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*DOI:*
10.1080/17474124.2018.1477589



*Document Version*
Peer reviewed version

*Citation for published version (Harvard):*
Townsend, S, Newsome, P & Turner, A 2018, 'Presentation and prognosis of liver disease in alpha-1 antitrypsin deficiency', *Expert review of gastroenterology & hepatology*. https://doi.org/10.1080/17474124.2018.1477589


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| Journal: | *Expert Review of Gastroenterology & Hepatology* |
| Manuscript ID | ERH-2018-0076.R1 |
| Manuscript Type: | Editorials |
| Keywords: | Alpha-1-antitrypsin deficiency, liver cirrhosis, liver transplantation, liver fibrosis, prognosis, PiZZ, PiSZ |
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## Editorial

# Presentation and Prognosis of liver disease in alpha-1 antitrypsin deficiency

Sarah Townsend[1], Philip Newsome[1] & Alice M Turner[2]

[1] National Institute for Health Research Liver Biomedical Research Unit at University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham

[2] Institute of Applied Health Research, University of Birmingham, Birmingham, B152WB, UK

**Correspondence**:

Sarah Townsend

National Institute for Health Research Liver Biomedical Research Unit at University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham - Centre for Liver Research, Institute of Immunology and Immunotherapy, College of Medical & Dental Sciences, University of Birmingham Edgbaston, Birmingham, B15 2TT, United Kingdom

Email: s.a.townsend@bham.ac.uk

**Keywords:** Alpha-1-antitrypsin deficiency; Liver cirrhosis; Liver fibrosis; PiZZ; PiSZ; Liver Transplantation; Prognosis

## 1. Introduction

Alpha-1 antitrypsin deficiency (AATD) affects approximately 3 million people worldwide (1), and yet its pathophysiology is poorly understood. In the lung, lack of alpha-1 antitrypsin leads to proteolytic damage to the connective tissue matrix, resulting in emphysema in approximately 75% of PiZZ patients (2). Point mutations lead to altered folding of the protein during biosynthesis, resulting in misfolded proteins being retained within hepatocytes (3). The aggregation of antitrypsin polymers within the endoplasmic reticulum (ER) of liver cells forms periodic acid-Schiff positive inclusions, which cause endoplasmic reticular stress, mitochondrial dysfunction and trigger autophagy. Hepatocytes with less abundance of mutant Z protein proliferate, and this chronic cycle of cell death and regeneration activates hepatic stellate cells and initiates hepatic fibrosis (4), although the true mechanism of injury is yet to be fully elucidated . A conundrum in AATD remains the phenotypic variability in both lung and liver disease. Children may experience jaundice during infancy but have no further complications, whilst others develop liver cirrhosis and require liver transplantation.

The ability to predict which individuals are at highest risk of developing significant liver disease would be useful clinically for prognostic purposes, planning of clinical services, and influencing lifestyle behaviours where appropriate. For example, in AATD-related lung disease, cigarette smoking is the greatest predictor of lung function deterioration, and so smoking cessation is strongly advised in these individuals. Here we summarise the patterns of presentation and prognosis in AATD-related liver disease in children and adults, and review the evidence for factors which may be influential in disease progression.

## 2. AATD in Children

AATD commonly presents in infancy with jaundice (5, 6), but it can also present with neonatal hepatitis, hepatosplenomegaly, or gastrointestinal haemorrhage without jaundice (5). From presentation, the disease takes a varied and fluctuating course, with only a small proportion of children (less than 1%) developing liver failure in infancy (5, 6), with others making a full recovery. A proportion (approximately 1%) of those children presenting in infancy recover to enjoy years of good health whilst later on developing severe disease (7) and require liver transplantation. This commonly occurs between the ages of 4 and 8 (8), but sometimes later on in the second decade of life (9, 10). Other children have no signs of disease during infancy but are diagnosed incidentally later in childhood following abnormal liver biochemistry tests (10, 11) in response to screening of family members of an affected individual (12). Others can present with advanced or even decompensated liver disease (11, 13).

AATD more commonly affects the Caucasian population, and in a recent systematic review, 97% of children diagnosed with the condition were of Caucasian origin (9). Interestingly, although males comprise only 35% of children diagnosed with AATD, boys accounted for over 60% of children undergoing liver transplantation for AATD, suggesting that disease progression is more likely in males (9).

Our recent systematic review found that 8% of children with polymerogenic AATD developed liver cirrhosis, and 16% required liver transplantation (9). The discrepancy between these figures is most likely due to ascertainment bias, with a large number of studies reviewed arising from liver transplant centres, and so it seems likely that the proportion of children with AATD that will develop cirrhosis and require liver transplantation is about 10%. The reason that such a small proportion of individuals with polymerogenic AATD develop significant liver disease is unknown. Some studies have suggested that differences in the ability of hepatocytes to transport polymerised proteins out of ER for degradation by proteasomes, or in hepatocyte autophagic degradation pathways between individuals, may play a role (14). In common with many chronic diseases it could be that genetic modifiers play a role, as they do in AATD lung disease (3)

Multiple studies have investigated potential predictive factors for poor prognosis in children with AATD related liver disease, but results have been mixed. Raised aspartate aminotransferase (AST) at presentation, particularly in combination with gamma-glutamyl transferase (GGT), was found to be a risk factor for requiring liver transplantation later in life in one study (11), but these findings were not replicated in other studies investigating liver biochemistry (13). Several studies identified jaundice, either at presentation (12, 15) or prolonged (>6 months) in those with neonatal hepatitis (11) as risk factors. However, in one study infants with severe prolonged jaundice (conjugated serum bilirubin above 2.0 mg/100ml at two to three months of age) went on to make a complete recovery, and another study looking at jaundice early in life made the same findings (16).

Some studies have proposed liver biopsy findings as potential predictors for development of liver disease, albeit with mixed results. Portal fibrosis and paucity of bile ducts are the features most consistently found at liver biopsy in infants who progress to liver cirrhosis (17) and/or require liver transplantation (9, 11).

For children with progressive disease that do require liver transplantation, outcomes are excellent, matching those for other indications, with no recurrence of liver disease and no development of AATD- related lung disease (11, 13, 18).

### 3. AATD in Adults

As in children, disease severity and mode of presentation varies widely in adults. AATD may be diagnosed incidentally in an otherwise unaffected individual whilst others develop cirrhosis and require liver transplantation (9). Adults requiring transplantation for AATD related liver disease have a median age of between 34 and 54 (9) suggesting that severe disease presents before the 5$^{th}$ decade in adults. As with children, the majority (93%) of adults with AATD related liver disease are Caucasian. Disease progression occurs more commonly in males, despite the diagnosis being made equally in women and men (53% male), and yet 73% of those requiring transplantation are male (9).

Increased body mass index (BMI) has been found to be a risk factor for requirement for liver transplantation in individuals with AATD related liver disease (10), as has concurrent viral infection (10, 19), and alcohol consumption (10, 20) in some studies. It seems likely that concurrent liver injury from such factors accelerates disease progression in AATD, however, cofactors are not identified in all adults with AATD related liver disease.

Whereas hepatocellular carcinoma (HCC) is not reported in children with AATD, its incidence in adults is similar to that for cirrhosis of other aetiologies, with an overall incidence of 1.3%.

Just over 10% of adults presenting with AATD related liver disease develop liver cirrhosis and require transplantation, and outcomes following transplantation for AATD related disease match those for other aetiologies (8, 18).

In summary, although there are recognised patterns of presentation for AATD-related liver disease, it can present at any age, and across a spectrum of disease severity. Whilst serum markers such as AST, GGT and bilirubin may be useful to predict disease progression, these factors, together with others such as biopsy findings, require more robust investigation through prospective studies. In the mean-time, use of non-invasive tools such as transient elastography (21) and Enhanced Liver Fibrosis (ELF) (22) test may help to identify those individuals who have liver fibrosis and are at risk of progression to cirrhosis, although research is required to validate this approach this cohort of patients. Finally, a better understanding of the pathophysiology of AATD-related liver disease may help not only to identify why certain individuals are more susceptible, but also contribute to the development of much needed treatment options.

**Funding**

This paper was not funded.

**Declaration of interest**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.



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