Alpha 1 antitrypsin deficiency – Full clinical guideline

Reference no: CG-T/2023/186

α1-AT deficiency is a common autosomal co-dominant disease of Caucasians of northern European ancestry (1: 1600 live births in Sweden) that can cause pulmonary disease and less frequently hepatic disease. α1-AT is the most common cause of paediatric metabolic liver disease. In liver disease structurally abnormal α1-AT protein accumulates within hepatocytes leading to direct cytotoxicity and potentially severe liver disease and liver failure (i.e. not related to deficiency cf. lung disease). α1-AT deficiency should be considered in the differential diagnosis of any patient with chronic hepatitis, cirrhosis or HCC of unclear aetiology (especially elderly cryptogenic cirrhotic).

Diagnosis:

- Serum α1-AT quantification (can be unreliable as acute phase reactant)
- Protease inhibitor phenotyping (isoelectric focusing) – gold standard
- Genotyping (useful in rare genotypes and genetic counselling)
- Histological analysis (peri-portal hepatocytes with diastase-resistant, PAS-positive intracellular globules +/- Kuppfer cells, 94% specificity)

α1-AT is a serine protease inhibitor with activity against neutrophil elastase. There is an Autosomal co-dominant pattern of inheritance; M ('main') allele produces normal levels of α1-AT. S ('slow') allele produces moderately low levels of α1-AT; Z ('slowest') allele produces very little protein. The homozygous Pi (protease inhibitor) ZZ phenotype usually results in profound deficiency of α1-AT predisposing to pulmonary and hepatic disease (for unclear reasons it is rare to have both).
Hepatic disease only occurs in 10-20% of patients with PiZZ α1-AT deficiency. This usually manifests in infancy as an acute jaundice illness, which may settle with representation in late childhood or early adulthood with liver cirrhosis.
PiSZ individuals are at increased risk of pulmonary disease (especially if smoke) but at low risk of hepatic disease. Pi MS and Pi MZ individuals may be at increased risk for cirrhosis / HCC when other co-existent liver insults are present e.g. ALD / viral hepatitis (1:40 Caucasians are Z allele carriers).
Patients with α1-AT associated liver cirrhosis have a higher risk of HCC as compared to many causes of liver cirrhosis. The risk is similar to those patients with cirrhosis due to viral hepatitis.

Management

- Advice all patients on avoiding/ cessation of smoking
- Non-cirrhotic PiZZ phenotype patients with normal LFT's should have annual LFT's and Fibroscan to assess for fibrosis progression every 2-3 years.
  No current therapy for hepatic disease (chaperone molecules hold promise)
- Cirrhotic patients should undergo HCC surveillance with AFP and Abdominal ultrasound every 6 months. Otherwise management is as for any other patient with cirrhosis.
- Family screening of first degree relatives can be offered and pre-pregnancy testing in high-risk individuals, however given incomplete penetrance this is an ethical minefield.

Documentation Controls (these go at the end of the document but before any appendices)

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<tr><td>Reference Number

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Final</td><td>Final</td></tr>
<tr><td rowspan="3">Version / Amendment History</td><td>Version</td><td>Date</td><td>Author</td><td colspan="2">Reason</td></tr>
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