EDITORIAL

Alpha- 1 Antitrypsin Deficiency Related Liver Disease: Is It Worth a Search in India?

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Alpha-1-antitrypsin deficiency (AATD) is the commonest genetic cause of liver disease in children from the West and also a major cause of emphysema and chronic obstructive pulmonary disease in adults. The mechanism of lung and liver injury are distinct and unique. The liver disease appears to involve a "gain of function" mechanism in which the retained mutant AAT molecule in the endoplasmic reticulum triggers a series of events which lead to programmed hepatocyte death, inflammation, fibrosis and cirrhosis. More than 100 mutant alleles have been identified, but only few are associated with liver disease. The commonest deficiency phenotypes are PIZZ, PISS and PISZ. Other rare alleles account for 5% of PI variants and include M_{malton} and M_{Duarte} among others(1).

In this issue of the Journal, Arora, *et al.*(2) have evaluated 1250 children (840 chronic liver disease [CLD], 410 neonatal cholestasis [NC]) and 450 controls for AATD. Authors carried out investi-gations of screening and phenotyping (PI) with isoelectric focussing (IEF) in all the subjects (*n*=1700). On screening 7.8% (98/1700) subjects were shown to be deficient (low serum AAT level or absent/faint alpha-1 globulin band on serum agarose electrophoresis or PAS positive diastase resistant globules on liver histology). Phenotyping was normal (MM) in 99.8% (*n*=1697) children and the other 3 subjects had other variants (MIE, MP, MC: one each), none of which are known to be associated with liver disease. Fifty subjects (CLD 34, NC 16) of the 98 screen positive were subjected to genotype sequencing; none had PIZ or PIS genotypes. However two children had a novel mutation at position 333 in exon V; both having cryptogenic CLD, low serum AAT levels and positive globules on liver biopsy on immune histochemistry, all pointing towards a diagnosis of AATD. The study suggests that the commonest AAT deficiency alleles of PIZ and PIS as described in the West are not seen in Indian children. Thus AATD is a rare cause of liver diseases in India.

We appreciate the authors for studying a large number of subjects including controls using phenotying/ genotyping. However it is felt that there are some limitations: (*a*) details about the number of subjects that were screened individually by different methods is lacking; (*b*) serum levels and "cut off" value taken for defining AAT deficiency are not provided; and (*c*) it is not clear whether all the subjects amongst 1250 liver disease cases had liver biopsy and also immunohistochemistry for AAT deposits. To support their conclusion and to be precise, the authors should have given a detailed break up of individual screening tests and their correlation with genotyping and phenotyping. Although 840 CLD and 410 NC cases were screened but the focus could have been directed towards children with unknown etiology (237 CLD and 126 NC).

This study highlights the difficulties in making a diagnosis of AATD. The measurement of serum/ plasma levels of AAT is the simplest test but it lacks both sensitivity and specificity and should not be used to exclude AATD. The phenotyping (PI type) by isoelectric focussing, though considered as the "gold standard" for diagnosis, is time consuming, requires expertise for interpretation of gels and is best done in a referral laboratory. The phenotyping also cannot identify null alleles and variants which have similar

or slightly different electrophoretic mobility than the normal M alleles as was seen in two cases described by Arora, *et al*.(2). Genotyping provides a definitive diagnosis and helps in identification of new mutations(3).

Snyder, *et al*.(4) suggest that genotyping with commercial assay for common alleles (S and Z) along with determination of serum AAT to identify samples with rare deficiency alleles not recognized by S and Z genotypes is a useful and simple approach to diagnosis of AATD. Phenotyping and direct sequencing may then be done only for samples with discordant results.

Only a small proportion of subjects with AATD ever develop liver disease, this is believed to be determined by genetic modifiers and/or environmental factors. Nearly 85-90% of all affected children present with NC, and the remaining 10-15% present later in childhood with hepatomegaly, failure to thrive, asymptomatic elevation of transaminases or cirrhosis. NCS in AATD can be severe with acholic stools and non- excretory hepatobiliary scan and often confused with biliary atresia. Some infants may also present with serious hemorrhagic complications. According to the landmark study of Sveger, *et al.*(5), nearly 80% of PIZZ infants presenting with NC are free of CLD by 18 years of age. Overall, the risk of progressive liver disease and poor quality of life due to pruritus requiring transplantation in childhood ranges from 3-5%(6).

AATD generally requires supportive management as there is no specific treatment. The diagnosis of AATD in childhood has the dual advantage of predicting the prognosis and counselling. This study highlights rarity of AAT despite best confirmatory tests applied in the study. Since we do see a sizeable proportion of metabolic disorders including AAT there is a need for developing a dedicated central diagnostic facility in India. This would be a cost-effective and highly valuable step in development of pediatric service and research.

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