OC-114

THE LIMITATIONS OF SERUM ALPHA-1 ANTITRYPSIN LEVELS IN PATIENTS WITH CHRONIC LIVER DISEASE AND HETEROZYGOUS ALPHA-1 ANTITRYPSIN DEFICIENCY

doi:10.1136/gut.2011.239301.114

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Introduction Alpha-1 antitrypsin deficiency (a1AT) is an inherited disease which can be fatal. It commonly affects the lung and liver and can present in a homozygous or heterozygous form. There is increasing evidence that a1AT is not a disease confined to the northern hemisphere and its distribution and inheritance is more widespread than expected. On this

pretext we wanted to determine what proportion of patients referred to our tertiary referral centre had liver disease attributable at least in part to α1AT deficiency and in what proportion of those the serum level of α1AT was in the normal range further supporting the argument that heterozygous liver disease is frequently missed by current screening methods.

Methods Patients were chosen from consecutive new adult referrals attending clinic between November 2004 and June 2006 who subsequently underwent diagnostic liver biopsy at Addenbrooke's Hospital in Cambridge. Serum α1AT was measured once following venesection at first clinic attendance by immunonephelometric assay, with a normal range defined as greater than or equal to 0.9 g/l. The α1AT phenotype was assessed by isoelectric focusing whenever α1AT deficiency was suspected, based on serum level and/or compatible liver biopsy findings. In liver biopsy specimens the presence of α1AT in tissue was assessed by staining for diastase resistant PAS positive granules and confirmed where appropriate by immunohistochemistry using a monoclonal antibody to the Z allele.

Results There were 840 new patients in the Hepatology clinic in the study period; a first diagnostic liver biopsy was performed in 325 cases (39%), all of which had a single measure of serum α1AT available in the two months prior to the biopsy. In total 54 patients (16.6%) were found to be heterozygotes. 34 patients in total had a normal a1AT level (0.9–1.2g/dl). 29 of these patients had a1AT deficiency changes as well as confounding pathology on their liver biopsy (2 AIH, 11 ALD, 10 NASH and 6 viral). 5 patients in particular had cirrhosis requiring liver transplantation. All of these patients were previously labelled as having cryptogenic cirrhosis on the basis of a normal a1AT level. There was no history of respiratory disease, family history of α1AT deficiency or family history of a liver disorder in any patients in this group.

Conclusion Standard testing of a1AT deficiency based on serum levels is inaccurate as a1AT can act as an inflammatory marker and phenotyping alone can miss null phenotypes. We advocate a low threshold for full screening including genotyping as heterozygote liver disease is often a confounding factor in liver disease, which in itself is not benign. The full prevalence and behaviour of this condition is underestimated.

Competing interests None.

Keywords alpha-1 antitrypsin deficiency, screening.