Clinical challenges involved in the psychiatric care of patients with leukodystrophy

Casey K. Gilman, M.D. 1, Kirsten Utter, M.D. 1, Jacob Ellis, M.D. 1, Nicholas Allen, M.D. 1
1Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA

INTRODUCTION

- Leukodystrophies are a group of >50 heterogeneous genetic diseases affecting 1 out of 7663 live births in the US. 1,2
- 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 accompanied by overlapping clinical syndromes that involve a mutation in the POLR3A or POLR3B genes. The prevalence is unknown, but suspected to be rare with only 10 affected individuals being described in scientific literature. 5
- Guidelines on psychiatric management for 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 medical stabilization, 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 characteristic “resistance” to DBT was recharacterized as leukodystrophy-related cognitive impairment

FIGURE 1. CASE

FIGURE 2. PSYCHIATRIC SYMPTOMS IN LEUKODYSTROPHIES

<table>
<thead>
<tr>
<th></th>
<th>PSYCHIATRIC SYMPTOMS IN LEUKODYSTROPHIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISORDER</td>
<td>NON-Psychiatric SYSTEMS</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>POLR3-Related Leukodystrophy</td>
<td>Gait ataxia, dysarthria, dysesthesia, tremor, abnormal involuntary movements, abnormal mentation, hypogyria, hypertrophic hyponogadism.</td>
</tr>
<tr>
<td>Adult-Onset Leukodystrophy With ALS</td>
<td>Motor impairs, including gait difficulties, pyramidal signs, and paresthesia.</td>
</tr>
<tr>
<td>AANL-Related Leukodystrophy</td>
<td>Extrapyramidal symptoms, cerebellar ataxia. Primary or secondary amenorrhea.</td>
</tr>
<tr>
<td>Adult-Onset Alexander’s Disease (AOAD)</td>
<td>Brainstem and cerebellar symptoms (e.g. bulbar or pseudobulbar signs, gait ataxia, and dysphagia).</td>
</tr>
<tr>
<td>Adult-Onset ADLCD</td>
<td>Autonomic dysfunction, progressive pyramidal signs, and ataxia.</td>
</tr>
<tr>
<td>Cerebrotendinous Xanthomatis (CTX)</td>
<td>Chronic diarrhea, juvenile bilateral cataracts, pan-endothelial, premature adrenarcheal, pulmonary dysfunction, and osteopathy; Psychiatric relaetions, stess, apathy.</td>
</tr>
<tr>
<td>Von Hippel-Lindau Disease (VWD)</td>
<td>Nausea, vomiting, signs of ovarian failure (amenorrhea, irregular menses, and infertility).</td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy</td>
<td>Peripheral neuropathy, pyramidal signs, seizures, and ataxia; gallbladder involvement (e.g. gallstones, cancer).</td>
</tr>
<tr>
<td>X-Linked Adrenoleukodystrophy</td>
<td>Progressive spastic paraparesis and spastic control problems; Adrenal insufficiency and leukodystrophy.</td>
</tr>
<tr>
<td>Cerebral Migraine with aura, ischemic events</td>
<td>Psychiatric symptoms may be the only observable symptoms of the disorder; Mood disturbance associated with adjustment disorders, unipolar major depression, bipolar disorder, psychotic disorders, and psychosis.</td>
</tr>
<tr>
<td>Rett Syndrome</td>
<td>Recurrent somatic events; alopecia.</td>
</tr>
<tr>
<td>Cerebral Migraine, stroke, dysphagia, gait disturbance</td>
<td>Cognitive impairment, mild behavioral changes and disorientation.</td>
</tr>
</tbody>
</table>

DISCUSSION

- Early recognition as critical to leukodystrophies may initially masquerade as or be masked by psychiatric conditions. 3
- 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 pathologic gene alleles in these individuals. 5
- Clinical features increasing probability of co-morbid leukodystrophy include:
  - Neurological signs: gait difficulties, motor impairs, 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 incarcerated bias and counterterrorism: Be Minnesota NICE
- Normalise – these are universal experiences in medicine and otherwise
- Insulate – collaborate with multidisciplinary learn to “keep the differential alive”
- Challenge – in broadening the differential once closed
- Educate – ourselves and others about leukodystrophies

REFERENCES

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

© Mayo Foundation for Medical Education and Research

1. PubMed
2. Textbook
3. Journal
4. Conference
5. Personal communication