

Clinical challenges involved in the psychiatric care of patients with leukodystrophy

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INTRODUCTION

- Leukodystrophies are a group of >50 heterogeneous genetic diseases affecting 1 out of 7663 live births in the US.^{4,5}
- Mutations in >100 genes lead to defects in myelin synthesis, stability, or destruction – most are neurodegenerative.^{3,4}
- Clinically, most are marked by motor and cognitive dysfunction, as well as early death. Psychiatric symptoms are also common and may be the initial presenting symptom, and in some cases, the only observable symptoms.^{2,4}
- POLR3-related leukodystrophy is encompassed by 5 overlapping clinical syndromes that involve a mutation in the POLR3A or POLR3B genes. The prevalence is unknown but suspected to be rare with only 100 affected individuals being described in scientific literature.⁵
- Guidelines on psychiatric management in these newly characterized leukodystrophies are virtually nonexistent.

CASE BACKGROUND

- A 25-year-old female with **borderline personality disorder (BPD), substance use, and newly diagnosed POLR3A leukodystrophy** was admitted for self-inflicted gunshot wound in the setting of job loss and feelings of abandonment.
- On the medical unit, she struggled with **impulsivity (elopement attempts), lability, as well as verbal and physical agitation**
- After medical stabilization, she was transferred to the acute inpatient psychiatric hospital, where she **continued to struggle with affective dysregulation, poor distress tolerance, and ineffective coping**
- Her treatment focused primarily on **dialectic behavioral therapy (DBT) skills**; however, her **cognitive deficits and coinciding inability to consolidate these skills was not fully appreciated.**
- Her characterological "resistance" to DBT was reformulated as leukodystrophy-related cognitive impairment**

FIGURE 1. CASE

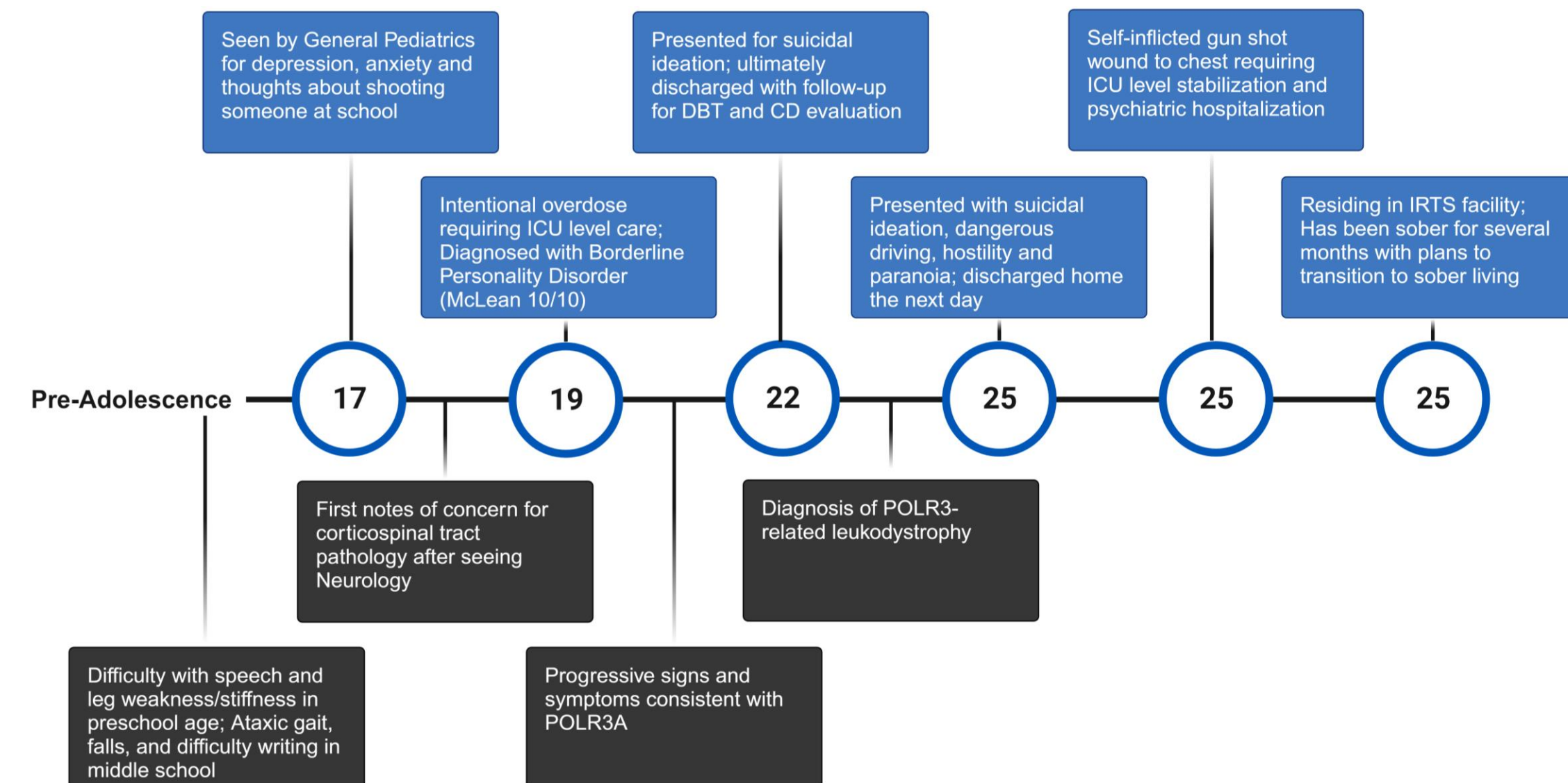


FIGURE 2. PSYCHIATRIC SYMPTOMS IN LEUKODYSTROPHIES

DISORDER	NON-PSYCHIATRIC SYMPTOMS	PSYCHIATRIC MANIFESTATIONS
POLR3-Related Leukodystrophy	Gait ataxia, dysarthria, dysmetria, tremor, abnormal eye movement, dystonia; Abnormal dentition; Hypogonadotropic hypogonadism.	Learning difficulties often seen by a plateau at school, difficulties with concentration and attention, intellectual disability, behavioral disturbances (e.g. executive functioning involving judgment)
Adult-Onset Leukoencephalopathy With ALSP	Motor impairments, including gait difficulties, pyramidal signs, and parkinsonism	Neuropsychiatric symptoms often are the initial symptoms; Progressive cognitive dysfunction and behavioral and personality changes (e.g. apathy, anxiety), mood lability
AARS2-Related Leukoencephalopathy	Extrapyramidal symptoms, cerebellar ataxia; Primary or secondary amenorrhea	Psychiatric symptoms precede neurological motor symptoms; Changes in personality, mood fluctuation, difficulties sustaining attention and planning, memory problems, psychosis, and behavior disinhibition
Adult-Onset Alexander's Disease (AOAD)	Brainstem and cerebellar symptoms (e.g. bulbar or pseudo-bulbar signs, gait ataxia, and spasticity)	Neurobehavioral changes reflecting behavioral-variant frontotemporal dementia without its specific MRI findings; Attention deficit, executive dysfunction, expressive deficits, memory loss, constricted affect, impulsivity, and symptoms of depression.
Adult-Onset ADLD	Autonomic dysfunction, progressive pyramidal signs, and ataxia	Slow cognitive decline and depressive symptoms
Cerebrotendinous Xanthomatosis (CTX)	Chronic diarrhea, juvenile bilateral cataracts, tendon xanthomas, premature atherosclerosis, pulmonary dysfunction, and osteoporosis; Psychomotor retardation, ataxia, epilepsy	Mood disorders (anxiety and depression as well as bipolar disorder), delusional disorder, and psychosis, with occasional reports of catatonia
Vanishing White Matter Disease/eIF2B-Related Disorders (VWMD)	Ataxia, spasticity; signs of ovarian failure (amenorrhea, irregular menses, and infertility)	Cognitive difficulties, depression and psychosis; stress (e.g.) head trauma or infection is a trigger for rapid neuropsychiatric deterioration
Metachromatic Leukodystrophy	Peripheral neuropathy, pyramidal signs, seizures, and ataxia; gallbladder involvement (e.g. polyps, cancer)	Cognitive and psychiatric features typical of frontal lobe dysfunction, usually behavioral disturbances and psychosis
X-Linked Adrenoleukodystrophy	Progressive spastic paraparesis and sphincteric control problems; Adrenal insufficiency and testicular dysfunction	Initial symptoms often psychiatric including signs of mania or psychosis; History of sexual dysfunction may also be present before onset of psychiatric disease and should orient the diagnosis
Cadasil	Migraines with aura, ischemic events	Psychiatric symptoms may be the only observable symptom of the disorder; Mood disturbances associated with adjustment disorders, unipolar major depression, bipolar disorder, psychotic disorders
Carasil	Recurrent ischemic events; alopecia	Disorientation, behavioral disturbances, compulsive behavior, and personality changes, including irritability and emotional lability
Carasal	Migraine; stroke; dysphagia; gait disturbance	Cognitive impairment, mild behavioral changes and disinhibition

DISCUSSION

- Early recognition is critical as leukodystrophies may initially masquerade as or be masked by psychiatric conditions.
- Awareness of the clinical features of leukodystrophies is particularly critical to provide equitable care to disproportionately affected populations, including patients of racial/ethnic minorities, as these diseases are known to be underdiagnosed despite the same or higher pathogenic gene alleles in these individuals.¹
- Clinical features increasing probability of co-morbid leukodystrophy include:
 - Neurological signs:** gait difficulties, motor impairments, seizures
 - Endocrine signs:** amenorrhea, alopecia, infertility
 - Resistance to standard treatment modalities**
- Ideal clinical management for patients with leukodystrophy and psychiatric comorbidities would include:
 - Collaborative, multidisciplinary care**
 - Consideration of a cognitive rehabilitation framework**
 - Dialectical behavioral therapy-skills system**
- Tips for managing anchoring bias and countertransference: Be Minnesota **NICE**
 - Normalize** – these are universal experiences in medicine and otherwise
 - Insulate** – collaborate with multidisciplinary team to "keep the differential alive"
 - Challenge** – in broadening the differential once closed
 - Educate** – ourselves and others about leukodystrophies

REFERENCES



DISCLOSURE

The authors have no financial conflicts of interest or personal relationships to disclose that are relevant to the concepts discussed in this poster.