial presentation showed atrophic pancreas; hepatic steatosis with no evidence of intra or extrahepatic bile duct dilatation. His common bile duct stent was removed six months after the insertion.

Patient 5 developed symptoms of inflammatory bowel disease three years later. Upper and lower GI endoscopies confirmed ulcerative proctitis and active colitis involving the transverse-distal colon. He was started on mesalazine with a good effect.

Four years from presentation he developed Type II diabetes mellitus and was commenced on metformin. His last ultrasound scan showed atrophic pancreas, liver parenchyma of increased reflectivity with moderate to marked fatty change and no ductal changes. His autoimmune profile remained within normal limits with normal pancreatic exocrine function and he is asymptomatic.

Patient 6

Patient 6 presented with an episode of epigastric pain at the age

of 12 years and raised serum amylase at 227 IU/L. She recovered within a few days of pancreatic rest but one month later she represented with a 2-day history of epigastric pain and raised serum amylase of 481 IU/L. Her abdominal pain resolved on the next day and her amylase improved to 106 IU/L.

She was seen in our centre two months later. Her serum amylase had normalised (62 IU/L), liver function tests were also normal and she was asymptomatic. Her total IgG, IgG subclasses and complement were within normal range. Serum ANA titre was 1/40 with a speckled pattern. All other autoantibodies were negative.

Abdominal ultrasound showed homogenous liver parenchyma with normal reflectivity and segmental right duct dilatation with no pancreatic duct irregularities. Her MRCP showed an atrophic pancreas, suggestive of a chronic burnt-out pancreatic inflammatory process with no focal pancreatic lesions or pancreatic duct dilatation/irregularities.

As there were no typical parenchymal or ductal features suggestive of AIP but only OOI level 1b the patient did not fulfil diagnostic criteria for probable/definitive AIP. There was no clinical indication for further histological investigation. In view of not fulfilling diagnostic criteria but with a strong clinical suspicion of AIP (chronic pancreatitis, positive autoantibodies, OOI) expectant approach was suggested with no justification for empirical steroids, as the pancreas was already atrophic.

At her last review two years ago her only symptoms were occasional, self-resolving episodes of abdominal discomfort with normal stool consistency and frequency. Pancreatic exocrine function is still preserved. Her last MRI pancreas showed no further evolution of the initial radiological changes. Total IgG levels and IgG subclasses remained normal. The patient was considered as AIP-not otherwise specified due to clinical suspicion. Since last appointment her care was transferred to local adult gastroenterology services and on personal communication due to recurrent abdominal pain with further bile duct dilatation and pancreatic atrophy and although she did not fulfil diagnostic criteria she has been commenced on oral prednisolone (60 mg/day) with symptom improvement.

Discussion

In this study we describe our centre's experience in diagnosing AIP in children. Patients 4 and 5 were previously described [7] and therefore we opted to focus on their medium term follow up. Out of 6 patients, 5 presented with abdominal pain and 3 with obstructive jaundice. This correlates well with report by Scheers et al. where acute abdominal pain and obstructive jaundice were also the most commonly reported symptoms at diagnosis [6]. All our patients who presented with jaundice had a proximal dilatation of the common bile duct narrowing distally toward the head of pancreas. Only one child had diffusely swollen pancreas, fulfilling the criteria of level 1 parenchymal imaging. Indeed, focal rather than diffuse pancreas enlargements were more frequent in children compared to adults making this finding more applicable in the paediatric population [6].

Two patients underwent ampullary biopsy at ERCP (Patient 2 and 3), whilst another 2 had CT-guided pancreatic biopsy (Patient 4 and 5). Patients 4 and 5 showed typical GELs in their histology. The biopsies from patients 2 and 3 showed only a small number of IgG4 positive cells. It is worth noting that the finding of increased IgG4+ cells in duodenal biopsies is not specific for AIP without the correct clinical context [8]. Although patient 2 had inflammatory infiltrate containing several neutrophils, the sample was size-limited and the classic features of GELs were not identified. The role of biopsy is important to differentiate AIP from pancreatic malignancies due to the different prognostic and therapeutic implications and pancreatic histology plays a pivotal role in the process. Due to the rarity of paediatric pancreatic neoplasms, a pancreatic mass causing biliary obstruction in children is more likely due to be AIP than a malignancy [9].

AIP remains a diagnostic challenge. In our cohort, only Patient 1 had a definitive diagnosis of type 1 AIP according to ICDC. This was based on raised Ig4 levels as well as pancreatic atrophy in association with mild dilatation of the pancreatic duct. Along with her response to steroid treatment, she would fit the criteria of definitive Type 1 AIP. With level 1 histological criteria (demonstration of GEL), Patients 4 and 5 fit into the diagnosis of definitive Type 2 AIP, with patient 4 having indeterminate radiological evidence and patient 5 having typical radiological criteria of Type 2 AIP. Patients 2 and 3, on the other hand, had level 2 radiological criteria for Type 2 AIP and with clinical response to steroids, they qualified for probable Type 2 AIP. Nevertheless, it is worth noting that Patient 3 also had biliary stent inserted, which could contribute to his symptomatic improvement. Suspected diagnosis of AIP-not otherwise specified in patient 6 is based on OOI and autoantibody positivity. These findings reflect the limitations of applying the adult criteria on paediatric population and the variability of diagnostic findings, which paediatricians need to interpret carefully within the clinical context. The presence of >10 IgG4 positive cells/HPF has been challenged in series of AIP adult patients fulfilling other AIP histological criteria making it more applicable to paediatric histology interpretation [10].

Only 4/6 (Patients 1, 2, 3 and 4) were treated with only oral steroids, which were weaned over a period of 1–2 years. Patient 4 initially did not get steroids as her symptoms resolved following placement of biliary stent. On follow up, all 4 patients remained well off steroids. Patient 6 was commenced on steroids five years after presentation due to biliary and pancreatic duct disease progression and strong clinical suspicion. The first patients were started on high dose steroids (60 mg maximum) and following a weekly weaning process they were kept on low dose of 5 mg, treatment similar to our centre's autoimmune liver disease protocol. At the initial stages when children were diagnosed with AIP there were no reports on paediatric experience and the authors felt more confident to treat children with a standardized internal regime. The lack of data on relapse rate and long-term prognosis in children also contributed to the author's decision in treatment duration. No attempts were made to stop steroid treatment earlier apart from patient 1. Currently, children with AIP are treated based on a 3–6 month weaning dose of prednisolone with good response.

It is interesting that this autoimmune process can be treated with immunosuppression for a short period of time with the majority of patients remaining in long clinical/symptomatic remission giving AIP a very good prognosis unless endocrine function gets affected. Autoantibody screening at presentation showed low positive titre in ANA (4/6) and in Smooth Muscle Antibody (SMA) (1/6). The presence of autoantibodies in AIP patients has been classified into organ and non-organ specific groups and ANA positivity has been described in up to 40% of AIP patients [11]. None though are deemed disease specific and autoantibody positivity has not been incorporated into the diagnostic criteria of AIP in contrast to other autoimmune conditions such as autoimmune liver disease [12].

Patient 1 and 5 developed Type 2 diabetes mellitus (DM), with the former acquiring diabetes shortly after steroid introduction, and the latter 2 years after cessation of steroids. The development of Type 2 DM in AIP may be multifactorial, and could be attributed to pancreatic endocrine insufficiency but also prolonged steroid use as well as obesity. The diagnosis of AIP should be made carefully, due to the potential side effects of the steroid treatment. Ito et al. looked into the characteristics of diabetes mellitus (DM) in adults

with AIP depending on whether DM preceded, concurred or followed diagnosis of AIP and treatment with steroids. There were no significant differences noted amongst subgroups but the incidence of DM was 66.5% in their study group. All diabetic patients also had a higher incidence of exocrine dysfunction [13]. However, data are scarce in AIP children with diabetes mellitus. In our cohort the remaining four patients had normal HbA1c levels at latest follow up. Azathioprine can be used for steroid-sparing effects in the patients who are steroid-dependant, but needs to be used with caution. Mannion et al. described the successful use of mycophenolate mofetil as a treatment in a 13 year old child with type 1 AIP [14] but also anti-CD20 monoclonal antibody treatment has been attempted in steroid intolerant/resistant adult cases with good response [15]. Further studies will be required on potential alternative immunomodulatory treatments for children with relapsing AIP, albeit rare so far.

Pancreatic exocrine insufficiency was found in only 2/6 during their follow up. Pancreatic exocrine dysfunction has been reported up to 83%–88% of adult AIP cases and in diabetes mellitus (DM) in 42%–78% [16]. Long term follow up of children past their 4th decade of life and later will shed light into the incidence of endocrine and exocrine insufficiency in AIP.

ERCP was performed in 4 out of 6 patients (Patients 2, 3, 4 and 5), for therapeutic purposes where pancreatic duct abnormalities were identified. Biliary stent was inserted in 3 patients and ampullary biopsy was performed in two patients. ERCP is a useful modality in this context but is only available in specialist centres making a case for centralised care for children with pancreatitis requiring intervention. Recently, with the increasing recognition of AIP, ERCP has been replaced by a trial of steroid therapy in some centres cases where AIP is strongly suspected due to perceived invasive nature of this procedure [6]. In paediatrics and while long-term treatment with steroids can have an impact on growth ERCP should still be the investigation/treatment of choice if indicated undertaken in centres with expertise.

Endoscopic ultrasound-guided biopsy may similarly be a useful modality in obtaining pancreatic biopsies in children. As shown in our series the evidence of pancreatic swelling and the need to establish histological diagnosis can be well served by EUS. Its utilisation remains controversial though in children with established pancreatic atrophy where the diagnostic yields is limited [10]. Currently, due to the lack of skilful paediatric endosonographers, technical limitations of EUS equipment and accessories, and the requirements for general anaesthesia, the use of EUS-guided biopsy is less common in children compared to the adults [17]. EUS may provide pancreatic tissue in selected patients, obviating the need for ERCP in selected patients.

IBD was diagnosed in only two of our patients with AIP type 2. The incidence of IBD can be up to 30% of adults and 25–27% of children with AIP and usually manifests in the form of UC. On the other hand the incidence of acute pancreatitis in children with IBD has been reported up to 14% [18,19] although its aetiology can partly be due to pharmacological agents used to treat IBD such as azathioprine. It remains unclear whether the inflammatory process is similar to the one observed in children with autoimmune hepatitis and sclerosing cholangitis where the incidence of IBD can be up to 20% and 45%, respectively [20]. Further longitudinal studies in children with AIP will be useful and collaborations will be welcomed to extract meaningful data.

In conclusion, AIP remains a rare pancreatic disease in children with good response to oral steroid treatment and variable incidence of exocrine and endocrine dysfunction. The diagnosis remains challenging and criteria fulfilment requires invasive procedures in specialised paediatric centres.

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