Grand Rounds

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Hepatic manifestations of telomere biology disorders

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Clinical vignette

A 51-year-old Caucasian male was referred for evaluation of variceal bleeding. Laboratory tests were remarkable for mild thrombocytopenia and moderate alkaline phosphatase elevation. Synthetic liver function was well preserved. Abdominal computed tomography scan revealed moderate splenomegaly, gastric varices, and normal hepatic contour. A transjugular liver biopsy was performed revealing findings of nodular regenerative hyperplasia with no significant fibrosis or necroinflammatory activity. Hepatic venous pressure gradient was elevated at 31 mmHg, consistent with clinically significant portal hypertension. The clinical course was complicated by refractory gastric variceal bleeding requiring a surgical portosystemic shunt. Approximately seven years after the initial presentation, the patient developed progressive dyspnoea and a diagnosis of idiopathic pulmonary fibrosis was made. Contrast-enhanced echocardiogram was not suggestive of hepatopulmonary syndrome or portopulmonary hypertension. Given this new diagnosis a telomere biology disorder was suspected. A flow-fluorescence *in situ* hybridisation analysis for telomere length assessment revealed telomere lengths below the first percentile in both lymphocytes and granulocytes. Next generation sequencing analysis identified a heterozygous mutation involving the *hTERT* gene (Histidine983Threonine). The lung disease unfortunately progressed in the subsequent two years, leading to the patient's death nine years after his initial presentation with portal hypertension. During those nine years two brothers also developed idiopathic pulmonary fibrosis.

The questions that arise from this case include:

I. What are telomere biology disorders?
II. What are the hepatic manifestations of telomere biology disorders?
III. How are telomere biology disorders diagnosed?
IV. Are there any potential therapeutic options for telomere biology disorders?

Keywords: Telomere; Telomere biology disorders; Portal hypertension; Nodular regenerative hyperplasia; Cryptogenic cirrhosis.

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I. What are telomere biology disorders?

Telomeres are repetitive DNA sequences located at the end of linear chromosomes, which combined with specialised proteins – known as the shelterin complex, help maintain chromosome integrity and stability (Fig. 1).[1] Telomerase is a specialised enzyme that synthesises the multiple tandem repeats of DNA (telomeric DNA) and consists of two essential core components: the telomerase reverse transcriptase (TERT) and the telomerase RNA (TR).[2] Telomere shortening is a universal phenomenon with advancing age and is associated with age-related pathology. Telomere maintenance is essential to slow the shortening that occurs with each cell division and consequent premature cellular ageing.

Telomere biology disorders (TBD) are accelerated ageing syndromes caused by inherited gene mutations resulting in shortened telomeres. As a consequence, organ systems with increased cell turnover such as bone marrow, skin, lungs and the gastrointestinal tract are affected, either in isolation or combination. Because of their wide-range of possible clinical presentations, TBDs are often difficult to identify and diagnose. Bone marrow failure, idiopathic pulmonary fibrosis (IPF), premature emphysema, nodular regenerative hyperplasia (NRH) and cryptogenic cirrhosis are some of the more common clinical manifestations; with mutations in dyskerin (*DKC1*), *TERT* and telomerase RNA component (*TERC*) being frequent causative aberrations.

II. What are the hepatic manifestations of telomere biology disorders?

The hepatic manifestations of TBDs include cryptogenic cirrhosis and NRH leading to non-cirrhotic portal hypertension. In fact, TBDs should be suspected in patients with cryptogenic cirrhosis or idiopathic portal hypertension, especially if there is personal or family history of unexplained cytopenias, premature greying of hair (<30 years of age) or IPF/emphysema and in patients under 40 years of age. TBD may also play a role in hepatocarcinogenesis, as a result of chromosome instability driven by telomere shortening. Conversely, telomere elongation and high telomerase activity are observed in half of hepatocellular carcinoma cases and are associated with poorly differentiated tumours. These findings suggest a dual role of

Key point

Telomere shortening is a universal phenomenon associated with ageing and age-related pathology.

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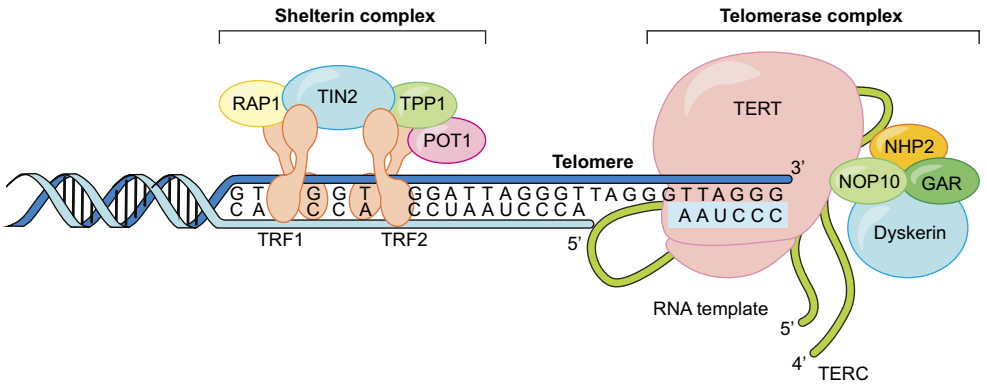

Fig. 1. Telomere maintenance components. Telomeres are composed of multiple *TTAGGG* repeats at the end of linear chromosomes and are coated by a protein complex, shelterin, which helps maintain its integrity. Shelterin also helps recruit and modulate the telomerase complex, the enzyme responsible for telomere elongation. Telomerase has a 4-protein scaffold (dyskerin, NOP10, NHP2, and GAR) and an RNA template (TERC) and reverse transcriptase (TERT). Adapted with permission from Townsley *et al.*[52]

Key point

Cryptogenic cirrhosis and nodular regenerative hyperplasia are hepatic manifestations of telomere biology disorders.

telomere dysfunction in tumour development and progression and further studies are needed to elucidate the impact of TBD in cirrhosis-related hepatocellular carcinoma.[3]

Cryptogenic cirrhosis

Despite significant diagnostic advances in the last several decades, approximately 5–30% of cirrhosis cases still lack a definite aetiology.[4,5] A concurrent diagnosis of cryptogenic cirrhosis has been reported in approximately 7% of patients with dyskeratosis congenita.[6] Additionally, TBDs often manifest as adult-onset fibrotic disease in slow-turnover tissues, such as lungs and liver. In contrast to dyskeratosis congenita, TBD-related cryptogenic cirrhosis presents at a mean age of 37 years (range 20–57).[7,8] Aside from a potential direct effect, telomere shortening secondary to telomerase gene mutations, also increases the risk of cirrhosis development in patients with chronic liver disease of different aetiologies. Two large independent studies identified a higher incidence of telomere-associated mutations in patients with sporadic cirrhosis of known causes compared to non-cirrhotic controls.[9,10] Additionally, the mean telomere length, measured by quantitative polymerase chain reaction (qPCR), in white blood cells of cirrhotic patients was significantly shorter than in age-matched controls (−0.114 *vs.* 0.001). Greater than 80% of cirrhotic patients had telomere lengths below the median for their age. These findings suggest that telomere shortening may play a role in cirrhosis development and/or progression even in patients with underlying chronic liver diseases.

The mechanisms of TBD-related cirrhosis remain unclear. Through quantitative fluorescence *in situ* hybridisation (FISH), telomere shortening was found to be limited to hepatocytes and to correlate with cellular markers of senescence.[11] These findings suggest impaired liver regeneration which in turn results in fibrosis development and progression. This hypothesis has been further corroborated in a telomerase-deficient mouse model, null for the essential telomerase RNA (mTR) gene. Defects in liver regeneration and accelerated fibrosis progression in response to chronic injury were observed. More interestingly, restoration of telomere function through adenoviral delivery of the mTR gene resulted in reduced hepatic fibrosis and improved liver function.[12] These results suggest a role for telomere directed therapy in prevention and/or reversal of TBD-related cirrhosis.

Nodular regenerative hyperplasia

NRH is characterised by small diffuse regenerative hepatic nodules in the absence of surrounding fibrosis.[13] The pathogenesis of NRH remains unclear, although hepatic blood flow alterations have been implicated. Various systemic conditions and medications have been associated with NRH (Table 1) and portal vein obliteration has been proposed as the common underlying mechanism leading to nodular parenchymal hypertrophy.[14–17] This theory, however, has been challenged with the development of an animal model of NRH through disruption of Notch1 signalling. Inducible Notch1 disruption in adult mice resulted in continuous proliferation of hepatocytes and consequent NRH morphology without vascular changes in the liver.[18] Moreover, endothelial Notch1 signalling has been found to be essential for hepatic vascular formation and function.[19] In humans, the expression of Notch1 was found to be significantly downregulated in liver biopsies of 14 patients with NRH.[20] Additionally, hepatoportal sclerosis and NRH have been reported in association with Adams-Oliver syndrome, a rare genetic disorder caused by Notch1 haploinsufficiency.[21]

The prevalence of NRH increases with age as demonstrated in a large autopsy study,[13] suggesting an age-dependent mechanism. Telomere shortening is thought to contribute to

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