Late-Onset Tay-Sachs (LOTS) Disease Presenting with Psychosis and Cerebellar Atrophy: A Model Case Describing an Integrated Approach to Rare Diseases with Neuropsychiatric Manifestations

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Introduction

Late-onset Tay-Sachs (LOTS) disease is a rare **Hexosaminidase A (*HEXA*) disorder** with relevance for **consultation-liaison psychiatrists** practicing in various settings[1]

Patients with LOTS typically develop **progressive neurologic and psychiatric manifestations** as **teens and young adults** – variability in symptoms often leads to **missed or delayed diagnoses[2]**

This case report describes the **presentation, diagnostic evaluation, and treatment** of a **22-year-old male with no prior medical or psychiatric history** who had **laboratory testing results diagnostic of LOTS**

Presenting Symptoms and Imaging Findings

- **Background:** 22-year-old male with no known prior medical or psychiatric history, previously completing coursework as a junior in college
- **Family history:** Twin brother with autism spectrum disorder, no family history of mood or psychotic disorders
- **From six to three months prior to admission:**
  - Engaged in bizarre behaviors, including wiring money to strangers online
  - Attended summer field camp in the Western US for six weeks and sent family members frequent text messages demonstrating atypical thought content
  - Returned to college campus in the Midwest, but continued to wear clothing and gear from field camp
  - Fell off bunk bed at school and sustained a 3-cm head laceration requiring staples, but no head imaging was completed during emergency department evaluation
  - Started running long distances (despite no prior running experience), sending rambling emails to professors, and getting lost in the community
  - During a family outing, flees a golf range and requires law enforcement assistance to be brought home
- **Imaging completed three months prior to admission:**

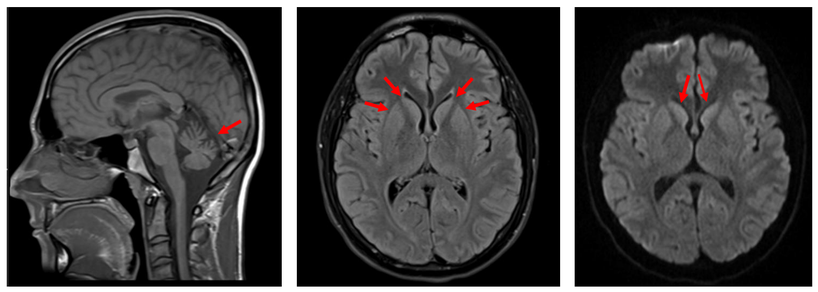

Figure 1: Brain MRI demonstrating **marked cerebellar atrophy** (left, T1 sequence) and **bilaterally symmetric increased T2 signal** in the **caudate nuclei** and **basal ganglia** (center, T2 FLAIR sequence; right, DWI sequence).

Treatment Course

First hospital admission (14 days)	• Admitted to Psychiatry and transferred to Internal Medicine for extensive metabolic, infectious, and inflammatory testing • **Findings:** MRI brain demonstrates ***cerebellar atrophy disproportionate for age[3]***, elevated TSH with normal T4 • **Exam:** Mild intermittent dysarthria and gait abnormalities documented • **Treatment:** Levothyroxine, five-day course of IV steroids for presumed autoimmune encephalitis, olanzapine titrated for psychotic symptoms
Return home	• Able to participate in college class, but sleeping greater than 14 hours/day • Delusional and disorganized thinking worsens at home, necessitating re-evaluation
Second hospital admission (12 days)	• Admitted to Psychiatry with disorganized behaviors (e.g., urinating on the floor) • **Exam:** Extremity movements and gait noted to be normal on admission • **Treatment:** No changes to treatment plan, discharged to attend a scheduled Autoimmune Neurology appointment
Return home	• Received three-day course of IV steroids – ***thought process becomes more delusional and disorganized***
Third hospital admission (7 days)	• Re-admitted to Psychiatry • **Exam:** Malar rash sparing nasolabial folds, mimicking movements, mild hand tremor, shortened stride • **Treatment:** Five days of IVIG, cross-titrated to risperidone due to urinary retention
Fourth hospital admission (26 days)	• Re-admitted to Psychiatry • **Exam:** Rigid posture, shuffling gait, diminished facial movements, and frequent bilateral upper lip twitching • ***Rigidity and facial movements improved with discontinuation of risperidone[4]*** • **Treatment:** Switched to quetiapine and lorazepam for psychotic symptoms and sleep
Return home	• Somnolent, frequent talking and laughing to self, required 24-hour supervision for safety concerns
Fifth hospital admission (14 days)	• Admitted to Psychiatry for impulsivity, disorganized thinking, auditory and visual hallucinations, and observed responses to internal stimuli • **Exam:** ***Moderate hypokinetic dysarthria***, left-sided dysmetria with coordination testing • ***Ultra-rapid whole genome sequencing completed with Clinical Genomics team*** • **Treatment:** Psychotic symptoms, thought organization, and sleep improved with aripiprazole and lorazepam

Confirmatory Testing

- Ultra-rapid whole genome sequencing completed through Variantyx Laboratories identified a **de novo pathogenic variant in the *HEXA* gene**, specifically a **paternally inherited c.805G>A (p. Gly269Ser)** and a **maternally inherited c.677C>T (p. Ser226Phe)**
- Biochemical testing identified a **low Hexosaminidase percent A level of 3%, confirming the diagnosis of LOTS**

Learning Points and Future Directions

- **Late-onset Tay-Sachs (LOTS) disease** is a **rare *HEXA* disorder** which may present with both neurologic and psychiatric symptoms in teens and young adults
  - Prominent features in this case included **psychotic symptoms, moderate hypokinetic dysarthria**, and a brain MRI demonstrating **cerebellar atrophy**
- **Key learning points:**
  - Need to consider rare diseases in the differential diagnosis when patients develop new-onset neurologic and psychiatric symptoms[5]
    - Ex: Gaucher's disease, Niemann-Pick disease, mitochondrial disorders, etc.
  - Importance of assessing response to treatment, including failure to respond to first-line treatments, as part of the diagnostic process
    - Case demonstrated failure to respond to steroid treatment, IVIG, and three antipsychotic medications
  - Role of subspecialty expertise (Neurology, Neuroradiology, Clinical Genomics, etc.) in the evaluation of patients with otherwise unexplained imaging findings
    - Relevant for C-L psychiatrists who may liaise within multidisciplinary teams
  - Benefits of timely access to whole genome sequencing for patients presenting with rare diseases with neuropsychiatric manifestations
    - 2022 recommendations suggest introducing whole genome sequencing when it may improve quality, efficiency, and/or diagnostic yield[6]
- **Future directions for LOTS patient care:**
  - Clarifying and describing the variety of psychiatric symptoms seen in this condition – ex: distressing visual hallucinations (sharks, knives, etc.)[7]
  - Updating data regarding the safety and efficacy of psychiatric medications in this population (including second-generation antipsychotics)[4]
  - Assessing safety of and response to electroconvulsive therapy if needed for severe depression or catatonia[8]

References available via QR code

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