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BMP9/10 in Pulmonary Vascular Complications of Liver Disease

To the Editor:

Advanced liver disease can cause two distinct pulmonary vascular complications. Portopulmonary hypertension (POPH) is characterized by increased pulmonary vascular resistance and pulmonary artery pressure in the absence of other etiologies of pulmonary hypertension (PH). Hepatopulmonary syndrome (HPS) is characterized by intrapulmonary vascular dilatations and arteriovenous malformations (AVMs) and an increased alveolar–arterial oxygen gradient (A–a gradient). These diseases occur in approximately 6% and 20% to 30% of patients evaluated for liver transplantation, respectively (1, 2).

The biologic determinants of these vascular complications are poorly understood. BMP9 (bone morphogenetic protein 9) and BMP10 are produced in the liver (and for BMP10, right atrium) and circulate either as homodimers or heterodimers (3, 4). BMP9 and BMP10 are ligands for BMP receptor type II, activin A receptor like type 1, and endoglin receptor complex (5). Receptor mutations cause hereditary hemorrhagic telangiectasia, a disease characterized by angiogenesis and pulmonary macrovascular and microvascular AVMs. The occurrence of pulmonary AVMs and cyanosis after the Glenn operation, where hepatic venous blood does not bathe the lungs normally, has been blamed on "hepatic factor," hypothesized to be BMP9 (6). In addition, studies show that abnormal BMP9 signaling causes PH (7, 8). Circulating BMP9 levels are decreased in patients with POPH, and administration of BMP9 attenuates PH (9). We hypothesized that circulating BMP9 and BMP10 levels would be lower in patients with POPH and HPS when compared with control patients with advanced liver disease.

Methods

The PVCLD2 (Pulmonary Vascular Complications of Liver Disease 2) study was a multicenter, prospective cohort study of adult patients with portal hypertension undergoing evaluation for liver transplantation or with POPH (10, 11). Patients with active infection, recent gastrointestinal bleeding, or a history of prior liver or lung transplantation were excluded. The study sample was drawn from 454 patients at the University of Pennsylvania, Mayo Clinic, University of Texas–Houston, University of Texas–Southwestern, University of Colorado, Vanderbilt University, Tufts Medical Center, and Cleveland Clinic between 2013 and 2017. The institutional review boards approved this study, and patients gave informed consent.

Research assessments included a history and physical examination, anthropometrics, pulse oximetry, phlebotomy and clinical laboratory testing, 6-minute-walk testing, arterial blood gas sampling, spirometry, and contrast-enhanced transthoracic echocardiogram (TTE). Cases with POPH had mean pulmonary artery pressure > 25 mm Hg, pulmonary artery wedge pressure ≤ 15 mm Hg, and pulmonary vascular resistance > 240 dyn · s/cm^5. Control subjects with liver disease had right ventricular systolic pressure < 40 mm Hg (if estimable) and absence of right ventricular dysfunction on TTE. We excluded patients with significant obstructive or restrictive ventilatory defects, HIV infection, or more than moderate aortic or mitral valvular disease or significant left ventricular systolic dysfunction.

HPS was defined by A–a gradient ≥ 15 mm Hg (or ≥ 20 mm Hg if age > 64 yr) and late passage of contrast on TTE. Control patients did not meet both the A–a gradient and late contrast criteria. We excluded patients with a significant obstructive or restrictive ventilatory defect or intracardiac shunting.

Plasma BMP9 and BMP10 concentrations were measured in duplicate with sandwich ELISA kits with plasma diluted in phosphate-buffered saline/1% bovine serum albumin/0.2% goat serum and 0.5% Triton X-100 (BMP9, diluted 1:4) or 0.1% Triton X-100 (BMP10, both neat and diluted 1:2) (DY3209 and DY2926, respectively; R&D Systems). Assays were performed with blinding to clinical information.

Rank sum tests, *t* tests, chi-square tests, and Fisher's exact tests were used. Multivariate linear regression models regressed natural log–transformed BMP levels on case and control status after adjustment for age, sex, and Model for End-Stage Liver Disease-Na (MELD-Na). A P value < 0.05 was considered significant (STATA/MP 16.0).

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Table 1. Patient Demographics, Comorbidities, and Liver Disease Characteristics

Characteristic	HPS (*n* = 80)	HPS Control Subjects (*n* = 121)	*P* Value	POPH (*n* = 35)	POPH Control Subjects (*n* = 186)	*P* Value
Age, yr	55.3 ± 9.6	57.3 ± 9.0	0.13	56.7 ± 8.5	56.6 ± 9.4	0.93
Sex, M	48 (60)	87 (72)	0.08	21 (60)	129 (69)	0.28
Body mass index, kg/m^2	31.7 ± 7.3	30.2 ± 7.1	0.17	29.9 ± 6.3	30.7 ± 7.2	0.52
Race/ethnicity			0.008			0.55
Non-Hispanic white	66 (83)	74 (62)		27 (77)	128 (69)	
Black	2 (3)	14 (12)		3 (9)	16 (9)	
Asian	0	2 (2)		0	2 (1)	
Hispanic white	11 (14)	29 (24)		4 (11)	37 (20)	
Hispanic other	1 (1)	1 (1)		0	2 (1)	
Other	0	1 (1)		1 (3)	1 (1)	
Liver disease*						
Hepatitis C	33 (41)	54 (45)	0.64	10 (29)	80 (43)	0.11
Alcohol	30 (38)	39 (32)	0.44	16 (46)	62 (33)	0.16
Nonalcoholic fatty liver disease	20 (25)	26 (21)	0.52	5 (14)	43 (23)	0.25
Autoimmune hepatitis	4 (5)	5 (4)	0.74	3 (9)	8 (4)	0.39
Primary biliary cholangitis	9 (11)	5 (4)	0.09	6 (17)	11 (5.9)	0.03
Primary sclerosing cholangitis	4 (5)	7 (6)	1.0	0	11 (6)	0.22
Hepatitis B	1 (1)	4 (3)	0.65	0	5 (3)	1.0
Cryptogenic cirrhosis	3 (4)	11 (9)	0.17	4 (11)	14 (8)	0.50
MELD-Na score	15.7 ± 4.7 (*n* = 78)	13.8 ± 5.5 (*n* = 119)	0.01	15.8 ± 6.7 (*n* = 25)	14.4 ± 5.2 (*n* = 182)	0.24
Alveolar–arterial oxygen gradient, mm Hg	29.5 ± 13.3	14 ± 9	<0.001	—	—	
Partial pressure of arterial oxygen, mm Hg	78.9 ± 12.2	92 ± 13	<0.001	—	—	
Hemodynamics						
Right atrial pressure, mm Hg	—	—	—	9.2 ± 5.0	—	—
Mean pulmonary artery pressure, mm Hg	—	—	—	46.2 ± 11.3	—	—
Pulmonary artery wedge pressure, mm Hg	—	—	—	10.4 ± 3.5	—	—
Cardiac index, L/min/m^2	—	—	—	2.9 ± 0.8	—	—
Pulmonary vascular resistance, Wood units	—	—	—	7.0 ± 3.8	—	—
6-minute-walk distance, m	387.9 ± 97.6 (*n* = 69)	429 ± 93.0 (*n* = 102)	0.006	367.5 ± 114.1 (*n* = 34)	417 ± 94.1 (*n* = 158)	0.007

Definition of abbreviations: HPS = hepatopulmonary syndrome; MELD = Model for End-Stage Liver Disease; POPH = portopulmonary hypertension.
Data expressed as mean ± SD or *n* (%).
*Patients may have had more than one liver disease etiology.

Results

There were 35 patients with POPH and 186 POPH control subjects and 80 patients with HPS and 121 HPS control subjects (Table 1). One patient had both POPH and HPS.

Patients with POPH had significantly lower BMP9 levels compared with control patients with advanced liver disease (Figure 1). This difference persisted despite adjustment for age, sex, and MELD-Na score (43% lower BMP9 levels in POPH) ($P = 0.006$; $n = 205$). BMP9 levels were not associated with baseline hemodynamics, functional class, or 6-minute-walk in POPH (data not shown). There was no difference in BMP10 levels between POPH cases and control subjects.

Patients with HPS also had significantly lower BMP9 levels compared with control patients with advanced liver disease (Figure 1). After adjustment for age, sex, and MELD-Na, BMP9 was 37% lower in HPS compared with control subjects ($P = 0.001$; $n = 197$). BMP10 was also significantly lower in patients with HPS (Figure 1) and was 33% lower even after adjustment for age, sex, and MELD-Na ($P = 0.02$; $n = 196$).

In patients with HPS, 10% lower BMP9 levels were associated with higher A–a gradient (0.4 mm Hg) even after adjustment for age, sex, body mass index, and MELD-Na ($P = 0.03$; $n = 78$). Lower BMP9 levels were also associated with higher World Health Organization functional class in HPS after adjustment for covariates ($P = 0.002$; $n = 78$).

Discussion

Portal hypertension and cirrhosis are systemic conditions of disordered angiogenesis, which also characterizes both HPS and POPH. We have shown that patients with HPS or POPH have decreased circulating BMP9 and (for HPS) decreased circulating BMP10 levels compared with cirrhotic control subjects. Modifying factors likely determine which phenotype is expressed when BMP signaling is reduced.

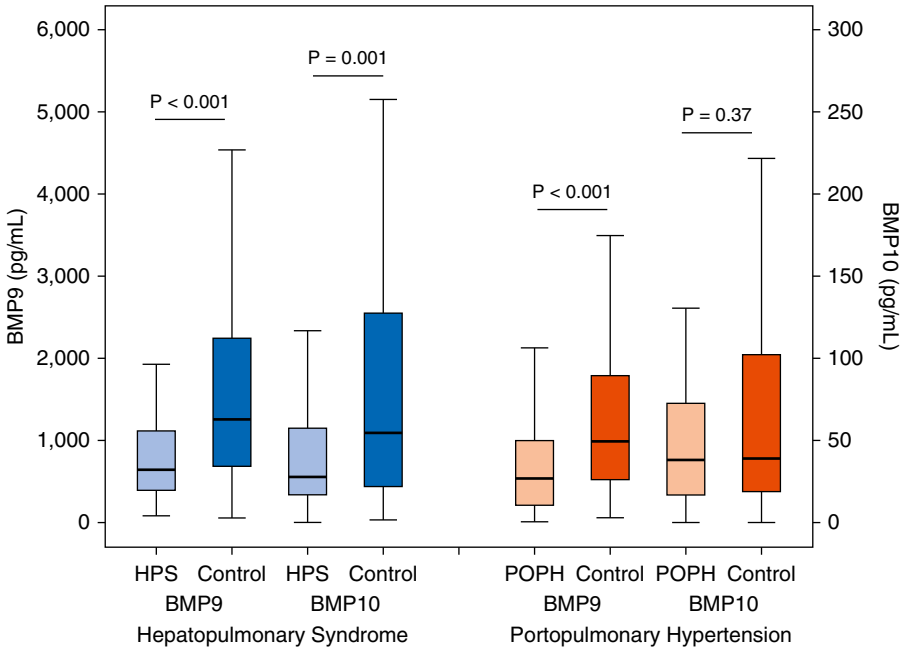

Figure 1. BMP9 (bone morphogenetic protein 9) and BMP10 levels for hepatopulmonary syndrome (HPS) ($n = 80$), cirrhotic control subjects ($n = 121$), portopulmonary hypertension (POPH) ($n = 35$), and cirrhotic control subjects ($n = 186$). Lines represent medians, boxes represent interquartile ranges, and whiskers show adjacent values.

BMP9 and BMP10 maintain vascular quiescence (5). Mutations in this pathway result in hereditary hemorrhagic telangiectasia, characterized by telangiectasias in the skin, nose, and gastrointestinal tract and pulmonary and hepatic microvascular dilations, AVMs, and/or PH. Researchers have hypothesized that BMP9 could be the "hepatic factor" (6), causing pulmonary AVMs after the Glenn procedure, which alters the perfusion of the lungs by liver effluent (12). Redirection of hepatic vein effluent into the pulmonary arterial bed resolves pulmonary AVMs.

Circulating BMP9 levels were decreased in patients with POPH or HPS when compared with other liver transplant candidates, and lower BMP9 levels were associated with more severe HPS. BMP10 was also lower in HPS. Further studies should examine the mechanistic roles of these BMPs in complications of cirrhosis and other diseases characterized by pulmonary AVMs. ■

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High-Dose First-Line Treatment Regimen for Recurrent Rifampicin-Susceptible Tuberculosis

To the Editor:

We read with interest the article by Dooley and colleagues, which showed that high-dose isoniazid (10–15 mg/kg) had early bactericidal activity for *Mycobacterium tuberculosis* (MTB) strains with *inhA* mutations similar to that observed with normal-dose isoniazid (5 mg/kg) for susceptible strains (1). The authors concluded that high-dose isoniazid represents a useful addition to second-line tuberculosis (TB) treatment regimens for patients with rifampicin-resistant TB and isolated *inhA* mutations.

We believe that high-dose isoniazid may also play an important role in first-line TB treatment. At present, the World Health Organization recommends adding a second-line TB drug (levofloxacin) to three first-line drugs (rifampicin, ethambutol, and pyrazinamide) in patients with TB resistant to isoniazid without concurrent rifampicin resistance. Isoniazid would not be included in this levofloxacin-strengthened first-line regimen (2). This recommendation has several major implications.

To implement this recommendation, rifampicin and isoniazid susceptibility testing should be performed, particularly in previously treated patients, who are at risk of initial resistance. Before prescribing levofloxacin for patients with rifampicin-susceptible/isoniazid-resistant TB, additional fluoroquinolone susceptibility testing is recommended (2). Access to rifampicin susceptibility testing has increased substantially, but access to isoniazid and fluoroquinolone susceptibility testing is still poor in most high-TB-burden countries, where samples still have to be transported to referral laboratories. Although novel diagnostic tools, such as Xpert MTB/XDR, are on the horizon, their widespread implementation will still take years. This will cause treatment delays of several months and result in losses to follow-up between the time of TB diagnosis and treatment initiation. In addition, not all rifampicin resistance is detected by frequently used rapid tests, such as Xpert MTB/RIF and

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