

Chapter 24

Neuropsychiatric Complications

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Introduction

People living with DC have a higher risk for structural brain abnormalities which may manifest as neurodevelopmental disorders, neuromotor impairment, and psychiatric diagnoses when compared with the general population. Thus, careful screening for these manifestations is indicated. Further study of this population has the potential to continue to yield significant insights into the pathobiological connections between telomere biology and development of neuropsychiatric conditions.

Telomeres and Psychiatric Disorders

There is significant research interest in the role of telomeres in psychiatric disorders. Cross-sectional studies have identified associations between shorter blood or buccal cell telomere length and psychiatric diagnoses such as major depressive disorder [1, 2], bipolar disorder [2], schizophrenia [3], and post-traumatic stress disorder (PTSD) in adulthood following childhood trauma [4]. One study found reduced levels of lymphocyte telomerase in individuals with schizophrenia [5]. Shorter germline telomeres were also noted in subjects with significant psychosocial stress, such as adult caregivers of the chronically ill [6], women who have experienced domestic violence [7], and in chronically institutionalized children from Romania [8]. There is some suggestion that cumulative number of stressors may have a differential impact on later telomere length [9]. Stress-induced hypothalamic-pituitary-adrenal axis activation may play a role in mediating the relationship between stressors and shortened telomeres [10], as cortisol is known to reduce telomerase activity.

Most of the above studies evaluated telomere length in peripheral blood leukocytes, which may not correlate with telomere length in other cells. A study of telomere length in cortical neurons showed no difference between patients with major depressive disorder and control subjects [11], while another study looking at cerebellar neurons demonstrated no link between telomere length and serious psychiatric illness [12]. It is important to note that in studies demonstrating telomere length association between cases and controls, the differences may be statistically significant, but are still relatively small when control telomeres are compared to the markedly short telomeres of dyskeratosis congenita (DC). Thus, it remains unclear whether short telomeres predispose patients to develop certain neuropsychiatric conditions, or that telomere shortening is a downstream consequence of the physical effects of psychiatric symptoms and stress [13]. Alternatively, telomere shortening in the face of neuropsychiatric conditions may be expressions of a common biological insult.

Neuropsychiatric Disorders and Dyskeratosis Congenita

There are limited data on the relationship between DC and neuropsychiatric conditions. Most individuals with DC have normal intelligence and achieve normal developmental motor milestones, although severely affected individuals may not. Developmental delay is present in two subtypes of DC: Hoyeraal Hreidarsson (HH) [14, 15] and Revesz Syndrome [15, 16]. Like classic DC, these disorders are characterized by the mucocutaneous triad described in Chapter 3, Diagnosing Telomere Biology Disorders. In addition, Revesz syndrome is remarkable for bilateral exudative retinopathy and intracranial calcifications. Immunodeficiency is seen in HH, and changes reported in neuroimaging, including cerebellar hypoplasia or atrophy, small brainstem, thin corpus callosum, and cerebral calcifications, may be confused with TORCH syndrome, caused by a group of neonatally acquired infections (Toxoplasmosis, Other, Rubella, Cytomegalovirus and Herpes infections).

There are relatively scant data about psychiatric illness in individuals with DC. Two case reports describe schizophrenia in these patients [17, 18] and a recent case describes an adult presenting with mood (mania) and psychotic symptoms [19]. In 2012, a preliminary study of six pediatric and eight adult patients with DC or DC-like conditions demonstrated a relatively high incidence of some form of neuropsychiatric disorder [20]. Participants had a wide variety of psychiatric concerns, but mood disorders were the most common. Neurodevelopmental diagnoses such as attention deficit hyperactivity disorder (ADHD), intellectual disabilities, learning disabilities, or autism spectrum disorder were also very common in this sample, with half of pediatric subjects and a quarter of adults carrying at least one of these diagnoses (Table 1). A more recent examination of 44 participants with telomere biology disorders (26 children, 18 adults) (31 DC, 12 HH, and 1 Revesz syndrome) included structural brain magnetic resonance imaging (MRI) and showed 25/44 (57%) patients had one or more structural brain abnormality or variant [20]. While this expanded longitudinal study included 10 patients previously reported [21], the data continue to support increased neuropsychiatric findings with 21 patients (48%) having neurodevelopmental disorders or psychomotor

abnormality and 12 patients (27%) having psychiatric diagnoses, including depression and/or anxiety disorders. In this study, shorter lymphocyte telomere length was associated with more brain MRI findings/neurodevelopmental abnormalities and persons with autosomal recessive or X-linked telomere brain disorders had more neurologic findings than those with autosomal dominant disease [20] (Table 1).

Table 1. CNS findings by age and mode of inheritance in patients with TBDs. Values in parentheses represent percentages. (Derived from Bhala et al, *Neurol Genet.* 2019 [20])

	X-linked or autosomal recessive		TINF2		Autosomal dominant		Gene unknown		All TBDs		
	Children n=11	Adults n=9	Children n=6	Adults n=3	Children n=4	Adults n=5	Children n=4	Adults n=2	Children n=26	Adults n=18	Total n=44
MRI Abnormalities	9 (82)	5 (56)	4 (67)	0	2 (50)	3 (60)	1 (25)	1 (50)	16 (62)	9 (50)	25 (57)
Cerebellar hypoplasia or atrophy	8 (73)	4 (44)	0	0	2 (50)	1 (20)	1 (25)	1 (50)	11 (42)	6 (33)	17 (39)
Cerebral atrophy	2 (18)	3 (33)	1 (17)	0	0	2 (40)	0	0	3 (12)	5 (28)	8 (18)
Periventricular cysts	2 (18)	1 (11)	3 (50)	0	0	1 (20)	1 (25)	0	6 (23)	2 (11)	8 (18)
Corpus callosum abnormalities	3 (27)	1 (11)	3 (50)	0	0	0	0	0	6 (23)	1 (6)	7 (16)
Small pons	2 (18)	0	1 (17)	0	2 (50)	0	0	0	5 (19)	0	5 (11)
Neurological	10 (90)	4 (44)	4 (67)	0	2 (50)	0	1 (25)	0	17 (65)	4 (22)	21 (48)
Neurodevelopmental disorder	10 (90)	4 (44)	3 (50)	0	2 (50)	0	0	0	15 (58)	4 (22)	19 (43)
Neuro-motor	8 (73)	2 (22)	3 (50)	0	2 (50)	0	1 (25)	0	14 (54)	2 (11)	16 (36)
Psychiatric	1 (9)	5 (56)	1 (17)	1 (33)	1 (25)	2 (40)	1 (25)	0	4 (15)	8 (44)	12 (27)
Depression, anxiety, OCD, ADHD, bipolar disorder	1 (9)	5 (56)	1 (17)	1 (33)	1 (25)	1 (20)	1 (25)	0	4 (15)	7 (39)	11 (25)
Autism	1 (9)	1 (11)	0	0	0	0	0	0	1 (4)	1 (6)	2 (5)
Substance abuse	0	1 (11)	0	0	0	1 (20)	0	0	0	2 (11)	2 (5)
Microcephaly	7 (64)	3 (33)	3 (50)	0	2 (5)	0 (0)	1 (25)	1 (50)	13 (50)	4 (22)	17 (39)

It is worth noting that common treatments for DC, including androgen therapy and preparatory regimens for bone marrow and stem cell transplant, can precipitate or

exacerbate psychiatric illness. As discussed more fully in Chapter 29, Navigating Telomere Biology Disorders, psychosocial sequelae of DC could also be associated with developing psychiatric problems. Living with a chronic illness that predisposes to the development of various cancers places additional psychological burdens on patients with DC and their families. Patient concerns arising from timing of diagnosis disclosure and management of aggressive treatments, such as bone marrow transplant, may initiate or aggravate pre-existing psychiatric symptoms.

Recommendations for Patients

Neurologic and psychiatric symptoms, as well as structural brain abnormalities, are common in telomere biology disorders. Comprehensive clinical care for patients with DC should include careful neurologic, neuropsychological and psychiatric assessments and consider baseline brain MRIs for early detection and appropriate specialty referral for brain-related findings. The relatively frequent finding of intellectual disabilities, autism spectrum and other learning disorders in this patient population suggests a need to routinely monitor children with DC for problems in academic performance and achieving developmental milestones. For those patients with identified concerns, early neuropsychological assessment and close collaboration with support at the child's school can help guide academic and therapeutic interventions. Specifically, speech and language, as well as occupational and physical therapy referrals may be indicated. In addition, the physiological and psychological impact of a chronic condition such as DC and its treatments can magnify underlying risks for development of psychiatric illness. Providers caring for DC individuals should include, at a minimum, a check-in about emotional symptoms at each routine visit. A referral list of local mental health providers should be maintained for patients who would benefit from further psychological and/or psychiatric evaluation or treatment.

Future Directions

Patients with DC may be a key population in which to study potential links between telomere biology and brain disorders as intact telomeres are clearly important for embryonic and adult neurogenesis and seem important in brain development though their specific roles are unknown. Longitudinal studies could help clarify the association between telomere shortening and psychiatric illness. Genotype-phenotype correlations between genes variants in DC and neuropsychiatric disorders may also yield important information on the contribution of these genes to neurodevelopment.

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