JOURNAL OF HEPATOLOGY

An autosomal dominant form of non-cirrhotic portal hypertension

To the Editor:

The familial aggregation idiopathic non-cirrhotic portal hypertension (INCPH) has been previously described, however, there have been no reports of Mendelian inheritance [1–5]. We describe the first case of autosomal dominant inheritance of INCPH in a single family.

Fig. 1 demonstrates the autosomal dominant inheritance pattern, including male-to-male transmission. I.6 suffered a fatal variceal haemorrhage and may have also been affected. In this patient however, secondary causes of portal hypertension could not be excluded given the lack of a comprehensive medical record. INCPH was diagnosed in all cases in accordance with criteria proposed by Schouten [6], excluding II.1 who died prior to liver biopsy being performed. The siblings and children of affected family members have been screened with upper gastrointestinal endoscopies, hepatosplenic ultrasound and full blood examination.

Case 1 – Proband

II.3, a 67-year old male was referred to our centre in 1999, then aged 52, for liver transplantation assessment. He had been diagnosed with apparent cryptogenic cirrhosis at age 44, based on findings of portal hypertension on computed tomography scanning, in addition to splenomegaly, low-grade hepatic encephalopathy (HE) and thrombocytopaenia. He had required prophylactic endoscopic variceal band ligation for oesophageal varices. He had reported that his older sister (II.1) and paternal uncle (I.6) both had died of variceal haemorrhage. His father (I.2) had also died of portal hypertensive complications in his fifth decade, however he had a history of transfusion-related chronic hepatitis B infection.

Over a period of 7 years follow-up the patient developed hepatopulmonary syndrome (HPS), ascites and worsening HE and subsequently underwent orthotopic liver transplantation aged 59. Portopulmonary hypertension was excluded on right-heart catheterisation. INCPH was diagnosed on the explant hepatectomy specimen. The patient remains well seven years post-transplantation, without clinical evidence of recurrent portal hypertension.

Case 2

II.4 was the younger sister of the proband and was referred for liver transplantation assessment at age 53 for progressive HE and HPS. She had been diagnosed with INCPH aged 29, after presenting with recurrent gastro-oesophageal variceal haemorrhage, which was managed with a lienorenal shunt. Intra-operative liver biopsy at the time of her surgical shunt demonstrated changes consistent with INCPH. A repeat liver biopsy at age 53 revealed identical findings. The patient died prior to being waitlisted for liver transplantation due to spontaneous intracranial haemorrhages aged 61.

Case 3

II.1 was the older sister of II.3 who suffered a fatal variceal haemorrhage aged 57. She did not undergo liver biopsy, however serological testing did not have evidence of secondary causes of INCPH. She did not have any risk factors for cirrhosis.

Case 4

III.1 is the nephew of II.3 and is a 54-year old male currently on the waiting list for liver transplantation for severe recurrent HE. He was first diagnosed with INCPH at age 27 following a variceal haemorrhage. He was managed initially with endoscopic sclerotherapy and subsequently variceal band ligation. Liver biopsy at the time excluded cirrhosis. He was stable for many years before developing HE. He has no evidence of HPS.

Case 5

IV.2 is a 29-year old male, who is the son of III.1. He was diagnosed with INCPH aged 22, after an oesophageal variceal haemorrhage. Liver biopsy demonstrated changes consistent with INCPH. He continues to undergo regular endoscopic variceal surveillance and is yet to develop other portal hypertensive complications.

The explant hepatectomy from II.3 (Fig. 2A–F) showed nodules of regenerative hepatocytes surrounded by cords of atrophic

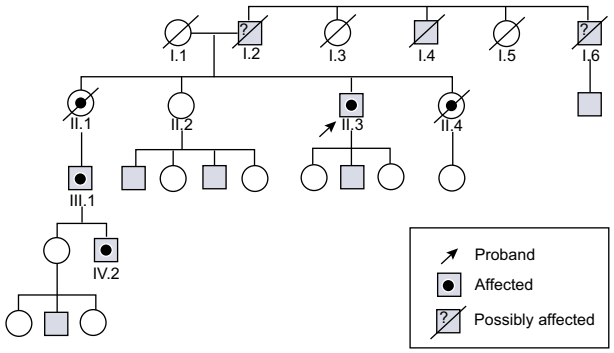

Fig. 1. Autosomal dominant inheritance pattern of affected family members with non-cirrhotic portal hypertension. "Possibly affected" denotes family member with fatal variceal haemorrhage of unclear aetiology due to incomplete medical record.

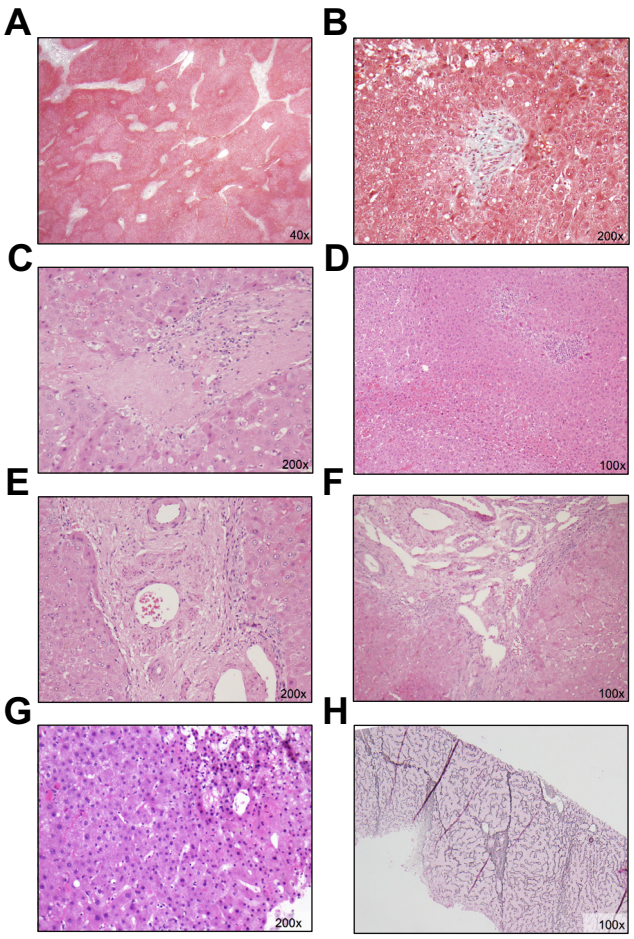

Fig. 2. Liver explant histopathology from II.3 (A–F), core biopsy from II.4 (G) and core biopsy from IV.2 (H). (A) Features of incomplete septal cirrhosis are seen with portal fibrous expansion and occasional delicate septa, but no well-developed nodularity or advanced fibrosis (trichrome stain, 40×). (B) Small portal tract with absent portal vein (trichrome, 200×). (C) Portal tract containing nodular fibrous scar at the site of portal vein branch (H&E, 200×). (D) Periportal hyperplasia and zone 3 atrophy with congestion (H&E, 100×). (E) Arterialised and narrowed portal vein branch (H&E, 200×). (F) Portal tract showing portal vein ectasia / "shunt vessels" (H&E, 100×). (G) Core biopsy from II.4 (aged 51) showing zonal congestion and atrophy with periportal hyperplasia, features suggesting nodular regenerative hyperplasia. There was also subtle architectural distortion, but no fibrosis (H&E, 200×). (H) Core biopsy from IV.2 (aged 22) showing subtle zones of atrophy and compression, with areas of regenerative hyperplasia, and delicate portal/periportal septa (reticulin stain, 100×). There were mildly prominent portal vein branches at the periphery of some portal tracts, and one large tract lacked an appropriately sized portal vein. There was no evidence of established cirrhosis. (This figure appears in colour on the web.)

hepatocytes (nodular regenerative hyperplasia), with congestion. The portal tracts were fibrotic with scarred, obliterated or arterialised portal veins, and slender portal-to-portal or incomplete peri-portal fibrous septa (incomplete septal cirrhosis). Inflammation was negligible. Biliary changes and cholate stasis were attributed to portal hypertensive biliopathy. Remote organised large portal vein thrombosis was favoured to be a secondary complication contributing to progressive liver disease and the need for transplantation. There were no other features to suggest an alternative cause (e.g. steatosis). Taken in the clinical context, these findings were consistent with a diagnosis of INCPH [7].

Review of extant core biopsy material from IV.2 and II.4 suggested a similar pattern of changes (Fig. 2G and H). Reports of core biopsies from III.1 and II.4 describe findings in keeping with same process.

To our knowledge, this is the first report of autosomal dominant INCPH. The phenotype of autosomal dominant INCPH appears to have more severe portal hypertensive complications, which are characterised by variceal haemorrhage, HE and HPS, compared to previous series of INCPH [1,5,8–10]. The implication of Mendelian inheritance of INCPH in this family is that there may potentially be a single gene or small group of genes responsible for the development of the disorder. Further studies are necessary to investigate the genetic origins of this condition, which may eventually lead to the identification of therapeutic targets for INCPH.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Author contributions

Avik Majumdar – acquisition of data, review and drafting of manuscript
Martin Delatycki – acquisition of data, review and drafting of manuscript
Peter Crowley – acquisition of data, review and drafting of manuscript
Julie Lokan – acquisition of data, review and drafting of manuscript
Benjamin Tharian – acquisition of data, review and drafting of manuscript
Peter Angus – acquisition of data, review and drafting of manuscript
Paul Gow – study concept, review of manuscript, study supervision

References

[1] Khanna R, Sarin SK. Non-cirrhotic portal hypertension – Diagnosis and management. J Hepatol 2014;60:421–441.
[2] Sarin SK, Mehra NK, Agarwal A, Malhotra V, Anand BS, Taneja V. Familial aggregation in noncirrhotic portal fibrosis: a report of four families. Am J Gastroenterol 1987;82:1130–1133.
[3] Barnett JL, Moseley RH, Appelman HD. Familial septal cirrhosis. Gastroenterology 1992;102:674–678.
[4] Dumortier J, Boillot O, Chevalier M, Berger F, Potier P, Valette P-J, et al. Familial occurrence of nodular regenerative hyperplasia of the liver: a report on three families. Gut 1999;45:289–294.
[5] Albuquerque A, Cardoso H, Lopes J, Cipriano A, Carneiro F, Macedo G. Familial occurrence of nodular regenerative hyperplasia of the liver. Am J Gastroenterol 2013;108:150–151.
[6] Schouten JNL, Garcia-Pagan J, Valla DC, Janssen HLA. Idiopathic noncirrhotic portal hypertension. Hepatology 2011;54:1071–1081.
[7] Hübscher S. Pathology of non-cirrhotic portal hypertension and incomplete septal cirrhosis. Mini-symposium: Liver pathology. Diagn Histopathol (Oxf) 2011;17:530–538.
[8] Hillaire S, Bonte E, Denninger M-H, Casadevall N, Cadranel J-F, Lebrec D, et al. Idiopathic non-cirrhotic portal hypertension in the West: a re-evaluation in 28 patients. Gut 2002;51:275–280.

[9] Krasinskas AM, Eghtesad B, Kamath PS, Demetris AJ, Abraham SC. Liver transplantation for severe intrahepatic noncirrhotic portal hypertension. Liver Transpl 2005;11:627–634.
[10] Schouten JNL, Nevens F, Hansen B, Laleman W, van den Born M, Komuta M. Idiopathic noncirrhotic portal hypertension is associated with poor survival: results of a long-term cohort study. Aliment Pharmacol Ther 2012;35:1424–1433.

Avik Majumdar[1,*]
Martin B. Delatycki[3,4]
Peter Crowley[5]
Julie Lokan[6]
Benjamin Tharian[7]
Peter W. Angus[1,2]
Paul Gow[1,2]
[1]*Gastroenterology and Liver Transplant Unit, Austin Hospital, Melbourne, Victoria, Australia*
[2]*University of Melbourne, Victoria, Australia*
[3]*Department of Clinical Genetics, Austin Hospital, Melbourne, Victoria, Australia*
[4]*Bruce Lefroy Centre, Murdoch Childrens Research Institute, Victoria, Australia*
[5]*Anatomical Pathology, Dorevitch Pathology, Melbourne, Victoria, Australia*
[6]*Anatomical Pathology, Austin Hospital, Melbourne, Victoria, Australia*
[7]*Department of Medicine, Mersey Community Hospital, La Trobe, Tasmania, Australia*
*Corresponding author. Address: Gastroenterology and Liver Transplant Unit, Austin Hospital, 145 Studley Road, Heidelberg, VIC 3084, Australia.
Tel.: +61 3 9496 5353.
E-mail address: avikmajumdar@me.com

Low ascitic fluid protein does not indicate an increased risk for spontaneous bacterial peritonitis in current cohorts

To the Editor:

We read with interest the results of a large multicenter trial on risk factors for spontaneous bacterial peritonitis (SBP) by Terg *et al.* in the *Journal of Hepatology* [1]. In their analysis including 95 patients with SBP, neither proton pump inhibitor use nor the concentration of ascitic fluid (AF) protein could be confirmed as a risk factor for SBP.

Low AF protein has been reported to predispose to SBP in decompensated cirrhosis according to several studies [2–5] dating from 1986 to 1993. This association was attributed to a lack of opsonic factors, since AF protein correlates with peritoneal immunoglobulin concentration and complement activity [6,7]. During hospitalization, patients with AF protein $\leqslant$10 g/L developed SBP ten times more often than patients with higher AF protein concentrations in an analysis including 17 patients with SBP [2]. Two prospective studies comprising 127 patients (13 with SBP) [4] and 110 patients (28 with SBP) [5] confirmed low AF protein concentration as an independent predictor of SBP. In addition, AF protein $\leqslant$10 g/L was shown to predict the recurrence of SBP [3]. Thus, current guidelines recommend the measurement of AF protein to identify patients at high risk for SBP [8].

Given the discrepancies of available data, we here report the results of a *post-hoc* analysis from two prospectively collected registries of patients with cirrhosis and ascites undergoing paracentesis in two German tertiary centers comprising 683 patients, of whom 220 had SBP. Among 347 patients receiving paracentesis with AF protein measurement between 12/2007 and 07/2014 in the Jena University Hospital, 13 patients presented with a documented history of SBP more than 30 days before inclusion and 81 patients presented with SBP at baseline or during follow-up. In the Bonn University Hospital, 336 patients with liver cirrhosis received baseline paracentesis with AF protein measurement between 05/2006 and 09/2013. Of these patients, 51 had a history of SBP while 75 developed SBP at baseline paracentesis or during follow-up. In both cohorts, AF protein concentrations were similar for patients who never had SBP and patients who developed SBP (Table 1). When patients were stratified according to a cut-off of less than 10 g/L or less than 15 g/L AF total protein, frequencies were comparable between the SBP and non-SBP group.

In line with previous findings that AF protein does not change during and after SBP [9], restricting the analysis to patients without a history of SBP did not alter the results. AF protein in patients with SBP at baseline (Jena: 15 g/L, interquartiles: 9–20, $p = 0.33$; Bonn: 11 g/L, 8–20, $p = 0.86$) and AF protein in patients with a first episode of SBP during follow-up (Jena: 12 g/L, 8–20, $p = 0.93$; Bonn: 12 g/L, 7–23, $p = 0.54$) did not differ from patients who never had SBP (Jena: 12 g/L, 8–20; Bonn: 11 g/L, 7–18).

We can only speculate about the causes that underlie the failure to replicate the association between SBP and AF protein, which has been reported in several studies more than 20 years ago. Based on the data of the first report on low AF protein as a risk factor for SBP [2], the power to detect a significant difference between the groups exceeded 80% for each of our cohorts by far. It is probable that changed epidemiology and/or different treatments for cirrhosis play a major part. We can exclude the widespread use of antibiotic prophylaxis, since Terg *et al.* [1] did not include patients receiving antibiotic prophylaxis, only 2.3% of the patients in the Jena cohort and 1.5% of the patients in the Bonn cohort received long-term primary prophylaxis with quinolones or cotrimoxazol. Changes in diuretic therapy may also account for the discrepancies. Diuretics have been shown to improve AF opsonic activity to a greater degree than the protein concentration [10], which may reduce the correlation of AF protein with opsonic activity and therefore diminish its role as a