A rare case of Leukodystrophy-Like Progressive MS in Adulthood: Unravelling a Diagnostic Dilemma

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Case presentation

A 42-year-old man presented with an **eight-month history** of progressive tremor, left-sided clumsiness, spastic dysarthria, and paraparesis with ataxic gait. He reports **progressive difficulty in walking, running, and climbing stairs**. Neurological examination revealed paraparetic gait, signs of pyramidal tract involvement in the left hemibody, mild strength deficit against resistance in the left hemibody by comparison, and intention tremor (left > right) bilaterally. Patient **denies family history of neurological diseases**, no previous neurologic events in his pathological remote history. He reports recreational alcohol consumption, denies substance use dependency, has a preserved sleep/wake cycle, and **no delay in achieving psychomotor developmental milestones.** He works as a marble worker.

Investigations

- **Brain MRI:** symmetric confluent subcortical white matter lesions with periventricular T1 "black holes", a flame-shaped pattern, and a small enhancing lesion in the right parietal lobe (figure 1 A-B-C).
- **Spinal MRI**: posterior cord T2 hyperintensities (figure 1D).
- **Cerebrospinal fluid analysis:** ↑ intrathecal IgG, positive type 2 oligoclonal bands, MOG-IgG negative, kappa index 558.34.
- **Cognitive tests:** deficit in memory, information processing speed, attention, and visuospatial learning. No behavioural disorders reported.
- **Blood investigations for metabolic, infectious, and rheumatological causes:** negative.
- **Genetic testing:** FXTAS and leukodystrophy negative.
- ***Mutation NOTCH3 c.3445C>T p.(Pro1149Ser)*** with uncertain significance

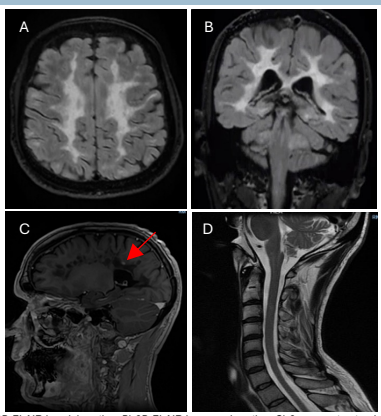

Figure 1: *A) 3D FLAIR in axial section; B) 3D FLAIR in coronal section; C) 3 mm contrast-enhancing lesion on T1w with gadolinium highlighted by the red arrow; D) Spinal cord lesions. T2 sagittal plane.*

Clinical Reasoning: Differential Diagnosis

Feature	PPMS	Adult-Onset Leukodystrophies	CSVD (including CADASIL)
Etiology	Autoimmune demyelinating disease	Genetic: ABCD1, ARSA,GFAP, CTLA4	-Genetic: NOTCH3, COL4A1, HTRA1 -Sporadic: Environmental and lifestyle factors
Age of Onset	**After 40**	**Between 20–50 years**	**-Genetic: Between 30-50 years -Sporadic: >60 years**
Progression	**Gradual, neurological decline without relapses**	Often progressive, may be stepwise or fluctuating	Gradual and progressive cognitive and neurological decline
Family History	Rarely familial	Often positive, though may be subtle	Often positive if an hereditary cause is present
MRI Findings	**Periventricular and spinal cord lesions, often with enhancement**	**Symmetric white matter changes, corpus callosum thinning**	White matter lesions, small deep infarcts (<15 mm), early cortical atrophy
CSF Findings	**Oligoclonal bands often present**	Usually negative for oligoclonal bands	Non-specific findings

Primary progressive MS was diagnosed based on clinical, MRI, and CSF inflammatory markers. Ocrelizumab treatment started with the following mobility improvements and an **increase in the strength of the lower limbs** at the neurological examination after 1 month of treatment.

Conclusions

- The NOTCH3 c.3445C>T p.(Pro1149Ser) variant is linked to CSVD predisposition, not CADASIL (figure 2).
- CSVD features have been observed in MS and correlate with greater progression risk and pathological evidence.
- Atypical for leukodystrophy: spinal cord and contrast-enhancing lesions, no family history, high k-index, and absence of early cognitive/behavioural decline.
- **Hypothesis**: NOTCH3-related endothelial dysfunction **may** increase BBB permeability, promoting immune cell trafficking, CSF compartmentalisation, picturing in this atypical progressive MS presentation. Genetic testing for leukodystrophy or vascular hereditary diseases might be useful in atypical cases of MS.

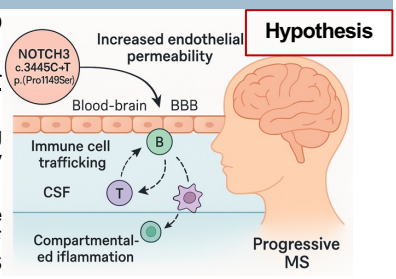

Figure 2: The NOTCH3 c.3445C>T p.(Pro1149Ser) variant.

References

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