Hepatopulmonary Syndrome Is a Frequent Cause of Dyspnea in the Short Telomere Disorders

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BACKGROUND: Telomere syndromes have their most common manifestation in idiopathic pulmonary fibrosis and emphysema. The short telomere defect in these patients may manifest systemically as bone marrow failure and liver disease. We sought to understand the causes of dyspnea in telomerase and telomere gene mutation carriers who have no parenchymal lung disease.

METHODS: Clinical and pathologic data were reviewed as part of a Johns Hopkins-based natural history study of short telomere syndromes including dyskeratosis congenita.

RESULTS: Hepatopulmonary syndrome (HPS) was diagnosed in nine of 42 cases (21%). Their age at presentation was significantly younger than that of cases initially presenting with pulmonary fibrosis and emphysema (median, 25 years vs 55 years; $P < .001$). Cases had evidence of intra- and extrapulmonary arteriovascular malformations that caused shunt physiology. Nodular regenerative hyperplasia was the most frequent histopathologic abnormality, and it was seen in the absence of cirrhosis. Dyspnea and portal hypertension were progressive, and the median time to death or liver transplantation was 6 years (range, 4–10 years; $n = 6$). In cases that underwent liver transplantation, dyspnea and hypoxia improved, but pulmonary fibrosis subsequently developed.

CONCLUSIONS: This report identifies HPS as a frequent cause of dyspnea in telomerase and telomere gene mutation carriers. While it usually precedes the development of parenchymal lung disease, HPS may also co-occur with pulmonary fibrosis and emphysema. Recognizing this genetic diagnosis is critical for management, especially in the lung and liver transplantation setting.

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ABBREVIATIONS: HPS = hepatopulmonary syndrome; IPF = idiopathic pulmonary fibrosis

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The short telomere syndromes are a group of Mendelian disorders that are caused by abnormalities in telomere length.¹ Telomeres function to protect chromosome ends from degradation; they are made up of tandem DNA repeats that are bound by specialized shelterin proteins.¹ Telomeres shorten with age and short telomeres predict an earlier onset of replicative senescence.² Because patients with telomere syndrome have abnormally short telomeres, these patients are thought to have a form of premature aging.¹ Three degenerative complications account for the majority of morbidity and mortality in patients with short telomere syndromes. Parenchymal lung disease is the most common; it manifests in adults as idiopathic pulmonary fibrosis (IPF) and emphysema. IPF is the first presentation in adults with moderate telomere shortening, and mutations in six telomerase and telomere genes account for one-third of familial pulmonary fibrosis cases.³⁻⁸ In smokers, emphysema, alone or combined with fibrosis, may be a first manifestation and the frequency of mutations in telomerase rivals α_1 -antitrypsin deficiency as a risk factor for

severe emphysema.⁹ Some patients may show other premature aging features, including early hair graying and osteoporosis.¹ Along with lung disease, bone marrow failure and liver disease are common causes of mortality in the short telomere syndromes.¹ The age at first presentation of these complications depends on the extent of telomere shortening.¹ Bone marrow failure is usually the first presentation in children who have very short telomeres.¹⁰ In rare cases, telomere syndromes manifest in dyskeratosis congenita, a disorder defined by abnormalities in the skin, nails, and the mucosa.^{1,11,12} Liver disease is estimated to complicate 10% of telomere syndrome cases^{11,13}; however, its natural history and pathophysiology are not fully understood.

Here, we report a stereotypic presentation of liver disease in patients with telomere syndrome that manifests as progressive dyspnea and is caused by hepatopulmonary syndrome (HPS). Its recognition is critical for diagnostic decisions and has direct implications for patient care.

Materials and Methods

Cases were evaluated from July 1, 2005, to September 1, 2014, as part of the Johns Hopkins Telomere Syndrome Registry.¹⁴ Subjects were included in this study if they had a confirmed pathogenic mutation in a telomere gene or had features of a telomere syndrome and abnormally short telomeres, as previously defined.¹⁵ At the time of analysis, 150 subjects were enrolled for diagnoses of bone marrow failure, interstitial lung disease, emphysema, liver disease, and enterocolitis, and one-half of the cases were asymptomatic mutation carriers. Telomere

length was measured on peripheral blood mononuclear cells using flow cytometry and fluorescence in situ hybridization.¹⁶ Genetic studies were performed as previously described.^{6,7} Subjects gave written informed consent, and the study was approved by the Johns Hopkins Medicine Institutional Review Board (approval no. NA_33072). The primary medical records were independently reviewed by three of the authors (A. I. G., N. L. J., M. A.). Radiographic and pathology studies were centrally reviewed at Johns Hopkins Hospital (R. A. A. and I. R. K., respectively). The criteria for HPS were as defined by Krowka.¹⁷

Results

By September 1, 2014, the Johns Hopkins Telomere Syndrome Registry had enrolled a total of 150 subjects. Among them, 42 subjects had progressive dyspnea alone as an initial presentation. Thirty-three cases (79%) had pulmonary fibrosis or combined fibrosis and emphysema, and they presented at a median age of 55 years (range, 40-77 years). In nine cases (21%), there was no parenchymal lung disease on chest CT scan ($n = 7$) or minimal fibrosis that did not explain the hypoxic defect ($n = 2$). These cases fulfilled the criteria for HPS.¹⁷ In contrast to the cases with pulmonary fibrosis and emphysema, the HPS cohort was significantly younger, with a median age of 25 years (range, 8-49 years; Mann-Whitney test $P < .001$).

The clinical, genetic, and molecular evidence supported all nine cases having a primary telomere syndrome (Figs 1, 2, Table 1). Six cases (67%) had evidence of

bone marrow failure. Premature hair graying, prior to age 20 years, was documented for six cases. Three cases had mucocutaneous features of classic dyskeratosis congenita, including skin hyperpigmentation and nail dystrophy, and all of them presented prior to age 20 years. The family history was positive for pulmonary fibrosis, aplastic anemia, or dyskeratosis congenita (six of nine cases, 67%). Telomere length was abnormally short in all the affected patients ($n = 6$) and, in cases where the telomere syndrome was recognized postmortem, in their affected first-degree relatives ($n = 3$) (Fig 1A). Six of the nine cases (67%) carried a mutant telomerase or telomere gene (*TERT*, $n = 4$; *DKC1*, $n = 1$; *RTEL1*, $n = 1$) (Table 1), and some of these mutations had been previously associated with short telomere syndromes.^{10,18,19}

The clinical and radiographic studies supported the diagnosis of HPS, as previously defined¹⁷ (Table 1). There

Figure 1 – Clinical, radiographic, and pathologic findings of patients with telomere syndrome with noncirrhotic portal hypertension. A, Lymphocyte telomere length by flow cytometry and fluorescence in situ hybridization in index cases ($n = 6$) or their first-degree relatives when the index case was identified postmortem ($n = 3$). The telomere length is shown relative to age-adjusted percentiles of 192 healthy control subjects. B, C, Images of digital clubbing typically seen. (The patients provided written consent for the use of these photographs.) D, High-resolution chest CT image showing minimal subpleural fibrotic changes in a patient at the time of liver transplantation. E, Postcontrast chest CT scan showing mildly dilated pulmonary vessels (arrows) with high-caliber pulmonary vasculature seen into the periphery of the lung, especially in the lower lobes. F, Transthoracic contrast-enhanced echocardiography image shows microbubbles injected into a peripheral vein accumulating in the RA and RV. Between cardiac cycles 3 and 6, microbubbles appear in the LA and LV, consistent with an intrapulmonary shunt. G, H, CT scan images of the liver in the portal venous phase showing caudate lobe hypertrophy, splenomegaly, and dilated main and left portal veins (arrows). I, Magnetic resonance arteriogram of the liver obtained in the venous phase revealed an enlarged portal vein (single arrow) and splenomegaly. In addition, there is evidence of arteriovascular malformations along the liver edge (three short arrows) and a prominent splenic vein (three long arrows). D-I, Paired images (D, G; E, H; F, I) from three patients. J, Hematoxylin-and-eosin-stained micrograph of a needle biopsy specimen demonstrates regions of hepatocellular hyperplasia (*) with compression of intervening hepatocytes at the edges (†) (original magnification $\times 10$). K, The compressed, atrophic hepatocytes are most pronounced on the reticulin stain (†) (original magnification $\times 4$). L, Prussian blue stain in the same region shows periportal iron deposition in the hepatocytes (original magnification $\times 10$). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Figure 2 – Natural history of telomere-mediated noncirrhotic portal hypertension. A–C, Sequential abdominal CT scan images show progressive signs of portal hypertension and right-lobe atrophy that progressed with the clinical course. The age at the time of imaging is shown in the left upper corner. Images are from case 6 (Table 1) and are representative. A, In early stages, splenomegaly and caudate lobe hypertrophy (arterial phase) are seen. B, Subsequently, the liver edge becomes more nodular and the right lobe appears atrophic. C, In decompensated portal hypertension, there is severe liver nodularity, worsening caudate lobe hypertrophy, and ascites. D, Schema summarizes the natural clinical, radiographic, and hallmarks of progression of telomere-mediated noncirrhotic portal hypertension. E, Schema showing typical age of onset and natural history of bone marrow failure, liver disease, and pulmonary fibrosis and emphysema in the telomere syndromes.

TABLE 1] Characteristics of Patients With Short Telomere Syndromes

Age at Diagnosis, y	Follow-up	M/F	Genetic Diagnosis	Clinical Features	Lung Parenchyma Status	Dlco, % predicted	Vascular Abnormality	Evidence for Liver Disease	Hematologic Data/Bone Marrow Cellularity	Case No.
8	d.17	M	<i>DKC1</i> IVS1+592 C>G	Cyanosis, clubbing	Normal	...	Pulmonary A-V fistulas ^a ; telangiectasia: skin, liver, bladder	Splenomegaly, ascites	Normocellular	1
13	d.18	M	<i>TERT</i> Val170Met	Cyanosis, clubbing, ↑A-a gradient	Normal	76	Dilated pulmonary vasculature; telangiectasia: skin	↑AST, ↑ALT, splenomegaly	Aplastic ^b	2
17	21	F	Classic DC autosomal dominant ^c	Clubbing, ↑A-a gradient	Normal	63	Dilated pulmonary vasculature	↑AST, ↑ALT, splenomegaly	Aplastic	3
24	26	M	<i>TERT</i> Gly135Glu ^c	Cyanosis, clubbing	Normal	68	Dilated pulmonary vasculature with shunt ^d ; visceral A-V malformations	↑AST, ↑ALT, splenomegaly	Hypocellular	4
25	25	M	<i>TERT</i> His983Tyr ^c	Clubbing	Normal	60	Dilated pulmonary vasculature	Splenomegaly	Hypocellular	5
34	d.40	M	Classic DC X-linked	Clubbing, ↑A-a gradient	Normal	40	Pulmonary A-V fistulas with shunt ^d ; telangiectasia: skin	↑AST, ↑ALT, splenomegaly, variceal bleed	Hypocellular	6
35	t.40, 47	M	<i>TERT</i> Lys1050Asn ^c	Clubbing, ↑A-a gradient	Normal	31	Dilated pulmonary vasculature with shunt ^d ; shunt resolved after liver transplantation	↑AST, ↑ALT, splenomegaly	Normal complete blood counts	7
44	d.54	F	Classic DC autosomal dominant ^c	Clubbing, ↑A-a gradient	Mild fibrosis	30	Dilated pulmonary vasculature with shunt ^d ; gastric A-V ectasia; telangiectasia: skin	↑AST, ↑ALT, intractable ascites	Hypocellular	8
49	t.53, 54	M	<i>RTEL1</i> Arg1010× ^c	Clubbing, ↑A-a gradient	Mild fibrosis	46	Dilated pulmonary vasculature with shunt ^{d,e} ; shunt resolved after liver transplantation	↑AST, ↑ALT, splenomegaly, intractable ascites	Normocellular	9

A-a gradient = alveolar-arterial oxygen gradient; ALT = alanine aminotransferase; AST = aspartate aminotransferase; A-V = arterio-venous; d = age at death; DC = dyskeratosis congenita; Dlco = diffusion capacity of lung for carbon monoxide; F = female; M = male; t = age at liver transplant.

^aDiagnosed by pulmonary angiogram.

^bPresentation was 4 y after bone marrow transplantation.

^cTelomere length shown in Figure 1A.

^dPositive bubble echocardiograph.

^ePositive albumin scan.

was evidence of cyanosis as well as digital clubbing (Figs 1B, 1C), and moderate splenomegaly was palpable on examination (eight of nine cases; 88%). Pulmonary function was intact by spirometry, but carbon monoxide diffusion capacity was decreased (seven of eight cases; 88%), and this was, at times, misattributed to an interstitial lung process, even though there was no evidence of parenchymal lung disease by high-resolution CT imaging or at autopsy (seven of nine cases; 78%). In the two cases that had some fibrotic changes (Fig 1D, Table 1), the interstitial abnormalities were insufficient to explain the degree of hypoxia and diffusion capacity impairment. Instead, contrast-enhanced CT imaging showed prominent pulmonary vascular dilatation and arteriovenous fistulas; these were confirmed by pulmonary angiography and at autopsy (nine of nine cases; 100%) (Fig 1E, Table 1). The vascular abnormalities were physiologically relevant, as intrapulmonary shunting was documented by agitated saline echocardiography, albumin scans, and pulmonary angiography in the evaluated cases within this cohort (six of six, 100%) (Figs 1F, 1G, Table 1).

To better define the liver pathology, we reviewed the liver function studies and found transaminase levels either normal or only mildly elevated (less than two times normal) in seven of nine cases (78%), and the model for end-stage liver disease score was normal at the time of diagnosis. There was, nevertheless, evidence of portal hypertension radiographically, with dilated portal veins and splenomegaly (eight of eight cases; 88%) (Figs 1G-I). Intrahepatic arterio-venous malformations were also visible on the liver surface (Fig 1I), as well as within the liver parenchyma (Table 1). Serial imaging during the clinical course showed a progressively altered liver contour, which became increasingly nodular (Figs 2A-C). The progression of the hypoxic defect was accompanied by worsening atrophy of the right lobe and compensatory hypertrophy of the caudate lobe (Fig 2B). In late stages, decompensated portal hypertension developed and manifested in intractable ascites (Fig 2C).

To define the mechanisms underlying the progressive HPS and portal hypertension, we reviewed liver explants and biopsy specimens ($n = 6$). None of the cases had bridging fibrosis, and hepatocyte morphology was noted to be normal even in explants from advanced portal hypertension cases that underwent transplantation (Table 2). Instead, the most common abnormality was nodular regenerative hyperplasia (four of six cases; 67%) (Figs 1J, 1K, Table 2). Perivascular and intrahepatocyte

iron deposits were also noted and iron deposits were seen in cases with no prior history of RBC transfusions (Fig 1L). The paucity of hepatocyte abnormalities and absence of fibrosis supported the diagnosis of noncirrhotic portal hypertension. The co-occurrence of nodular regenerative hyperplasia with blood vessel dysmorphology suggested that vascular/endothelial insufficiency may underlie the telomere-mediated pathology.

The natural history of telomere-mediated HPS-noncirrhotic portal hypertension was progressive, and patients eventually succumbed to complications of severe hypoxia and portal hypertension. The median time to death or liver transplantation was 6 years from the onset of dyspnea symptoms (range, 4-10 years; $n = 6$) (Table 1). In the two patients who underwent liver transplantation, the hypoxia and dyspnea resolved within 3 months, but both patients subsequently developed symptomatic IPF. The patient who had subtle pulmonary fibrosis pretransplant had worsening disease within 18 months and again become oxygen dependent, while the patient who had no lung disease at the time of transplant developed IPF 12 years later.

Discussion

We report here a stereotypic pattern of liver disease in patients with short telomere syndromes that causes hypoxia because of intrapulmonary vascular shunting (Figs 2A-D). Its recognition is important for clinical management, as these individuals present with symptoms that mimic or co-occur with pulmonary fibrosis. Because of the paucity of liver function abnormalities, these patients are often initially evaluated by pulmonologists, but their hypoxic defect is secondary to liver disease. In contrast to pulmonary fibrosis and emphysema, which usually manifest after the fifth decade, telomere-mediated HPS often presents in the first 4 decades of life (Fig 2E). Therefore, in younger patients with short telomere syndromes who present with dyspnea, shunt physiology should be suspected over parenchymal lung disease. A mixed parenchymal-vascular defect should also be considered in patients with pulmonary fibrosis and emphysema whose hypoxic defects are disproportionate to the extent of parenchymal disease.

Noncirrhotic portal hypertension is a rare cause of liver pathology and underlies 3% to 5% of portal hypertension cases.²⁰ HPS is also an uncommon complication of noncirrhotic portal hypertension, occurring in approximately 10% of cases.²¹⁻²⁴ The co-occurrence of noncirrhotic portal hypertension with HPS in the genetically homogenous group of patients we studied

TABLE 2] Liver Pathology in Telomere Syndrome Cases With Hypoxia and Shunting (n = 6)

Age at Biopsy, y	Parenchyma	Vasculature	Iron Accumulation	Fibrosis	Case No. ^a
17	...	Telangiectasia	None	None	1
25	NRH, minimal portal chronic inflammation ^b	Normal	Moderate in hepatocytes ^b	None	4 ^c
34	NRH, early mild steatosis ^b	Prominent portal vessels ^b	None	None	6 ^c
40	NRH, bile duct paucity, diffuse cholestasis, noncaseating granulomas ^b	Prominent portal vessels ^b	Mild in hepatocytes and periportal ^b	Minimal patchy-portal and periportal	7 ^c
52	Normal	Sinusoidal dilatation ^b	None	None	8
53	NRH, chronic inflammatory infiltrate ^b	Some portal areas without veins ^b	Mild in hepatocytes and periportal ^b	None	9 ^c

NRH = nodular regenerative hyperplasia.

^aCase identifiers refer to Table 1.

^bA recurrent abnormality shared by two or more cases.

^cThese biopsies/explants were reviewed centrally as part of this study.

supports a unique natural history for this telomere-mediated pathology. Nodular regenerative hyperplasia is a rare histopathology; however, its characteristic appearance increases with age,²⁵ suggesting it may be a marker of premature aging in the subjects with short telomeres we studied. The isolated reports of children with dyskeratosis congenita in whom dyspnea was a prominent presenting symptom of liver disease suggest a specific association of HPS with telomere dysfunction.^{13,26-32}

Although our experience suggests HPS is a common presentation of liver disease in patients with short telomere syndrome, it is possible that there are alternate presentations of hepatic pathology, including overt cryptogenic cirrhosis. Regardless, recognizing the short telomere syndrome diagnosis is important for management, especially in the transplant setting where these patients have increased rates of acute complications related to myelosuppressive and other medications.³³

Several pieces of evidence point to a vascular defect as the cause of the noncirrhotic portal hypertension we report

in the short telomere syndromes. For example, nodular regenerative hyperplasia has been suggested to represent microvascular insufficiency and altered blood flow.³⁴ The finding of perivascular iron deposits in our series also supports that vascular fragility may be a driving event. Neovascularization is a secondary response to tissue hypoxia and abnormal blood vessel formation, and it is possible that endothelial dysfunction in the liver may underlie the shunting physiology. Our clinical observations suggest a model whereby endothelial abnormalities in the liver drive perivascular hepatocyte necrosis, such as that seen in nodular regenerative hyperplasia, while promoting neovascularization in the lung. Telomere dysfunction causes senescence in slow turnover tissues,^{35,36} and intrahepatic endothelial cells, which have slow turnover, may be particularly prone to “second hits,” given their unique microenvironment in the portal circulation. Future research will be needed to better define how telomere dysfunction may perturb vascular integrity in the liver and provoke vascular malformations in the lung.

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Author contributions: M. A. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. A. I. G., N. L. J., and M. A. designed the study and reviewed all the clinical data; S. E. S. performed the genetic studies; A. I. G., N. L. J., A. K., A. E. D., J. E. W., J. P. H., J. H.-F., A. R. C. and M. A. analyzed the data; S. C. S. and R. A. A. reviewed the pathology; I. R. K. reviewed the radiographs; A. I. G. and M. A. wrote the paper; and all the authors reviewed the manuscript.

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