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CASE REPORT

Progression of Neuroimaging Features Associated with Dyskeratosis Congenita and Short Telomere Syndrome: A Case Report

Devina Espinoza[1], Daniel Thomas Ginat MD[2]

[1]Geisel School of Medicine at Dartmouth, Hanover, NH, USA.
[2]Pritzker School of Medicine, Chicago, IL, USA.

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ABSTRACT

Background: Dyskeratosis congenita is a rare genetic disorder resulting from mutations that lead to shortened telomeres and premature cellular aging. Although it classically presents with a triad of mucocutaneous abnormalities, it has diverse clinical manifestations, affecting multiple organ systems. Neurological involvement, often seen in severe variants, constitutes a significant element of the disease's pathophysiology, highlighting the vast array of observed complications.

Case Presentation: A 5-year-old girl with a known diagnosis of dyskeratosis congenita due to a WRAP53 mutation presents with bloody stools and epilepsy. Her clinical course was marked by gastrointestinal disturbances, hematologic sequelae, and severe hepatic manifestations, including recurrent bleeding episodes.

Discussion: This case highlights the complex interplay between telomere dysfunction and the systemic and neurological manifestations in dyskeratosis congenita. The serial brain MRI findings reveal progressive white matter disease, brain volume loss, and choroid plexus calcifications, indicating a rapid neurodegenerative progression and premature aging. Enhanced surveillance and tailored management strategies are crucial to mitigate disease-associated morbidity.

Conclusion: Dyskeratosis congenita due to a WRAP53 mutation enriches our understanding of its neurodegenerative dimensions and emphasizes the pivotal role of telomeres in systemic and neurological health. Integrating advanced imaging with comprehensive multidisciplinary management improves disease monitoring and optimizes patient care.

Introduction

Dyskeratosis congenita (DKC) stands as a paradigm of telomere biology gone awry, a rare genetic disorder characterized by defective telomere maintenance leading to accelerated cellular aging[1]. First documented by Zinsser et al. in 1906, DKC classically manifests with a triad of mucocutaneous abnormalities—abnormal skin pigmentation, nail dystrophy, and oral leukoplakia[2,3]. However, beneath this dermatologic veneer lies a systemic pathology of profound complexity and severity, permeating multiple organ systems and significantly impacting patient prognosis.

Telomeres and Their Role

Telomeres, repetitive nucleotide sequences capping chromosomal ends, serve as guardians against genomic instability by preventing chromosomal fusion and degradation during cellular replication[4]. In DKC, mutations disrupting telomere maintenance genes—DKC1, TERC, TERT, and WRAP53—unleash a cascade of accelerated telomere shortening, a hallmark of the disease[5,6,7]. This chromosomal instability precipitates a spectrum of clinical manifestations encompassing not only bone marrow failure, a leading cause of mortality in DKC, but also pulmonary fibrosis, hepatic fibrosis, and an increased predisposition to malignancies[5,6,8,9,10,11].

Neurological Involvement in DKC

Neurological involvement, though less frequently discussed in clinical discourse than the classic dermatologic findings, constitutes a significant element of DKC's pathophysiology[5].

More severe variants of DKC, such as Hoyeraal-Hreidarsson syndrome and Revesz syndrome, are more commonly associated with neurological presentations such as intracranial calcifications, brain atrophy, hydrocephalus, and cerebellar hypoplasia, highlighting the spectrum of neurological complications observed in these complex cases[12,13,14,15,16]. Manifestations such as progressive white matter disease, brain atrophy, and intracranial calcifications demonstrate a neurodegenerative trajectory that complicates patient management and prognosis[17,18,19]. These neurologic sequelae underscore the critical role of telomeres not only in maintaining chromosomal stability but also in preserving neuronal integrity, necessitating vigilant surveillance and multidisciplinary care in affected individuals.

This article presents a poignant case of a 5-year-old girl afflicted with DKC due to a WRAP53 mutation. Her clinical journey epitomizes the systemic ravages of the disorder, characterized by gastrointestinal disturbances, hematologic sequelae, and hepatic manifestations culminating in recurrent bleeding episodes. WRAP53, an inherited mutation that results in severe DKC, plays critical roles in intracellular trafficking of telomerase, DNA repair, and Cajal body function[7,20,21,22,23]. These roles are particularly significant in understanding the rapid progression observed in severe DKC cases. Notably, serial brain MRIs reveal rapidly progressive neuroimaging findings, delineating a trajectory of premature aging through white matter disease progression, brain volume loss, and the emergence of choroid plexus calcifications—a constellation emblematic of severe dyskeratosis congenita[18, 19, 24].

In elucidating this case of DKC due to a WRAP53 mutation, we aim to enrich the understanding of DKC's neurodegenerative dimensions, thereby underscoring the pivotal role of telomeres in both systemic and neurological health. This comprehensive documentation of progressive neurological manifestations alongside systemic complications illustrates the broader impact of telomere dysfunction in DKC. Approximately 30% of patients exhibiting clinical signs of DKC do not have a confirmed identified mutation; this case report adds valuable information from a patient with a known WRAP53 mutation[5,25]. Additionally, the serial imaging in this report uniquely demonstrates a child's rapid progression of neurodegeneration, contributing to the literature by providing critical insights into the swift premature aging process seen in some with DKC. The detailed neuroimaging findings and clinical course enrich current understanding by highlighting the rapid

neurodegenerative progression characteristic of DKC, thereby illuminating avenues for enhanced surveillance, tailored management strategies, and future therapeutic interventions aimed at alleviating DKC-associated morbidity.

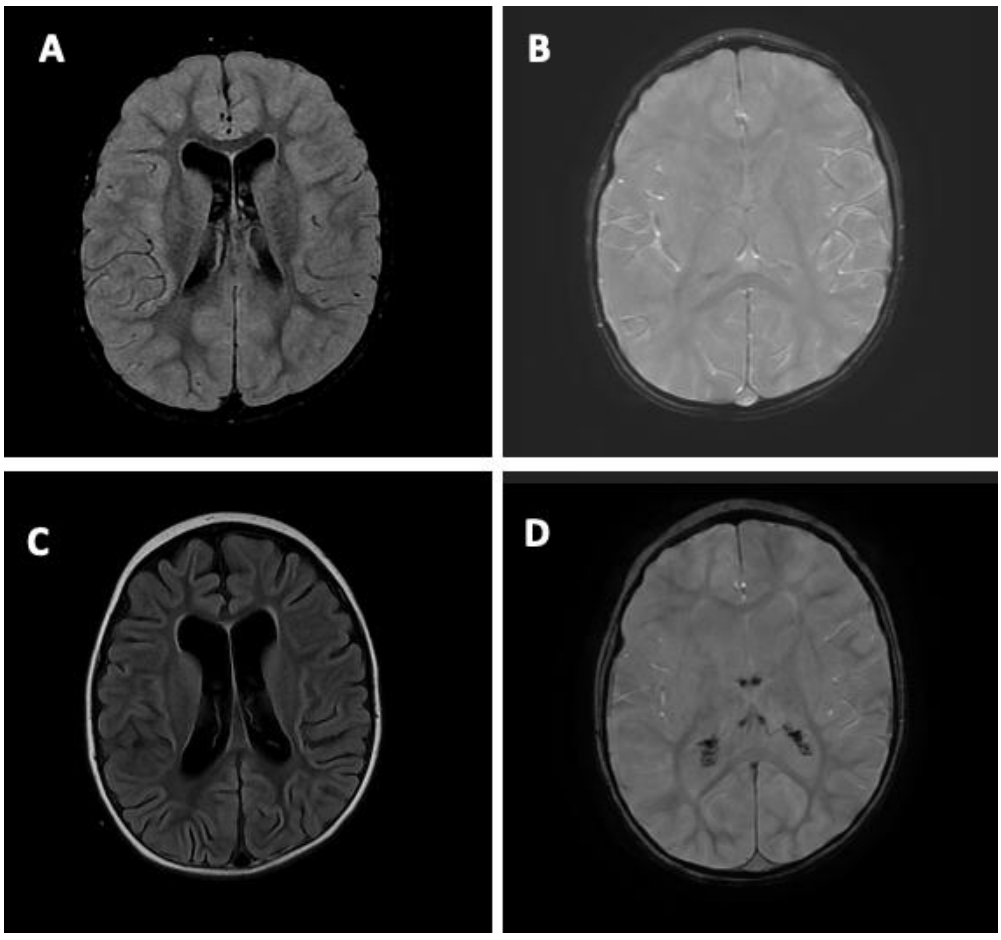
Case Report

A 5-year-old girl presented with a known diagnosis of dyskeratosis congenita (DKC) due to a WRAP53 mutation, manifesting with significant clinical complexities. Chief complaints included recurrent episodes of bloody stools and epilepsy, prompting a multidisciplinary evaluation. Her medical history was notable for a 7/8 mismatched unrelated donor allogeneic transplant, undertaken in the context of bone marrow failure secondary to DKC. Despite the transplant, she continued to experience residual thrombocytopenia attributed to poor platelet engraftment. Additionally, she was diagnosed with diabetes and suffered from iron overload due to chronic transfusions.

Hepatic involvement was profound, with evidence of fibrosis leading to portal hypertension and the subsequent development of esophageal varices and gastric antral vascular ectasia, culminating in recurrent episodes of gastrointestinal bleeding. These systemic manifestations underscored the multisystem impact of DKC, necessitating ongoing management and surveillance.

Neurologically, the patient underwent serial MRI scans without contrast to monitor disease progression. Initial imaging (Figure 1, Image A) revealed diffuse periventricular white matter hyperintensities and brain volume loss, indicative of ongoing neurodegeneration. Subsequent imaging (Figure 1, Image C) performed five months later of the brain abnormalities with increased white matter involvement and further brain atrophy. Concurrently, mineralization of the choroid plexus was observed (Figure 1, Image B), becoming more pronounced in later scans (Figure 1, Image D).

Figure 1:



Axial T2-weighted FLAIR (A and C) and SWI MRI (B and D) obtained five months apart show interval progression of periventricular white matter abnormality, brain volume loss, and the development of choroid plexus calcifications.

Discussion

Dyskeratosis congenita is a multifaceted genetic disorder characterized by defective telomere maintenance, resulting in accelerated cellular aging and a spectrum of clinical manifestations[1,2,3]. This case report details the clinical journey of a 5-year-old girl with DKC due to a WRAP53 mutation, emphasizing both systemic and neurological complications that underscore the extensive impact of telomere dysfunction.

Neurological Manifestations

The patient presented with progressive white matter disease, brain volume loss, and choroid plexus calcifications, as evidenced by the brain MRIs, highlighting significant neurodegenerative changes characteristic of severe variants of DKC[8]. These findings underscore the critical role of telomeres in maintaining neuronal integrity and stability[8]. The observed progression over a relatively short interval underscores the accelerated aging process within the brain attributed to telomere dysfunction, echoing previous reports in similar genetic disorders [2,5].

Systemic Complications

Beyond neurological implications, the patient exhibited a complex array of systemic complications typical of DKC. These included residual thrombocytopenia, iron overload secondary to chronic transfusions, hepatic fibrosis leading to portal hypertension, and recurrent gastrointestinal bleeding secondary to esophageal varices and gastric antral vascular ectasia. These manifestations underscore the multisystem nature of DKC and the challenges inherent in its management, necessitating a coordinated, multidisciplinary approach [5,6].

Clinical and Therapeutic Implications

Neurological involvement in DKC, although not a classic presentation compared to other systemic manifestations, significantly impacts patient quality of life and long-term outcomes[5]. This case underscores the importance of regular neuroimaging surveillance in DKC patients to detect and monitor progressive neurodegenerative changes early. Advanced imaging techniques such as FLAIR and SWI MRI are indispensable tools, enabling clinicians to track disease progression and tailor therapeutic strategies accordingly.

Moreover, this case highlights the urgent need for further research into targeted therapies addressing telomere dysfunction in DKC and related disorders. By integrating advanced imaging modalities with comprehensive clinical and genetic evaluations, clinicians can enhance their understanding of disease mechanisms and optimize management strategies to improve patient outcomes.

Conclusions

This case of DKC due to a WRAP53 mutation deepens our understanding of the disorder's neurodegenerative aspects and emphasizes the pivotal role of telomeres in both systemic and neurological health. By documenting progressive neurological symptoms alongside systemic complications, it underscores the broader impact of telomere dysfunction in DKC. The detailed neuroimaging findings and clinical course highlight the rapid neurodegenerative progression typical of DKC, suggesting opportunities for enhanced surveillance, tailored management, and future therapeutic interventions to mitigate DKC-related morbidity. Integrating advanced imaging techniques with comprehensive clinical and genetic evaluations enables more effective disease monitoring and optimized patient care. Further research is needed to explore targeted therapies addressing telomere dysfunction in DKC and related disorders, aiming to delay premature cellular aging and improve patient outcomes.

Conflict of Interest:

The authors declare no conflicts of interest.

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References:

1. Khattab S, Nasser H, Al-Janabi MH, Hasan F. Dyskeratosis congenita: a rare case report. *Oxford Medical Case Reports*. 2024;2024(5). doi:10.1093/omcr/omae049

2. Zinsser F. Atrophia cutis reticularis cum pigmentione, dystrophia unguium et leukokeratosis oris Ikonogr Dermatol. 1906;5:219–23

3. Chalkoo Ah, Kaul V, Wani La. Zinsser-Cole-Engmann syndrome: A rare case report with literature review. *Journal of Clinical and Experimental Dentistry*. Published online 2014:e303-6. doi:10.4317/jced.51274

4. Blackburn EH. Switching and Signaling at the Telomere. *Cell*. 2001;106(6):661-673. doi:10.1016/s0092-8674(01)00492-5

5. Savage SA, Alter BP. Dyskeratosis Congenita. *Hematology/Oncology Clinics of North America*. 2009;23(2):215-231. doi:10.1016/j.hoc.2009.01.003

6. Armanios M, Blackburn EH. The telomere syndromes. *Nature Reviews Genetics*. 2012; 13(10):693-704. doi:10.1038/nrg3246

7. Gadelha RB, Machado CB, Pessoa FMC de P, et al. The Role of WRAP53 in Cell Homeostasis and Carcinogenesis Onset. *Current Issues in Molecular Biology*. 2022;44(11):5498-5515. doi:10.3390/cimb44110372

8. Nelson ND, Bertuch AA. Dyskeratosis congenita as a disorder of telomere maintenance. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*. 2012;730(1-2):43-51. doi:10.1016/j.mrfmmm.2011.06.008

9. Mason PJ, Bessler M. The genetics of dyskeratosis congenita. *Cancer Genetics*. 2011;204(12):635-645. doi:10.1016/j.cancergen.2011.11.002

10. Walne AJ, Dokal I. Advances in the understanding of dyskeratosis congenita. *British Journal of Haematology*. 2009;145(2):164-172. doi:10.1111/j.1365-2141.2009.07598.x

11. Dokal I. Dyskeratosis congenita in all its forms. *British Journal of Haematology*. 2000;110(4):768-779. doi:10.1046/j.1365-2141.2000.02109.x

12. Zhang M, Cao Y, Wu H, Li H. Brain imaging features of children with Hoyeraal-Hreidarsson syndrome. *Brain and Behavior*. 2021;11(5). doi:10.1002/brb3.2079

13. Feldstein J, Fernandez Garcia S. The diagnosis and treatment of dyskeratosis congenita: a review. *Journal of Blood Medicine*. Published online August 2014:157. doi:10.2147/jbm.s47437

14. Bhala S, Best AF, Giri N, et al. CNS manifestations in patients with telomere biology disorders. *Neurology Genetics*. 2019;5(6). doi:10.1212/nxg.0000000000000370

15. Glousker G, Touzot F, Revy P, Tzfati Y, Savage SA. Unraveling the pathogenesis of Hoyeraal–Hreidarsson syndrome, a complex telomere biology disorder. *British Journal of Haematology*. 2015;170(4):457-471. doi:10.1111/bjh.13442

16. Bakar Ö, Işik U, Canpolat C, Alanay Y. Hoyeraal–Hreidarsson Syndrome: An Extremely Rare Dyskeratosis Congenita Phenotype. *Pediatric Dermatology*. 2015;32(6). doi:10.1111/pde.12693

17. Liu H, Yang Y, Xia Y, et al. Aging of cerebral white matter. *Ageing Research Reviews*. 2017; 34:64-76. doi:10.1016/j.arr.2016.11.006

18. Xiong YY, Mok V. Age-Related White Matter Changes. *Journal of Aging Research*. 2011;2011:1-13. doi:10.4061/2011/617927

19. Fujita S, Mori S, Onda K, et al. Characterization of Brain Volume Changes in Aging Individuals With Normal Cognition Using Serial Magnetic Resonance Imaging. *JAMA Network Open*. 2023;6(6):e2318153. doi:10.1001/jamanetworkopen.2023.18153

20. Bergstrand S, Böhm S, Malmgren H, et al. Biallelic mutations in WRAP53 result in dysfunctional telomeres, Cajal bodies and DNA repair, thereby causing Hoyeraal–Hreidarsson syndrome. *Cell Death &; Disease*. 2020;11(4). doi:10.1038/s41419-020-2421-4

21. Venteicher AS, Abreu EB, Meng Z, et al. A Human Telomerase Holoenzyme Protein Required for Cajal Body Localization and Telomere Synthesis. *Science*. 2009;323(5914):644-648. doi:10.1126/science.1165357

22. Mahmoudi S, Henriksson S, Weibrecht I, et al. WRAP53 Is Essential for Cajal Body Formation and for Targeting the Survival of Motor Neuron Complex to Cajal Bodies. *PLoS Biology*. 2010;8(11):e1000521. doi:10.1371/journal.pbio.1000521

23. Tycowski KT, Shu MD, Kukoyi A, Steitz JA. A Conserved WD40 Protein Binds the Cajal Body Localization Signal of scaRNP Particles. *Molecular Cell*. 2009;34(1):47-57. doi:10.1016/j.molcel.2009.02.020

24. Vulliamy T, Beswick R, Kirwan M, et al. Mutations in the telomerase component NHP2 cause the premature ageing syndrome dyskeratosis congenita. *Proceedings of the National Academy of Sciences*. 2008;105(23):8073-8078. doi:10.1073/pnas.0800042105

25. Brailovski E, Tsui H, Chen YB, Velsher L, Liu J, Buckstein R. Previously unreported WRAP53 gene variants in a patient with dyskeratosis congenita. *Annals of Hematology*. 2021;101(4):907-909. doi:10.1007/s00277-021-04678-7

