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Pearls and 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 (PPA) as the presenting feature in a patient with Huntington disease (HD). The patient initially developed progressive language impairment including impaired naming, object knowledge and single word comprehension and then developed chorea and behavioural changes. Magnetic resonance imaging (MRI) of the brain showed left anterior temporal lobe and hippocampal atrophy. A neurological 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 one allele. This case outlines the substantial overlap between the clinical presentation of HD and frontotemporal lobar degeneration (FTLD) syndromes and provides commentary on the investigation of these neurodegenerative diseases.

PEARLS

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

The patient scored 37/100 on the Addenbrooke's Cognitive Examination (ACE-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.

[Insert Video 1].

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

[Insert Figure 1].

A neurological 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 pathological repeat expansion in either allele, however testing of the huntingtin (*HTT*) gene revealed an expansion of 39 CAG repeats in one allele and 18 repeats in the other.

[Insert Figure 2].

The findings of a progressive language disorder, chorea, and behavioural 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 primary progressive aphasia (PPA) were noted prior to the emergence of the typical movement disorder. The patient was referred for genetic counselling 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 characterised 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 as well as 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. At the time of 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 earlier onset of classic disease[9]. Intermediate expansions of 36-39 repeats are considered 'reduced penetrance' alleles, but the majority of patients with 39 repeats phenoconvert to HD by age 75[9]. Metabolic disorders, inflammatory and paraneoplastic syndromes, as well as 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 FTLD syndromes in patients with choreiform movement disorders or confirmed HD. Sutovsky et. al. report a patient with genetically confirmed HD presenting with probable behavioural variant frontotemporal dementia (bvFTD)[12]. Dewan et. al. more recently described three patients, two with bvFTD and one with the non-fluent variant of PPA, harbouring the huntingtin CAG repeat expansion following analysis of whole-genome sequence data from over 2000 patients diagnosed with FTD/Amyotrophic Lateral Sclerosis[13].

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 mutations in multiple potential genes[14]. These technologies utilize 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 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 post-mortem evaluation.

WNL-2023-000266_vid1 ---- http://links.lww.com/WNL/C828

VIDEO AND FIGURES

(VIDEO FILE ATTACHED SEPARATELY)

Video 1: The patient is asked to describe his breakfast and then describes the Cookie Theft Picture. Note the fluent speech with impaired naming and object knowledge. There are choreiform movements of the hands and shoulders.

Figure 1

MRI brain.

Anterior temporal lobes shown in coronal plane on T1-weighted (A) and T2-weighted (B) MR 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.

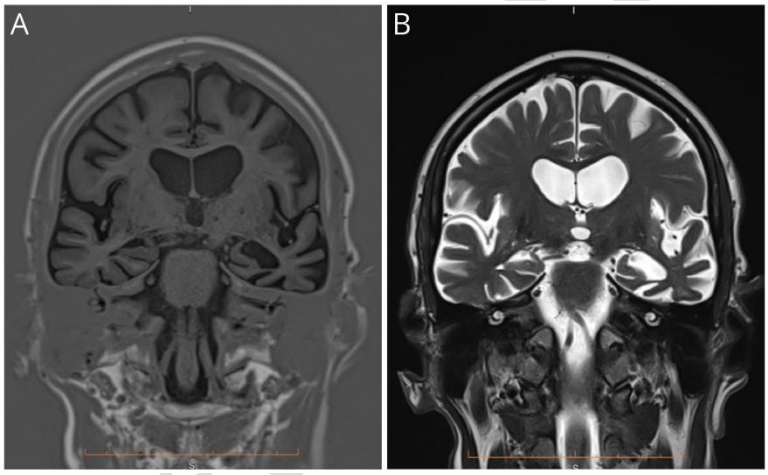
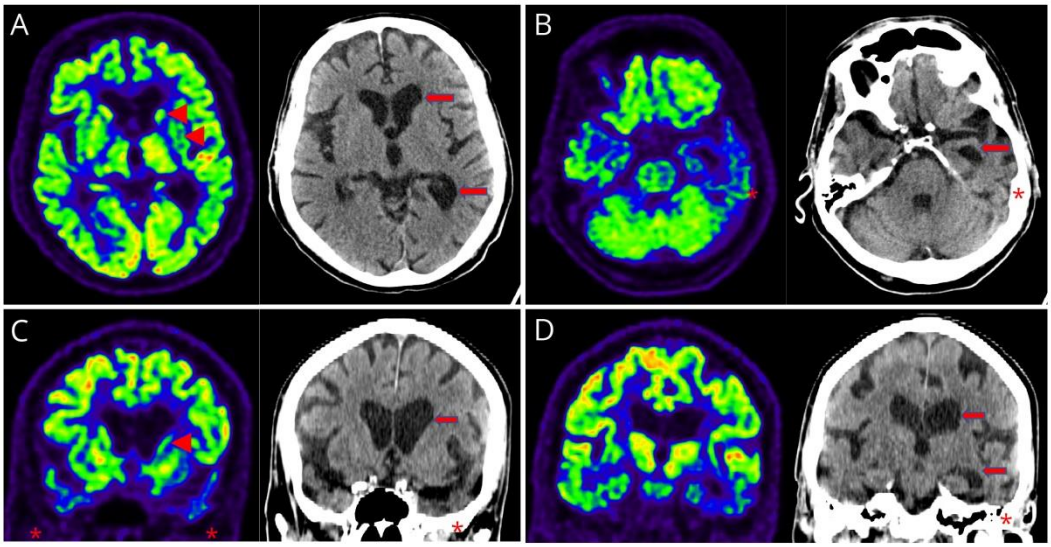


Figure 2

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 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).



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