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Clinical Correlates and Treatment Outcomes for Patients With Short Telomere Syndromes

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Abstract

Short telomere syndromes (STSs) are accelerated aging syndromes with multisystemic manifestations that present complex management challenges. In this article, we discuss a single-institution experience in diagnosing and managing patients with inherited STSs. In total, we identified 17 patients with short telomeres, defined by flow-fluorescence in-situ hybridization telomere lengths of less than first centile in granulocytes/lymphocytes OR the presence of a characteristic germline pathogenic variant in the context of a highly suggestive clinical phenotype. Genetic variations in the telomere complex were identified in 6 (35%) patients, with 4 being known pathogenic variants involving *TERT* (n=2), *TERC* (n=1), and *DKC1* (n=1) genes, while 2 were variants of uncertain significance in *TERT* and *RTEL1* genes. Idiopathic interstitial pneumonia (IIP) (n=12 [71%]), unexplained cytopenias (n=5 [29%]), and cirrhosis (n=2 [12%]) were most frequent clinical phenotypes at diagnosis. At median follow-up of 48 (range, 0-316) months, Kaplan-Meier estimate of overall survival, median (95% CI), was 182 (113, not reached) months. Treatment modalities included lung transplantation for IIP (n=5 [29%]), with 3 patients developing signs of acute cellular rejection (2, grade A2; 1, grade A1); danazol therapy for cytopenias (n=4 [24%]), with only 1 out of 4 patients showing a partial hematologic response; and allogeneic hematopoietic stem cell transplant for progressive bone marrow failure (n=2), with 1 patient dying from transplant-related complications. In summary, patients with STSs present with diverse clinical manifestations and require a multidisciplinary approach to management, with organ-specific transplantation capable of providing clinical benefit.

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Telomeres are hexanucleotide (TTAGGG) DNA-protein structures at chromosome ends that prevent attrition of genetic material with each asymmetric DNA replication. A complex array of genes is responsible for telomere synthesis, assembly, trafficking, and maintenance.[1] Defects in 1 or more of these genes can cause accelerated telomere shortening and consequently affect multiple organ systems with high cell turnovers, thereby resulting in manifestations such as premature graying of hair, idiopathic interstitial pneumonia (IIP), bone marrow failure (BMF), cryptogenic cirrhosis of the liver, nodular regenerative hyperplasia (NRH) with portal hypertension, and immune dysfunction.[2] Although there is no consensus on a commonly accepted nomenclature, we prefer to identify disorders associated with short telomeres as "short telomere syndromes" (STSs). A pathognomic subtype of STSs is dyskeratosis congenita (DKC), a genetically inherited disorder commonly seen in pediatric patients, secondary to mutations involving *DKC1* (and additional genes), presenting with a classic triad of nail dystrophy, abnormal skin pigmentation, oral leukoplakia, and progressive BMF.[3,4] Mutations in human telomere-associated genes have been identified in telomeric core components (*TERT*,

TERC),[5] telomere biogenesis (*NHP2*, *GAR1*, *NOP10*, *PARN*, *NAF1*, *DKC1*),[5-9] DNA synthesis (*RTEL1*),[10,11] shelterin complex (*RAP1 TINF2*, *TPP1*, *TRF1*, *TRF2*),[12,13] telomere trafficking (*TCAB1*),[14] and CST (*CTC1, STN1, TEN1*) complex.[15,16] However, only approximately 40% of patients with shortened telomeres have an identifiable pathogenic variant, suggesting that there are undiscovered genetic/epigenetic abnormalities affecting telomere lengths (TLs).

Management of STSs is fraught with significant challenges such as delayed diagnoses, lack of routinely available diagnostic modalities, and standardized treatment guidelines. With a view to address some of these shortcomings in literature, we report a single-institution experience detailing a multidisciplinary approach to STSs.

METHODS

In a retrospective cohort study design, we identified consecutive cases of STSs, defined as TL of less than first centile of the normal population in either granulocytes or lymphocytes (TL in lymphocytes only in case of an underlying myeloid malignancy or BMF syndrome) as detected by the flow-fluorescence in-situ hybridization methodology or the presence of a known STS pathogenic genetic variant in the context of a clinical phenotype. Because of clinical heterogeneity and diagnostic uncertainty, we excluded patients with TLs between 1st and 10th centiles, in the absence of a known STS-associated mutation. Seventeen patients, meeting our inclusion criteria, were identified after surveying clinicians working in the pediatric and adult divisions of pulmonary and critical care medicine, gastroenterology, and hematology. Flow-fluorescence in-situ hybridization testing was performed at an external reference laboratory, while a standard 8 gene next-generation sequencing (NGS) panel consisting of the genes *DKC1*, *RTEL1*, *TINF2*, *NHP2 (NOLA2)*, *TERC*, *TERT*, *NOP10 (NOLA3)*, and *WRAP53 (TCAB1*, *WDR79)* was sent either to an external laboratory or performed at our institution. In patients with short telomeres and a negative NGS panel, research-based whole-exome sequencing was conducted under Mayo Clinic's premyeloid and BMF precision genomics protocol (NCT02958462).[16]

RESULTS

Demographic and clinical features of the 17 patients included in our study are presented in the Table; 14 (82%) were male. Telomere testing results were available in 14 (82%) patients, of whom 11 (65%) had TLs of less than first centile in both granulocytes and lymphocytes, whereas 3 (18%) patients had TLs of less than first centile in granulocytes, but in the 1st to 10th centile range in lymphocytes (latter cases did not have any objective evidence of an underlying myeloid malignancy). Three (18%) patients (2, *DKC1*; 1, *TERC*) were diagnosed solely through NGS testing because they had a clear STS clinical phenotype. Median age at objective evidence of disease onset (defined by either imaging or morphologic evidence of unexplained pulmonary fibrosis, cirrhosis, or BMF) was 57 (range, 2-74) years, whereas age at actual diagnosis was 60 (range, 9-66) years, and median time from symptom onset to diagnosis was 24 (0-81) months. At diagnosis, the most frequent disease manifestation was IIP (n=12 [71%]; although it is debatable whether telomere-related pulmonary fibrosis should be called IIP, we decided to keep the terminology because the classification of chronic lung disease has not yet changed), followed by unexplained cytopenias (n=5 [29%]) and NRH (n=1 [6%]), whereas at last median follow-up of 48 months (range, 0-316), there were 4 deaths, and the Kaplan-Meier estimate of overall survival (OS), median (95% CI), was 182 (113, not reached) months. Three patients had cirrhosis and/or NRH, IIP, and BMF; 3 had IIP and BMF; 1 had IIP and cirrhosis; 1 had BMF and cirrhosis; 6 had IIP only; and 3 had BMF only. At median (range) follow-up of 48 months (0-316), of the patients with fibrotic lung disease either at diagnosis or at subsequent follow-up, patterns of fibrosis could be ascertained in 11 patients (5, biopsy and imaging; 6, imaging only): 3 with usual interstitial pneumonia, 2 with nonspecific interstitial pneumonia, 1 with pleuroparenchymal fibroelastosis, 1 with combined features of IIP and emphysema, and 4 in the "unclassifiable" category. Only 3 (18%) patients had a history of premature graying of hair (hair graying $\leq$30 years of age). Family history with at least 1 family member with either premature graying of hair or unexplained cytopenias/cirrhosis/IIP was available in 8 (47%) patients. Among patients with IIP (n=12), 6 (50%) were habitual smokers,

TABLE. Demographic characteristics, clinical features, associated genomic variants, and outcomes for our cohort of patients with short telomere syndromes

Case no.	Age at symptom onset/sex	Diagnosis	Organ system manifestations	Flow-FISH results (centile telomere lengths in granulocytes/ lymphocytes)	Genomic aberration identified	Zygosity	Minor allelic frequency	SIFT/Polyphen2 predictions
1	2/F	DKC	Bone marrow failure, liver cirrhosis, IIP	NA	NA	NA	NA	NA
2	64/F	STS	Bone marrow failure, ILD (NSIP)	<1st centile/<1st centile	*TERT*, exon 12, missense, H983T amino acid substitution	NA	NA	NA
3	57/M	STS	Bone marrow failure, cirrhosis, IIP	<1st centile/<1st centile	Not tested	NA	NA	NA
4	54/M	STS	IIP (unclassifiable)	<1st centile/<1st centile	*TERT* VUS c.2030G>A, p.G677D	Heterozygous	0%	Deleterious/Prob. damaging
5	63/M	STS	IIP (UIP)	<1st centile/1-10th centile	Ongoing	NA	NA	NA
6	47/M	STS	IIP (UIP)	<1st centile/<1st centile	Ongoing	NA	NA	NA
7	62/F	STS	IIP (pleuroparenchymal fibroelastosis)	<1st centile/1-10th centile	*RTEL* VUS c.101A>G, p.Q34R	Heterozygous	NA	Tolerated/benign
8	56/M	STS	IIP (UIP)	<1st centile/1-10th centile	Not identified	NA	NA	NA
9	74/M	STS	IIP, bone marrow failure	<1st centile/<1st centile	NA	NA	NA	NA
10	56/M	STS	IIP (NSIP), macrocytosis without anemia	<1st centile/<1st centile	NA	NA	NA	NA
11	53/M	STS	NRH, IIP (UIP), macrocytosis without anemia	NA; documented short telomeres	NA	NA	NA	NA
12	4/M	DKC	Bone marrow failure with transfusion dependence	Not done	*DKC1 (Variant details NA)*	NA	NA	NA
13	58/M	STS	Bone marrow failure, IIP	Not done	*TERC (n.214G>C, noncoding variant)*	Heterozygous	0%	NA
14	17/M	DKC	Bone marrow failure	<1st centile/<1st centile	*TERTc.2768C>T; p.P923L; CSF3R VUS* c.2422G>A; p. G808K	TERT: Heterozygous CSF3R: Heterozygous	TERT: 0.00041% CSF3R: 0.62%	TERT: Deleterious/ Prob. damaging CSF3R: Deleterious/ Prob. damaging
15	63/M	STS	Bone marrow failure, IIP (unclassifiable)	<1st centile/<1st centile	–	–	–	–
16	66/M	STS	Cryptogenic cirrhosis, IIP (unclassifiable), bone marrow failure	<1st centile/<1st centile	Ongoing	NA	NA	NA
17	60/M	STS	Crytpogenic cirrhosis, IIP (with combined emphysematous changes)	<1st centile/<1st centile	Ongoing	NA	NA	NA

Continued on next page

with 1 developing concurrent emphysematous changes.

Genetic alterations were identified in 6 (35%) patients (all through commercial NGS testing), with 4 being known pathogenic heterozygous variants, namely, 2 *TERT*, 1 *TERC*, and 1 *DKC1*, while 2 patients had variants of uncertain significance (VUS) in *TERT* and *RTEL1* genes

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TABLE. Continued

Sequencing approach	HSCT	SOT; type	Other treatments	Best response to treatment	Progression to AML	Comments	At OS (95% CI) 182 mo (113, not reached), death status/age at death in years	Cause of death
–	Yes	No	Danazol	None	No	Diagnosed elsewhere	Dead/17	End-stage cirrhosis
–	No	No	No	–	No	–	Dead/66	Acute exacerbation of IIP
–	No	No	No	–	No	–	Alive/57	–
NGS	No	Yes/lung	Danazol	Mild improvement in WBC count	No	–	Alive/60	–
NGS	No	Yes/lung	No	–	No	Pirfenidone used for IIP; grade A1 allograft rejection, managed with prednisone	Alive/66	–
WES ongoing	No	Yes/lung	No	–	No	Grade A2 allograft rejection, managed with prednisone	Alive/49	–
NGS	No	Yes/lung	No	–	No	Grade A2 rejection managed with prednisone; developed SCC of skin & tongue around 17 y before diagnosis	Alive/64	–
NGS	No	Yes/lung	No	–	No	–	Alive/63	–
–	–	–	–	–	–	Developed SCC of skin	–	–
–	–	–	–	–	–	Lost to follow-up	Alive/57	–
NA	No	No	No	–	–	*N*-Acetylcysteine used	Dead/63	Acute exacerbation of IIP
NGS	Yes, details NA	No	Danazol	None	–	Classic DKC phenotype of oral leukoplakia, narrow tear ducts & lacy skin pigmentation	Alive/30	–
NGS	Yes	No	No	–	–	Progressed to MDS-EB-2; developed SCC of skin	Dead/59	Complications from allogeneic HSCT
NGS	No	No	Immunosuppressive treatment with ATG & cyclosporine	Mild improvement in platelet count	No	Being considered for allogeneic HSCT; cytogenetic abnormalities show del(7)(q22)	Alive/81	–
WES	No	No	Danazol	None	No	Developing complications from IIP	Alive/67	–
WES ongoing	No	No	No	–	No	End-stage cryptogenic cirrhosis	Alive/68	–
WES ongoing	No	No	No	–	No		Alive/61	–

DKC = dyskeratosis congenita; F = female; FISH = fluorescence in-situ hybridization; HSCT = hematopoietic stem cell transplantation; IIP = idiopathic interstitial pneumonia; M = male; MDS-EB-2 = myelodysplastic syndrome with excess blasts-2; NA = not available; NGS = next-generation sequencing; NRH = nodular regenerative hyperplasia; NSIP = nonspecific interstitial pneumonia; OS = overall survival; *Prob.*, probably; SCC = squamous cell cancer; SOT = solid-organ transplant; UIP = usual interstitial pneumonia; WBC = white blood cell; WES = whole-exome sequencing panel.

(details in the Table). The TLs were available in 3 of the 6 aforementioned patients, with 2 demonstrating TLs of less than first centile in lymphocytes and granulocytes, whereas 1 had TL of less than first centile in granulocytes but in the 1st to 10th centile range in lymphocytes.

At a median follow-up of 48 (range, 0-316) months, there were 4 deaths. The Kaplan-Meier estimate of OS, median (95% CI), was 182 (113, not reached) months, with the most common cause of death being acute exacerbations of IIP (n=2), while 1 patient each died from complications of cirrhosis and allogeneic hematopoietic stem cell transplant (HSCT), respectively. One patient with a *TERC* (n.214G>C, noncoding) pathogenic variant at diagnosis presented with an aggressive myeloid neoplasm (myelodysplastic syndrome with excess blasts-2), while another patient with the *TERT* (c.2768C>T; p.Pro923Leu) pathogenic variant developed clonal cytopenias (abnormal cytogenetics [46, XY, del(7)(q22)[1]/46,XY[39]]) without bone marrow dysplasia. Four (24%) patients were treated with danazol for cytopenias, with only 1 showing a partial improvement in white blood cell count. Three (18%) patients developed squamous cell carcinoma of skin, 2 of whom were chronically immunosuppressed.

Five (29%) patients underwent lung transplant (all for IIP: 3, bilateral; 2, single lung), while 2 (12%) underwent allogeneic HSCT, 1 for progressive BMF and 1 for progression to high-risk myelodysplastic syndrome (myelodysplastic syndrome with excess blasts-2). The patient with progression to myelodysplastic syndrome had concurrent IIP and died from posttransplant multiorgan failure. Of the patients who underwent lung transplant, 3 developed signs of acute cellular rejection (2, grade A2; 1, grade A1), which were managed with low-dose prednisone therapy with no deaths.

DISCUSSION

Pathogenic variants associated with short telomeres have been well described in invertebrates such as yeast; however, only a small number of genes have been identified in human beings, signifying the need for a precision genomics-based approach to identify novel genetic and epigenetic mechanisms of TL regulation.[17] The clinical implications of this process are profound, because a considerable percentage of these patients are treated with either solid-organ or HSCT,[18] procedures mandating search of donors within the same family (bone marrow and liver) and more importantly, screening of family members, including children. For example, siblings may have the same pathogenic variants as patients, thereby making them unsuitable donors.

In a study authored by Armanios et al,[19] frequency of heterozygous pathogenic germline alterations in *TERT* or *TERC* genes in patients with IIP has been reported to be around 8% and TLs in mutation carriers were found be less than 10th centile of normal age-matched controls.[19] In our cohort, most (59%) patients had IIP at diagnosis with diverse patterns of fibrosis. The clinical/radiological heterogeneity (fibrotic nonspecific interstitial pneumonia, usual interstitial pneumonia, pleuroparenchymal fibroelastosis, unclassifiable and combined emphysematous changes), along with the characteristic uniform disease progression seen in this series, is consistent with previous reports on patients with telomere-related lung fibrosis.[20] Gastrointestinal manifestations, often overlooked in STSs, are seen in approximately 16% of patients with short telomeres.[21,22] In our cohort, 26% patients developed either cryptogenic cirrhosis or NRH, 1 of whom died from related complications. Interestingly, patients with IIP or cirrhosis had a trend toward worse OS, suggesting a negative prognostic impact related to the involvement of these organs.

A considerable proportion of patients with IIP underwent lung transplant (29%), and all of them developed persistent cytopenias (>3 months) thereafter, which is consistent with a previous report by Silhan et al.[23] Furthermore, these patients were intolerant of standard antimetabolite medications and their leukopenias were managed with colony-stimulating factors. Published data suggest that lung transplant recipients with shorter TLs have decreased likelihood of developing acute cellular rejection; however, 3 out of 5 patients who underwent a lung transplant in our series developed rejection.[24]

CONCLUSION

Short telomere syndromes are multisystemic disorders with protean clinical manifestations and outcomes. Early recognition of these premature aging syndromes should be encouraged with consideration for organ-specific

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transplantation based on clinical phenotype. With the help of this patient series, we demonstrate the potential of using a targeted genomics approach through a unique clinic to identify novel genetic abnormalities associated with short telomeres, and follow such patients prospectively. Our standard approach, in the context of a relevant phenotype, includes a thorough history and physical examination, followed by TL measurement and NGS. If the aforementioned testing result is negative, we proceed to perform a research-based whole-exome sequencing after discussion in a multidisciplinary tumor board comprising clinicians, bioinformaticians, and molecular biologists.

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Abbreviations and Acronyms: **BMF** = bone marrow failure; **DKC** = dyskeratosis congenita; **HSCT** = hematopoietic stem cell transplant; **IIP** = idiopathic interstitial pneumonia; **NGS** = next-generation sequencing; **NRH** = nodular regenerative hyperplasia; **OS** = overall survival; **STS** = short telomere syndrome; **TL** = telomere length

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