LONDON CANCER ALLIANCE

Chronic Pancreatitis Patient Pathway

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1 Background

With the reorganisation of hepatic and pancreatobiliary (HPB) cancer services in England there was a recognition that specialised services for benign HPB disease should be identified and protected. Chronic pancreatitis (CP) is a condition characterised by inflammation leading to irreversible damage and scarring resulting in loss of exocrine and endocrine function. The condition is prevalent worldwide and is associated with considerable morbidity as well as premature mortality. There are important implications of the disease upon healthcare provision. There are aspects of diagnosis and management of chronic pancreatitis that may require specialist HPB services. Chronic pancreatitis is recognised as a premalignant condition and cancer surveillance programmes for high risk cases are now being developed.

2 Diagnosis

There are several recognised aetiological factors:

- toxic-metabolic; including alcohol
- idiopathic including early and late onset: tropical
- genetic mutations including PRSS-1, SPINK-1, CFTR and others
- autoimmune
- recurrent and severe acute pancreatitis related
- obstructive; including pancreas divisum, sphincter of Oddi disorders and post traumatic duct strictures.

In the western world alcohol is the commonest recognised aetiology. There is increasing evidence that in many cases of CP the disease is the end point of an interaction between environmental and genetic influences. Several gene mutations have been linked to CP and are likely to be responsible for many of the cases presenting in childhood and early adulthood.

A gene mutation screen should be carried out in most cases in which the diagnosis of CP is made under the age of 40. Currently the screening is limited to a bank of the most common cystic fibrosis mutations as well as mutations related to SPINK-1 and PRSS-1. There is increasing evidence that these mutations are the tip of an iceberg and the screening process will require considerable expansion. There are important cost implications if this is to occur and currently these may not be balanced by clinical benefits from identifying specific mutations. Autoimmune pancreatitis (both types 1 and 2) is a recognised cause of chronic pancreatitis and the diagnosis is important because of the steroid responsiveness of the disease. IgG4 is a serological marker in type 1 disease.

In most cases the diagnosis of CP is made in secondary care based upon the clinical history and compatible imaging. Trans abdominal ultrasound is likely to identify features of CP particularly calcification and pancreatic duct dilatation. Confirmatory evidence will be provided by CT scanning (including dual phase pancreatic sequences). MRI and MRCP may provide additional evidence particularly in the presence of ductal abnormalities. Endoscopic ultrasound (most likely to be found in the tertiary care setting) is used when doubt about the diagnosis remains after the above imaging or specifically for assessing complications of chronic pancreatitis including pseudocyst formation and the possible development of malignancy.

Assessment and monitoring pancreatic exocrine function is an important part of diagnosis and management of CP. Faecal fat collections are unpopular with patients and laboratories alike and are rarely

used. Faecal elastase provides an alternative assessment. This pancreatic specific enzyme is not degraded in the intestine and has high concentrations within the faeces. Diminished levels may be detected in moderate as well as severe pancreatic insufficiency. This test has largely replaced the more sensitive direct assessments which rely upon the analysis of duodenal aspirate following pancreatic stimulation (Lundh meal or cholecystokinin/secretin). Similarly the oral pancreatic function tests using N-benzoyl-L-tyrosyl-p-aminobenzoic acid (basis of PABA test) and fluorescein dilaurate (both substrates for pancreatic enzymes), whilst still commercially available, are seldom employed.

3 Referral

Patients who fulfil the referral criteria outlined in this guidance should be referred either to the Gastrointestinal/HPB Medicine Unit at Hammersmith Hospital , where there is a specific clinic allocated to chronic pancreatitis, or to the 'Pancreatitis Service' at King's College Hospital NHS Foundation Trust. The Pancreatitis Service at King's comprises HPB surgeons and liver unit gastroenterologists, enabling the referral to be triaged appropriately. In practice, many of the King's referrals for chronic pancreatitis will be made by the designated HPB surgeons who service the local MDMs in the referring Trusts, mirroring the cancer referral pathway.

4 Management

Specific diagnosis-related therapy includes long-term abstinence in those patients in whom alcohol excess is considered a factor. Autoimmune pancreatitis is steroid responsive and failure to do so would question the diagnosis. Relapse is common when the steroids are withdrawn and long term immunomodulators (e.g. azathioprine) may be required.

General measures are directed towards the following features of chronic pancreatitis:

- pain control
- nutritional deficit
- exocrine failure
- endocrine failure
- bile duct obstruction
- pseudocyst formation
- cancer development

In many cases these issues can be addressed in secondary care and management is not discussed here in detail. There are, however, a significant proportion of patients who show considerable debility as a result of multifactorial problems. There is often a cascade of issues with poor pain control leading to reduced food intake which combined with poor management of malabsorption can result in significant nutritional deficit. A coordinated approach to care in such cases may be optimally provided in a specialised pancreatic centre.

Chronic pain associated with CP may be recurrent severe or persistent. Both endoscopic and surgical interventions have been used for definitive management. This is particularly the case in patients with chronic calcific disease with a dilated pancreatic duct upstream of a ductular stricture and/or stone. The endoscopic approach has centred upon improving duct drainage by removing intraductal stones and duct

stenting to maintain patency. Extracorporeal shock wave lithotripsy has been used to fragment stones within the head of pancreas.

Surgical intervention usually involves a duct drainage procedure which can be combined with partial resection of the diseased head of pancreas. Recent trials have reported improved pain control following surgical intervention as compared with the endoscopic approach. Drainage operations are now carried out by the laparoscopic approach. However, many patients have a high level of debility (and often continued alcohol excess) and are unsuitable for major surgery. In such circumstances endoscopic therapy is justified as a first measure and there is no evidence this adversely influences subsequent surgery if required. There is some non trial evidence that the use of removable fully covered metal stents to drain the pancreas may have advantages as compared to the use of plastic stents. The development of this approach should be restricted to prospective studies in specialist centres.

Common bile duct obstruction is a common complication of CP. High grade obstruction and jaundice does not present a difficulty of diagnosis. Low grade obstruction which may not be readily recognised may be a cause of persistent abdominal pain and can lead to secondary biliary liver disease. The endoscopic approach to management relied upon the placement of a single 10f plastic stent often being replaced at 3 monthly intervals over a period of 12 months. The long term outcome with this approach was unsatisfactory with stricture resolution in no more than 25% of cases. The introduction firstly of multiple plastic stent placement and more recently fully covered (and removable) metal stents has markedly improved the outcome from endoscopic intervention (> 80% stricture resolution). Surgical bypass is still required in a small proportion of patients and may also be required for the small number of patients who develop gastric outlet obstruction secondary to CP.

Pseudocyst formation is the most common structural complication of chronic pancreatitis. These usually occur in relationship to a period of enhanced inflammatory activity within the pancreas giving abdominal pain, but may develop silently during what would appear to be a stable phase. Intra- or retroperitoneal rupture, bleeding or cyst infection may occur. The larger cysts may occlude nearby structures including the duodenum and the bile duct. In pseudocysts less than 6cm in diameter, spontaneous resolution can be anticipated. In larger cysts that have been present for a period in excess of 6 weeks, resolution is less common and a long-term complication rate of approximately 30% can be anticipated. Many pseudocysts are closely opposed to the posterior wall of the stomach or duodenum and can be successfully drained endoscopically using endoscopic ultrasound to identify the optimum drainage site. This approach will be successful in approximately 75% of cases. Surgical drainage is required for failures of endoscopic therapy or in circumstances in which the pseudocyst anatomy does not allow endoscopic access.

Pancreatic cancer is a recognised complication in patients with chronic pancreatitis. The risk of malignancy is closely related to the duration of the inflammatory process. The highest incidence has been reported in hereditary pancreatitis with a 50 fold increase and a lifetime risk as high as 40%. This reflects the early onset (in childhood) of the disease. Twenty to thirty fold increases have been described in patients carrying other gene mutations and early onset of disease. The lifetime risk of malignancy in other causes of chronic pancreatitis such as alcohol, which develop much later in life, is 10-15 %. Cancer surveillance programs have been proposed within specialist centres for the very high risk groups (hereditary pancreatitis and other causes of early onset disease), usually starting around the age of 40 years and relying upon yearly imaging and tumour marker measurement.

5 Summary of Pathway Recommendations

In most cases the diagnosis and management of CP will be undertaken in secondary care. However, there remains a group of patients in whom the diagnosis requires specialised imaging techniques, in particular endoscopic ultrasound. In those cases presenting below the age of 40, a tertiary centre referral should be considered to investigate genetic and other factors that may be contributing to the CP process. The management of CP patients with significant debility, often with pain predominance, is optimally carried out in specialist centres which provide a benign MDT for this purpose. Both endoscopic and surgical options should be available. A cancer surveillance program should be available within the network for high risk patients. Those presenting below the age of 40 and including all cases with a genetic predisposition should be entered into this program.

6 Bibliography

Amed Ali U, Pahlplatz JM, Nealon WH et al. Endoscopic or surgical intervention for painful obstructive chronic pancreatitis. *Cochrane Database of Systematic Reviews*. 2015; Issue 3.

Conwell DL, Lee LS, Yadav D et al. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines. *Pancreas*. 2014; **43**(8): 1143–62.

Shelton CA and Whitcomb DC. Genetics and treatment options for recurrent acute and chronic pancreatitis. *Curr Treat Options Gastroenterol*. 2014; **12**(3): 359–71.

Talukdar R and Nageshwar Reddy D. Endoscopic therapy for chronic pancreatitis. *Curr Opin Gastroenterol*. 2014; **30**(5): 484–9.