Clinical Reasoning: A 57-Year-Old Man With Chronic Gait Unsteadiness and Diminished Lower Extremity Sensation

Radhika Rawat,[1] Sarah Marie Brooker,[2] Grace Elizabeth Naylor,[2] Marcello Cherchi,[3] and Puneet Opal[4]

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Correspondence
Dr. Rawat
radhika.rawat@northwestern.edu

Abstract

A 57-year-old man presented with a 5-year history of progressive gait unsteadiness, diminished lower extremity sensation, and a chronic cough. His symptoms began as episodic balance issues and visual disturbances but progressively worsened, leading to frequent tripping. Physical examination revealed sensory deficits in the lower extremities and cerebellar signs, including nystagmus, dysmetria, and a broad-based gait. Readers will walk through a stepwise approach to the case, developing a comprehensive differential diagnosis and questioning likely etiologies to arrive at a final diagnosis. This case illustrates the challenges of diagnosing complex ataxia and highlights the importance of considering multisystem disorders.

Section 1

A 57-year-old man presented with 5 years of gait unsteadiness. Five years before presentation, he began noticing gait imbalance in the dark and after only 1 alcoholic drink. He became abstinent from alcohol because of these symptoms. His symptoms continued to progress and became constant. Four years before presentation, he noticed blurry vision, especially when looking to either side. He then began developing numbness in his feet. Additional symptoms included a 30-pound unintentional weight loss over 2 years and 5 years of chronic dry cough. He reported frequent tripping without falls and endorsed mild episodic headaches without aura, prodrome, photophobia, or phonophobia. He denied diplopia and dizziness. Medical and surgical histories were unremarkable. He took no medications, antiepileptics, neuroleptics, or mood stabilizers.

He had Polish ancestry and family history of type 2 diabetes, hypertension, coronary artery disease, and Alzheimer dementia, without ataxia or other neurodegenerative conditions. His siblings and children were healthy.

He lived in a suburban 1-family home, worked in a metal factory, and was sexually active with only his spouse. He stopped drinking alcohol 5 years ago, had no substance or smoking history and no recent travel history, and was fully immunized.

On examination, his speech was fluent without dysarthria or voice changes. His pupils were equal and reactive, with visual acuity 20/30 bilaterally. Dilated fundoscopic examination with slit-lamp testing was unremarkable. Downbeat nystagmus was present during vertical smooth pursuit, and horizontal smooth pursuit was interrupted by saccadic intrusions. Horizontal optokinetic responses were diminished in amplitude. Video head impulse testing suggested bilateral vestibular weakness with compensatory saccades. Dix-Hallpike testing was negative. Visual fixation suppression was normal.

[1]Medical Scientist Training Program, Feinberg School of Medicine, Northwestern University, Chicago, IL; [2]Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, IL; [3]Department of Neurology, University of Chicago, IL; and [4]Denning Ataxia Center, Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, IL.

Cranial nerves and hearing were intact. Motor examination revealed normal strength and tone without bradykinesia. Sensory examination demonstrated absent vibration, proprioception, and temperature sensation below the ankles, preserved in the upper extremities. He had mild dysmetria on finger-to-nose testing; dysdiadochokinesia on rapid alternating movements; 3+ reflexes in the biceps, triceps, brachioradialis, and patellar tendons; and absent Achilles reflexes. The plantar reflex was downgoing bilaterally. The Hoffman sign was negative bilaterally. His gait was broad-based, the Romberg sign was positive, and he was unable to perform tandem gait.

Questions for Consideration:

1. Where would you localize these findings?
2. What categories of diagnoses are in your differential?

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Section 2

Gait ataxia is an important feature of this case. These questions guide the ataxia workup:

1. Time course: is it acute, subacute, or chronic?
2. Ataxia features: is it due to cerebellar dysfunction, sensory impairment, or both?
3. Additional symptoms: are there other localizing signs?

Time course is crucial. Acute onset suggests neurologic emergencies while subacute or chronic cases are usually suited for outpatient evaluation. His symptoms were chronic and progressive.

His ataxia features should be assessed next. Nystagmus, dysmetria, dysdiadochokinesia, and broad-based gait indicate cerebellar dysfunction. Decreased temperature and vibration senses, and proprioception show sensory involvement. His video head impulse testing and rotatory chair testing indicate bilateral vestibular weakness. Overall, his examination suggests a mixed cerebellar and sensory ataxia. In adults with chronic progressive cerebellar ataxia and sensory impairment, the differential diagnosis is broad, including toxic-metabolic, autoimmune, neoplastic, and genetic ataxias. This patient's occupational history suggested chronic heavy metal exposure (e.g., to lead and mercury), which can cause neurotoxicity. Systemic symptoms (weight loss and chronic cough) raise concerns for paraneoplastic or infectious causes.

Genetic ataxias, either inherited or de novo, may present progressively in adulthood even without family history. Delayed-onset variants such as late-onset Friedreich ataxia and fragile X–associated tremor/ataxia syndrome (FXTAS) often appear after age 50. Autosomal dominant spinocerebellar ataxias (SCAs) (SCA6, SCA8, SCA12, SCA27B, and others) and sporadic degenerative ataxias, including multiple system atrophy–cerebellar type, can also manifest in middle age or later. Other neuropathic conditions with overlapping features (e.g., sensory ataxic neuropathy with dysarthria and ophthalmoparesis or mitochondrial syndromes such as Roussy-Lévy) should also be considered. Comprehensive testing is essential to differentiate among these possibilities.

Question for Consideration:

1. What further testing would you order to narrow the differential diagnosis?

GO TO SECTION 3

Section 3

The diagnostic workup of cerebellar ataxia should be systematic (Figure 1). To rule out structural etiologies, an initial MRI brain was performed, and it revealed mild cerebellar atrophy without brainstem lesions or damage to the basal ganglia (Figure 2A). Spine MRI showed mild degenerative changes of the lumbar spine. Initial laboratory tests were unremarkable (Figure 2B).

Nerve conduction studies demonstrated absent sensory nerve action potentials across all tested nerves, including the right median, right radial, bilateral sural, and bilateral peroneal nerves. Motor studies of the bilateral tibial and peroneal nerves were normal. Therefore, the nerve conduction study was consistent with severe sensory neuropathy or sensory neuronopathy. Electromyography showed no spontaneous activity, normal motor unit morphology, and intact recruitment, confirming a pure sensory neuropathy without motor involvement.

Secondary testing (Figure 2C) was largely unremarkable. Notable findings included borderline low iron and hemoglobin A1c of 6.4%. Heavy metal testing, autoimmune panels, celiac laboratory results, gammopathy testing, and syphilis screening were negative. Chest X-ray and PET-CT showed no infiltrate or malignancy.

Question for Consideration:

1. Because secondary testing was unrevealing, the patient was consented for genetic testing. Which type(s) of genetic testing would be appropriate at this point?

Genetic testing was first performed using the Spinocerebellar Ataxia Repeat Expansion and Ataxia Xpanded panels (Genedx), which tested for single-nucleotide variants, copy number variants, and some DNA repeat disorders, including *POLG* (associated with mitochondrial ataxia syndromes) and *SPG7* (overlapping with some hereditary spastic paraplegias). They returned negative, effectively ruling out many autosomal dominant and recessive ataxias and common repeat expansion disorders, including the most common SCAs.

Because these tests were limited to exon sequences, some ataxias caused by DNA repeat expansions—such as FXTAS, adult-onset Friedrich ataxia, and cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS)—might not be detected. Specialized intron sequencing for repeat expansions was sent and revealed a biallelic AAGGG repeat expansion in the *RFC1* gene (University of Chicago Genetic Services Laboratory).

Discussion

CANVAS is an autosomal recessive neurodegenerative disorder caused by sequence variations in the replication factor C subunit 1 (*RFC1*) gene, which encodes a subunit of the DNA polymerase accessory protein involved in replication and repair.

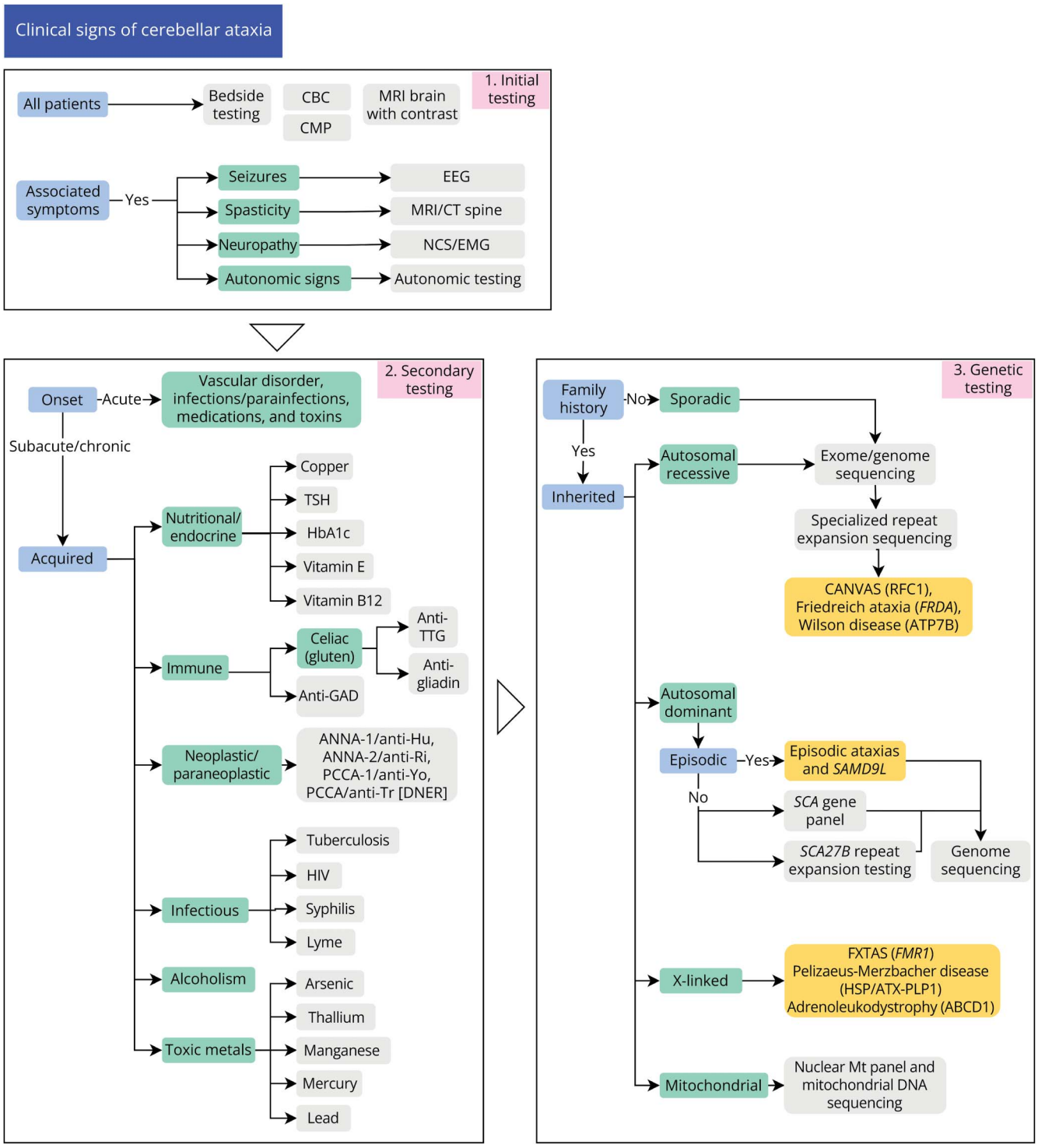
CANVAS classically presents in adults older than 50 years with sensory neuropathy, cerebellar ataxia, and bilateral vestibular areflexia. For unclear reasons, a chronic cough often precedes neurologic symptoms. Although headaches are not commonly described, patient presentations vary. Given its diverse symptomatology, a combination of clinical findings and targeted diagnostic testing is essential for diagnosis.

On examination, despite absent or reduced sensory nerve action potentials, patients sometimes display normal to brisk deep tendon reflexes.[1] Bedside head impulse testing should prompt further evaluation. The most specific finding is an abnormal visually enhanced vestibulo-ocular reflex, combining impaired VOR due to vestibular dysfunction and impaired smooth pursuit due to cerebellar dysfunction.[2] Nerve conduction studies typically reveal a sensory neuropathy or neuronopathy affecting both the upper and lower extremities.[3] Brain imaging may reveal cerebellar atrophy, particularly of the dorsal vermis, and neuropathologic examinations may show loss of Purkinje cells and neurons in the dorsal root, vestibular ganglia, and posterior columns.[3-5]

Diagnosing CANVAS involves genetic testing for the AAGGG repeat expansion in the *RFC1* gene.[6,7] However, RFC1 expansions are not detected on standard ataxia panels or whole-exome sequencing,[6] making CANVAS an underrecognized cause of late-onset ataxia and sensory neuropathy.[2,6,8] In a study of idiopathic sensory neuropathy, 34% of affected patients had homozygous *RFC1* expansions,[9] suggesting significant underdiagnosis. Because CANVAS's early clinical presentation often lacks specificity and *RFC1* genetic testing is not standard, and without a high index of suspicion, the diagnosis may be overlooked.

The carrier frequency of the expansion is 0.7%. Some cases involve compound heterozygotes, with pentanucleotide expansion on 1 allele and a truncating nonsense mutation on the other.[10] Pathogenic repeats such as AGGGC, AAGGC, and AGAGG have also been identified,[11] further suggesting underdiagnosis due to limitations in current genetic testing. AAGGG expansion on 1 allele is not enough to cause CANVAS. If a patient has a CANVAS phenotype but only 1 allele shows expansion, further genetic analysis is warranted. They may have a truncating mutation or novel expansion on the other chromosome.[7] It remains unclear how *RFC1* sequence variations, potentially involving a loss of function in RFC1's role in DNA repair, cause neuronal toxicity. Other genes in the DNA damage pathway (e.g., *TDP1*, *SETX*, and *COA7*) also lead to ataxias,[9,12,13] suggesting a possible mechanism.

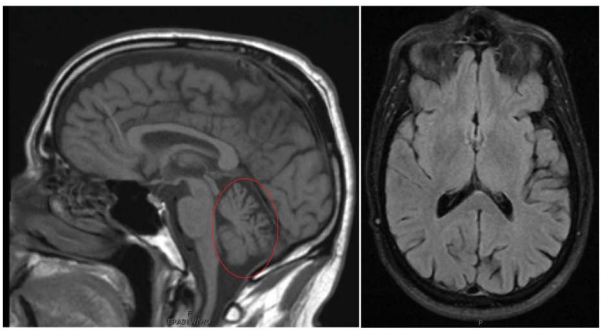
Figure 1 Systematic Approach to Cerebellar Ataxias



This flowchart illustrates the general diagnostic pathway for patients presenting with clinical signs of cerebellar ataxia. Initial testing includes a detailed history and physical examination, basic laboratory studies (e.g., complete blood count and metabolic panels), imaging, and symptom-guided neurophysiologic tests (e.g., NCS/EMG and autonomic testing). Based on the presentation, secondary testing should target potential acquired causes (e.g., nutritional deficiencies, autoimmune processes, infections, and/or toxins). If previous testing is inconclusive or a family history suggests a genetic etiology, genetic testing (e.g., gene panels and exome/genome sequencing) may be pursued to identify hereditary ataxias. Light blue boxes represent key components of history and examination to guide the evaluation. Gray boxes represent imaging modalities and tests. Green boxes represent potential etiologies of cerebellar ataxia. Yellow boxes highlight select clinical diagnoses and disorders relevant to this case. ABCD1 = ATP binding cassette subfamily D member 1; Anti-GAD = anti-glutamic acid decarboxylase; Anti-Tr/DNER = Delta/Notch-like epidermal growth factor–related receptor; Anti-TTG = anti-tissue transglutaminase; ATP7B = ATPase copper transporting beta; CBC = complete blood count; CMP = comprehensive metabolic panel; EMG = electromyography; FMR1 = fragile X mental retardation 1; FRDA = Friedreich ataxia; FXTAS = fragile X–associated tremor/ataxia syndrome; HbA1c = hemoglobin A1c; HSP = hereditary spastic paraplegia; Mt = mitochondrial; NCS = nerve conduction study; PCCA = Purkinje cell cytoplasmic antibody; PLP1 = proteolipid protein 1; RFC1 = replication factor C subunit 1; SCA = spinocerebellar ataxia; SAMD9L = sterile alpha motif domain–containing protein 9-like; TSH = thyroid-stimulating hormone.

Figure 2 Case Imaging and Results

A. Imaging



B. Preliminary laboratory results

Component	Reference	Value
CMP		
GOT/AST	≤37 Units/L	20
GPT/ALT	<64 Units/L	34
Alk phosphatase	45–117 Units/L	70
Albumin	3.6–5.1 g/dL	4.7
Protein, total	6.4–8.2 g/dL	7.7
Globulin	2–4 g/dL	3
A/G ratio	1–2.4	1.6
Bilirubin, total	0.2–1 mg/dL	0.7
Calcium	8.4–10.2 mg/dL	9.5
BUN/ Cr ratio	12–20	15
Sodium	135–145 mmol/L	138
Potassium	3.4–5.1 mmol/L	3.8
Chloride	98–107 mmol/L	106
Carbon dioxide	21–32 mmol/L	26
Anion gap	10–20 mmol/L	10
Glucose	65–99 mg/dL	92
BUN	6–20 mg/dL	14
Creatinine	0.67–1.17 mg/dL	0.9
GFR	>90 mL/ min/ 1.73 m^2	>90

Component	Reference	Value
CBC		
WBC	4.2–11 K/mcL	7
RBC	4.5–5.9 mil/mcL	5.2
HGB	13–17 g/dL	15
HCT	39–51 %	43
MCV	78–100 fl	83
MCH	26–34 pg	28
MCHC	32–36.5 g/dL	34
PLT	140–450 K/mcL	220
Neutrophil %		58
Lymphocyte %		34
Mono %		6
Eosinophil %		1
Basophil %		1

C. Secondary laboratory results

Component	Reference	Value	
Metabolic/nutritional			
TSH	0.35–5.00 µU/mL	0.77	
Hemoglobin A1c	<6.5%	0.064	
CK	39–308 Units/L	129	
Vitamin B12	**211–911 pg/mL**	**>2,000**	***High**
Vitamin E, alpha	6.0–23.0 mg/L	17	
Vitamin E, gamma	**0.3–3.2 mg/L**	**0.2**	***Low**
Folate	≥5.5 ng/mL	23	
Vitamin D, 25-Hydroxy	**30.0–100.0 ng/mL**	**117.4**	***High**
Metals			
Ceruloplasmin	22.0–58.0 mg/dL	27	
Lead, blood - venous	≤4.9 mcg/dL	<2.0	
Zinc, blood	70–120 mcg/dL	78	
Manganese, blood	4.4–15.2 ug/L	5.7	
Arsenic, blood	≤5.0 mcg/dL	<1.0	
Mercury, blood	≤1.0 mcg/dL	<1.0	
Arsenic, urine	≤100 mcg/L	<10	
Mercury, Urine	≤20 mcg/L	<2	
Iron studies			
Ferritin	26–388 ng/mL	174	
Iron	**65–175 mcg/dL**	**58**	***Low**
Iron binding capacity	250–450 mcg/dL	307	
Iron, % saturation	15–45 %	19	
Monoclonal gammopathy, serum			
Protein, total	6.4–8.2 g/dL	7.3	
Total globulin	2.1–4.2 g/dL	2.5	
Albumin	3.5–4.9 g/dL	4.8	
Alpha 1	0.2–0.4 g/dL	0.3	
Alpha 2	0.5–0.9 g/dL	0.6	
Beta	0.7–1.2 g/dL	0.7	
Gamma	0.7–1.7 g/dL	1	
Lambda, free	0.57–2.63 mg/dL	1.27	
Kappa/lambda ratio	0.26–1.65	0.96	
Oligoclonal Banding			
Serum Bands	<2 bands	0	
CSF Bands	<2 bands	0	
CSF Olig Bands	<2 bands	0	
RPR	Nonreactive	Nonreactive	

Component	Reference	Value
Autoimmune/Paraneoplastic		
AMPA-R Ab CBA, CSF	Negative	Negative
Amphiphysin Ab, CSF	Negative	<1:2
AGNA-1, CSF	Negative	<1:2
ANNA-1, CSF	Negative	<1:2
ANNA-2, CSF	Negative	<1:2
ANNA-3, CSF	Negative	<1:2
CASPR2-IgG CBA, CSF	Negative	Negative
CRMP-5-IgG, CSF	Negative	<1:2
DPPX Ab IFA, CSF	Negative	Negative
GABA-B-R Ab CBA, CSF	Negative	Negative
GFAP IFA, CSF	Negative	Negative
IgLON5 IFA, CSF	Negative	Negative
LGI1-IgG CBA, CSF	Negative	Negative
mGluR1 Ab IFA, CSF	Negative	Negative
NIF IFA, CSF	Negative	Negative
NMDA-R Ab CBA, CSF	Negative	Negative
PCA-Tr, CSF	Negative	<1:2
PCA-1, CSF	Negative	<1:2
PCA-2, CSF	Negative	<1:2
		*<1:2 is a negative result
Meningitis Panel (NAT), CSF		
Escherichia coli K1, CSF	Negative	Negative
Haemophilus influenzae, CSF	Negative	Negative
Listeria monocytogenes, CSF	Negative	Negative
Neisseria meningitidis, CSF	Negative	Negative
Streptococcus agalactiae, CSF	Negative	Negative
Streptococcus pneumoniae, CSF	Negative	Negative
Cytomegalovirus (CMV), CSF	Negative	Negative
Enterovirus, CSF	Negative	Negative
Herpes Simplex Virus 1 (HSV-1), CSF	Negative	Negative
Herpes Simplex Virus 2 (HSV-2), CSF	Negative	Negative
Human Herpesvirus 6 (HHV-6), CSF	Negative	Negative
Human Parechovirus, CSF	Negative	Negative
Varicella-zoster Virus (VZV), CSF	Negative	Negative
Cryptococcus neoformans/gattii, CSF	Negative	Negative
Aerobic Culture w/Gram Stain Report	No Growth at 3 days. No Organisms. Rare WBCs	

The patient's primary and secondary imaging and laboratory findings were unremarkable. Component names, reference ranges, and patient results are provided. (A) MRI of the brain showed mild cerebellar atrophy without significant brainstem involvement. The T1-weighted sagittal image (left) demonstrated cerebellar volume loss (indicated by red circle) while the T2/FLAIR axial image (right) confirmed no abnormalities in the brainstem or deep structures. (B) Initial laboratory testing included a CBC and CMP, which were within normal limits. (C) Secondary testing included autoimmune, infectious, nutritional, and paraneoplastic panels. Serum protein electrophoresis demonstrated a normal kappa/lambda ratio, and iron studies were unremarkable. CSF analysis revealed no oligoclonal bands and no growth on aerobic cultures. Abnormal laboratory results are indicated in bold and with an asterisk and annotated with "high" or "low." AGNA = anti-glial nuclear antibody; ANNA = anti-neuronal nuclear antibody; CASPR2 = contactin-associated protein 2; CBC = complete blood count; CMP = comprehensive metabolic panel; CMV = cytomegalovirus; FLAIR = fluid-attenuated inversion recovery; GFAP = glial fibrillary acidic protein; HSV = herpes simplex virus; LGI1 = leucine-rich glioma-inactivated protein 1; PCA = Purkinje cell antibody; VZV = varicella-zoster virus.

CANVAS progresses slowly. Treatment is supportive with physical therapy, assistive devices for balance, and medication for neuropathic pain. Regular follow-ups are essential to monitor progression. Genetic counseling is recommended for patients and their families.

Author Contributions

R. Rawat: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S.M. Brooker: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. G.E. Naylor: drafting/revision of the manuscript for content, including medical writing for content. M. Cherchi: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. P. Opal: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data.

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Disclosure

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