# Pearls & Oy-sters: Huntington Disease Presenting as Primary Progressive Aphasia

## A Case of Semantics

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## Abstract

We present a case of semantic variant primary progressive aphasia as the presenting feature in a patient with Huntington disease (HD). The patient initially developed progressive language impairment including impaired naming and object knowledge and single-word comprehension and then developed chorea and behavioral changes. An MRI of the brain showed left anterior temporal lobe and hippocampal atrophy. A neurologic FDG PET/CT showed reduced metabolism in the head of the left caudate nucleus. Huntingtin gene testing revealed an expansion of 39 CAG repeats in 1 allele. This case outlines the substantial overlap between the clinical presentation of HD and frontotemporal lobar degeneration syndromes and provides commentary on the investigation of these neurodegenerative diseases.

## Pearls

- When patients present with overlapping clinical signs, genetic testing can complement structural and functional imaging to provide diagnostic clarity, even in the absence of a known family history.
- Emerging long-read sequencing platforms will allow testing for short tandem repeats in multiple genes in parallel to minimize the need for serial testing.

## Oy-sters

- The clinical syndrome of semantic variant primary progressive aphasia (PPA) can arise from different underlying neurodegenerative pathologies.
- Single-gene testing may not be sufficiently comprehensive, and panel testing based on next-generation sequencing technology may not detect disorders caused by short tandem repeats.

## Case

A 76-year-old White man was referred for evaluation of a 3-year history of language difficulties. The patient's family and colleagues noted he had difficulty with naming and verbal recall. During initial neurologic consultation, history and examination revealed involuntary movements of his fingers and shoulders and impulsive and disinhibited behaviors. Of relevance, there were no stereotypies, hyperorality, visual hallucinations, or features of dream enactment. He had a medical history of localized prostate cancer treated with androgen deprivation therapy and osteoarthritis. Both parents died in their 40s due to complications related to alcohol consumption. He had 1 younger male sibling and 5 children who were well. He achieved university-level education and managed a livestock property before working as a mortgage broker.

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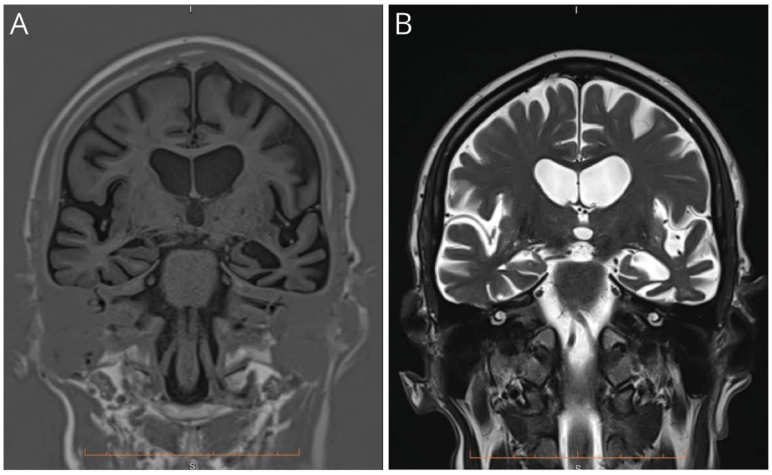
**Figure 1** MRI Brain




Anterior temporal lobes shown in coronal plane on T1-weighted (A) and T2-weighted (B) magnetic resonance sequences. There is asymmetrical atrophy of the left mesial temporal lobe with corresponding enlargement of the temporal horn of the lateral ventricle. There is also volume loss of the left frontal lobe with prominence of the sulcal spaces around the frontal and temporal lobes.

The patient scored 37/100 on the Addenbrooke Cognitive Examination-III[1] with points lost in multiple subdomains. Specifically, he scored 14/18 for the attention subdomain, 6/26 for memory, 1/14 for fluency, 3/26 for language, and 13/16 for visuospatial function. Confrontational naming, single-word comprehension, and object knowledge were severely impaired with spared repetition and speech production (Video 1). There were frank choreiform movements of the hands, shoulders, and lower limbs. He had occasional involuntary orobuccal movements with oromandibular dyskinesia and motor impersistence of tongue protrusion. His gait was narrow based and apraxic. There was no bradykinesia or rigidity. Luria sequencing was abnormal, and he had a positive grasp reflex bilaterally. He had no pyramidal signs, weakness, or sensory change.

Serologic testing for acquired conditions such as metabolic derangements, vitamin deficiencies, and infective, autoimmune, and paraneoplastic causes was noncontributory. An MRI of the brain showed marked asymmetric left anterior temporal lobe and left hippocampal and bilateral caudate atrophy. There was also mild-to-moderate generalized supratentorial atrophy without abnormal white matter signal (Figure 1).

A neurologic FDG PET/CT showed asymmetric (left more than right) temporal lobe atrophy with marked glucose hypometabolism. There was reduced metabolism in the head of the left caudate nucleus (Figure 2). *C9ORF72* gene testing showed no pathologic repeat expansion in either allele; however, testing of the huntingtin (*HTT*) gene revealed an expansion of 39 CAG repeats in 1 allele and 18 repeats in the other.

The findings of a progressive language disorder, chorea, and behavioral changes, with supportive MRI and PET/CT findings and a borderline repeat expansion in the *HTT* gene, were consistent with Huntington disease (HD). Notably, features consistent with semantic variant PPA were noted before the emergence of the typical movement disorder. The patient was referred for genetic counseling to consider additional family testing and community support.

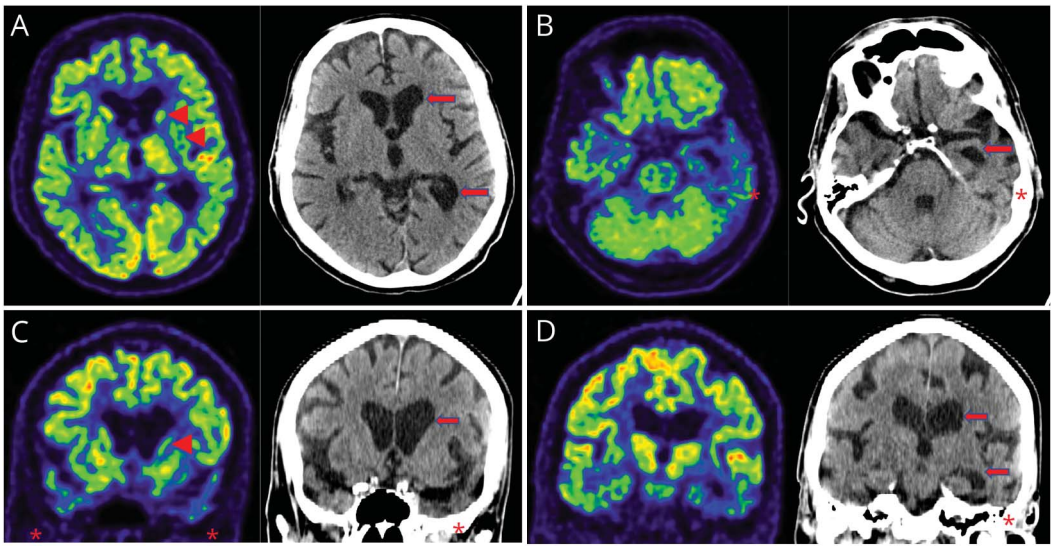
## Discussion

Our case describes the semantic variant of PPA as the initial clinical manifestation of HD. HD is typically characterized by the triad of psychiatric changes, cognitive impairment, and a movement disorder due to pathogenic CAG triplet expansions in the *HTT* gene. The patient had atypical presenting symptoms of HD, with clear structural and functional imaging supporting a PPA variant of HD. The semantic subvariant of PPA is characterized by anomia and severely impaired single-word comprehension with sparing of repetition and motor speech.[2]

Language impairment can be a prominent feature in individuals diagnosed with HD and typically progresses with advancing dementia and movement abnormalities.[3] Verbal and letter fluency has been implicated in frontostriatal physiopathology, which occurs early in HD.[3-5] Similarly, impaired performance on word generation tasks may reflect frontostriatal disruption of word retrieval processes and executive dysfunction.[3,5,6] As the disease progresses, temporal and parietal cortical atrophy contributes to language dysfunction manifesting as impaired naming and object knowledge.[6] The patient's work as a mortgage broker may have drawn attention to his language impairment earlier in the disease course. During his presentation, the functional and anatomical imaging demonstrated temporal lobe atrophy, supporting the contribution of cortical degeneration to cognitive symptoms in HD.[7,8]

Longer expansions in *HTT* are associated with an earlier onset of classic disease.[9] Intermediate expansions of 36–39 repeats are considered "reduced penetrance" alleles, but most patients

**Figure 2** Paired FDG PET/CT Imaging




Paired FDG PET/CT transaxial (top row) and coronal (bottom row) images at the level of the basal ganglia (A, C) and inferior temporal lobes (B, D). In A and C, there is markedly reduced glucose metabolism in the head of left caudate nucleus and putamen (arrowheads) with asymmetric enlarged frontal and left occipital horns (arrows) and hypometabolism in both anterior temporal lobes (left > right, star). In B and D, there is marked temporal lobe atrophy (left > right, star) with enlargement of left temporal and frontal horns (arrow) and corresponding markedly reduced metabolism in both temporal lobes (left > right, star).

with 39 repeats phenoconvert to those with HD by the age of 75 years.[9] Metabolic disorders, inflammatory and paraneoplastic syndromes, and a range of genetic neurodegenerative conditions can mimic the HD clinical presentation.[10] For example, hexanucleotide expansions in the *C9ORF72* gene, while usually the major genetic cause of familial and sporadic frontotemporal dementia (FTD), were found to be the most common genetic HD phenocopy in a UK cohort.[11] Conversely, there is limited literature describing the diagnosis of frontotemporal lobar degeneration (FTLD) syndromes in patients with choreiform movement disorders or confirmed HD. One case report described a patient with genetically confirmed HD presenting with probable behavioral variant frontotemporal dementia (bvFTD).[12] Dewan et al.[13] more recently described 3 patients, 2 with bvFTD and 1 with the nonfluent variant of PPA, harboring the huntingtin CAG repeat expansion after analysis of whole-genome sequence data from more than 2,000 patients diagnosed with FTD/amyotrophic lateral sclerosis.

Genetic testing using targeted gene panels, whole-exome sequencing, or whole-genome sequencing is increasingly available for adult-onset neurodegenerative conditions and can identify pathogenic variations in multiple potential genes.[14] These technologies use next-generation sequencing platforms, which can miss disease-causing repeat expansions, such as the *C9ORF72* and *HTT* expansions, due to the short read length of each fragment. Emerging sequencing technologies harnessing long-read sequencing have the potential to test for multiple tandem repeat expansion disorders simultaneously, including with accurate quantification of expansion length.[14] This technology allows for the evaluation of pathogenic expansions in different genes in parallel in addition to other sequence variants captured by next-generation sequencing.

Our case adds to the growing literature supporting the overlap between *HTT* repeat expansions and the FTLD syndromes, including PPA, with recent studies suggesting that neurodegenerative pathologies can potentially coexist.[15] Genetic testing in this case supported the diagnosis of atypical HD, presenting with semantic variant PPA, and prompted further discussion of additional testing of the patient's children. Definitive confirmation of the underlying neurodegenerative process contributing to this patient's temporal lobe atrophy, however, requires postmortem evaluation.

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CORRECTION

# Characteristics and Clinical Implication of White Matter Lesions in Patients With Adult Moyamoya Disease

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In the Research Article "Characteristics and Clinical Implication of White Matter Lesions in Patients With Adult Moyamoya Disease" by Yang et al.,[1] the y-axis of Figure 2D should read "Periventricular-to-subcortical ratio." The editorial staff and publisher regret the error.

## Reference


1. Yang W, Jung KH, Kang DW, et al. Characteristics and clinical implication of white matter lesions in patients with adult moyamoya disease. *Neurology*. 2023;100(18):e1912-e1921.

# Pearls & Oy-sters: Huntington Disease Presenting as Primary Progressive Aphasia: A Case of Semantics

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