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# Clinical Reasoning: Juvenile neurocognitive decline

## A "snaky" diagnosis

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### SECTION 1

**Clinical presentation.** A 13-year-old girl referred from psychiatry had a 3-year history of declining school performance and behavioral change. She was previously a high achiever academically, and was healthy until age 10 years. Over several months, she showed deterioration in schoolwork and became socially withdrawn, culminating in significant intellectual disability requiring resource help and constant supervision. At age 13 years, she presented with a frontally mediated behavior pattern characterized by agitation, poor self-awareness, perseveration of speech and action, impaired working memory, poor sequencing, motor restlessness, and apathy. She also exhibited echolalia, self-mumbling, forgetfulness, and emotional lability. Fine motor skills deteriorated and she was generally clumsy. Medical, birth, and family histories were noncontributory (she had 2 healthy siblings). During examination, she behaved immaturely and was disinhibited and emotionally labile. Examination of outstretched arms revealed subtle myoclonic jerks (video on the *Neurology*® Web site at Neurology.org). Neurologic examination was otherwise normal, including funduscopy.

**Questions for consideration:**

1. How would you classify this presentation?
2. What is your initial approach to investigations?

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## SECTION 2

**Disease categorization.** Neurodevelopmental regression (progressive intellectual and neurologic deterioration) may occur in previously healthy children or in children with previously presumed static encephalopathies/developmental delay where the regression has not yet commenced. Regression may also occur in children with or without preexisting developmental disorders where there may be suggestive patterns of presentation (e.g., autistic regression, Down syndrome disintegrative disorder, childhood disintegrative disorder).

Age at onset, history, examination, and pattern of involvement (i.e., CNS, with or without peripheral or multisystem involvement) are the most important components to preliminary disease categorization. Particular attention to the degree of gray matter (e.g., seizures/cognitive/behavioral decline) vs white matter involvement (e.g., pyramidal signs), extrapyramidal signs (including movement disorder), ataxia, neuropathy, ophthalmologic involvement, visceromegaly, and skin manifestations guide specific investigations.[1]

**Differential diagnoses and investigations.** The differential diagnosis and approach to investigations for neurodevelopmental regression is often broad, particularly when initial presentation is nonspecific. Neurometabolic genetic disorders comprise the most commonly identified etiologies overall. Prominent cognitive regression (over months to years) in a previously healthy juvenile is a relatively rare presentation and a variety of conditions should be considered (table e-1). In this case, as myoclonus accompanied the cognitive presentation, the progressive myoclonus epilepsies (PMEs) should be considered.

A variety of first-line blood and urine screening tests and neuroimaging (brain magnetic resonance scan in all cases) is recommended.[1,2] Neurophysiologic investigations—e.g., EEG, nerve conduction studies/EMG, visual evoked responses (VER), and electroretinogram (ERG)—may help in further delineating the underlying pathophysiologic processes.

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## SECTION 3

**Preliminary diagnosis and clinical evolution.** EEG showed slowing of the background with runs of rhythmic delta activity, and occasional generalized spike-wave epileptiform discharges, in addition to epileptic myoclonus (upper limb jerks) (figure 1A, video). Photic stimulation, hyperventilation, and sleep did not bring out further EEG abnormalities. MRI brain demonstrated subtle cerebellar atrophy and excluded hydrocephalus, mass lesions, or white matter abnormality (e.g., leucodystrophy). Baseline blood tests and metabolic screening tests were all noncontributory (table e-2).

PME was now the principal diagnosis. Over the subsequent months and years, cognitive deterioration progressed (figure 1B) and occasional overt seizures emerged (myoclonus and occasional tonic-clonic seizures), which did not respond to antiepileptic drugs (levetiracetam/clonazepam/clobazam/valproate). EEG background remained slow, with spike-wave bursts becoming more elaborate and emergence of a photoparoxysmal response.

**Questions for consideration:**

1. What is your investigative approach to childhood-onset PME?
2. How would you narrow the differential diagnosis?

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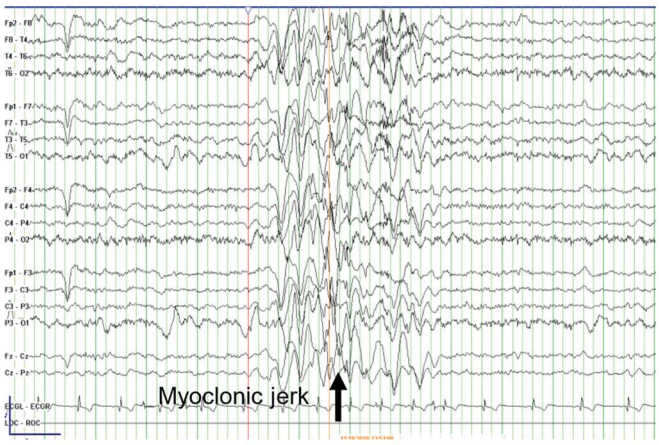
**Figure 1** EEG at presentation and cognitive profile over time

A




B

| WISC-IV Scores | 13 years | 14 years | 15 years | 17 years |
|---|---|---|---|---|
| Verbal comprehension | 81 | 67 | 61 | 50 |
| Perceptual reasoning | 82 | 67 | 75 | 45 |
| Working memory | 56 | 77 | 62 | 50 |
| Processing speed | 68 | 68 | 59 | 50 |
| **Full-scale IQ** | **79** | **62** | **57** | **40** |

(A) EEG shows elaborate burst of generalized spike-wave activity. Myoclonus/jerks occurred during some of these bursts (see video for clinical myoclonus). (B) Composite Wechsler Intelligence Scale for Children (WISC) scores, established 3 years into course of illness presentation, demonstrate progressive cognitive decline.

## SECTION 4

**Approach to PME.** Investigation from the outset concentrated on PME (table e-3); however, considering age at presentation and associated symptoms, parallel investigations were extended to screen for further neurometabolic, acquired inflammatory, autoimmune, and infectious disorders (table e-2).

Lafora body disease is one of the most common causes of PME associated with cognitive decline, but skin histopathology (complete sweat gland duct visualization) was normal. The epilepsy in this case was not as severe as in Lafora body or Unverricht-Lundborg disease. However, Unverricht-Lundborg disease is the most common cause of PME (usually with preserved cognition) and was nevertheless excluded by *CSTB* mutation analysis.

The neuronal ceroid lipofuscinoses, the most common cause of PME in early childhood, could present at this age, and were virtually excluded by negative investigations as follows: vacuolated lymphocytes, enzyme analysis of serum palmitoyl-protein-thioesterase, tripeptidyl-peptidase, buffy coat/lymphocyte and skin biopsy for ultrastructural analysis, VER, ERG, and *CLN6* gene sequencing.

Muscle biopsy for mitochondrial respiratory chain enzyme analysis, mitochondrial depletion studies, mitochondrial DNA sequencing, and staining for myoclonic epilepsy with ragged-red fibers was negative. Although MRI was not typical, CSF analysis for markers of prion disease/Creutzfeldt-Jakob disease (S-100b, 14-3-3) and for measles antibodies (subacute sclerosing panencephalitis) were negative. Blood chitotriosidase level and filipin staining of skin fibroblasts for Niemann-Pick type C disease were normal. Single gene testing for other causes of PME, i.e., juvenile Huntington disease (*HTT*) and childhood-onset dentatorubral-pallidoluysian atrophy (*ATN1*), were negative.

At age 15 years, there was ongoing cognitive and behavioral decline with minimal motor signs and rare seizures, without significant change in EEG or neuroimaging. Brain biopsy was considered to determine further clues to underlying pathology; however, prior enrollment into the Helsinki Progressive Myoclonus Epilepsy Study[3] identified a de novo heterozygous mutation in *SERPINI1* (c.1175 G>A; p.G392E) consistent with a diagnosis of neuroserpinopathy.

## DISCUSSION

Neurodevelopmental regression encompasses a wide range of inherited and acquired neurologic disorders. Finding a specific diagnosis for a significant proportion of children has not always been possible, even following exhaustive investigations. In 2010, one epidemiologic study reported 1114 diagnoses of 2,636 affected children spread across 147 different disorders.[2] Since then, advances in next-generation sequencing technology have allowed us to determine the genetic basis of many such disorders more efficiently. However, in order to accurately assign molecular diagnosis to a condition utilizing next-generation sequencing, our approach still very much depends on careful consideration of the clinical features. In this report, age at onset, history, physical signs, neuroimaging, and EEG enabled categorization into PME, the key to appropriate interpretation of the exome sequencing findings and diagnosis of neuroserpinopathy.

PMEs are a group of predominantly recessive disorders characterized by myoclonic seizures, tonic-clonic seizures, and neurologic deterioration. Traditionally, investigations for specific PMEs have been based on age at onset, coexisting symptoms and signs (preservation or loss of cognition), enzyme assays, neurophysiologic tests (EEG, VER, ERG), tissue biopsy (usually skin), and sequential gene testing. In many cases, even with such investigations, a specific etiologic diagnosis is not made.[4,5] In this case, despite extensive initial investigation, and exclusion of the commonly associated PME disorders, molecular diagnosis remained elusive until exome sequencing identified a *SERPINI1* mutation, a rare cause of PME. Similarly, advances in next-generation sequencing have clarified the genes responsible for several novel PMEs[3] (table e-3) and will likely lead to earlier diagnoses in the future, obviating the need for protracted or irrelevant neurometabolic and single gene investigations.[3] However, precise phenotyping will remain the key to molecular interpretation of PME diagnoses in the genomics era and will allow us to expand the phenotypes associated with this group of epilepsies.

*SERPINI1* codes for a neuron-specific serine proteinase inhibitor (serpin or neuroserpin), which plays an important role in protecting synapses. When mutated, serpin progressively polymerizes in endoplasmic reticulum, neuropathologically characterized by intracytoplasmic rounded inclusions (Collins bodies, figure e-1). Correlation exists among the types of mutation, instability of the conformational protein, and severity of presentation.[6] Our case confirms a genotype–phenotype correlation[6] where the mutation (glycine replaced by glutamate at position 392, exon 8) leads to greatest disruption of serpin molecule stability, earlier age at onset, and clinical severity. Only one other girl with the G392E mutation, PME, and dementia (who died at 19 years) has been described.[6,7] Mutations affecting other codons lead to less marked serpin molecule instability and later onset manifestations including dementia (table e-4).

PMEs are a diagnostically challenging group of disorders that typically, although not exclusively, present in childhood or adolescence in association with neurologic regression. In patients with unexplained

PME and prominent cognitive decline (particularly frontal lobe dysfunction), neuroserpinopathy should be included in the differential diagnosis. Next-generation sequencing has transformed our approach to diagnosis, characterization, and discovery of new PME disorders[3] and will likely reduce the burden of investigations for PME and other neurodevelopmental disorders. In the genomics era, however, the clinical approach to these disorders guides interpretation and genetic diagnosis.

## AUTHOR CONTRIBUTIONS

N.A. wrote the first draft and edited subsequent drafts of the manuscript. M.D.K. initiated the project and edited all drafts of the manuscript. A.S., C.M., T.N., and M.D.K. provided clinical care. All authors synthesized data for publication and approved the final manuscript.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## DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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