Huntington's disease-like 2: a phenocopy not to miss

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ABSTRACT

A 67-year-old Brazilian man of African ancestry and his 60-year-old sister both presented with choreiform movements, although in the man these were significantly overshadowed by additional parkinsonism. The man also had a history of four epileptic seizures. Neurological examination in each also found slow saccades and a dysexecutive syndrome. Genetic tests for Huntington's disease were negative but were positive for Huntington's disease-like 2. There are various genetic causes of chorea diseases, and their correct identification is important for appropriate clinical management and genetic counselling.

CASE REPORT

A 67-year-old Brazilian man of African ancestry (the proband) had a 4-year history of choreiform movements, particularly in the orofacial region, together with parkinsonism. His sister had very similar symptoms, present for 2 years. The parkinsonism rapidly overshadowed chorea in both patients, and particularly the man, who developed a resting tremor. The man also had a history of four focal-onset seizures with impaired awareness. There were no overt psychiatric symptoms. Their father had died prematurely, but there was no family history of chorea. Their neurological examination also identified slow saccades and dysexecutive syndrome (video 1). Muscular strength and reflexes were normal and there were no other movement disorders. MR scan of brain showed prominent diffuse cortical atrophy, particularly of the caudate and lentiform nucleus (figure 1). Genetic tests for Huntington's disease were negative but were positive for Huntington's disease-like 2 with 44 CTG repeats. We gave levodopa for the parkinsonism and valproic acid for the man's epilepsy.

DISCUSSION AND LESSONS

Huntington's disease-like 2 was first described in an African–American family in 2001[1] as a phenocopy of Huntington's disease, presenting in middle age with progressive chorea, psychiatric and cognitive abnormalities. It has a broad clinical phenotype, initially characterised by dementia, chorea and oculomotor abnormalities, then progressing to a akinetic–rigid state. The average age of onset is 41 years, and death follows usually 10–20 years after disease onset.[2] It is very rare, with fewer than 50 families reported worldwide. Thus, its exact prevalence and incidence are unknown, which vary between populations of different ethnic make-up. Huntington's disease-like 2 is the most frequent Huntington's disease phenocopy in South America.[3]

Huntington's disease-like 2 is clinically indistinguishable from Huntington's disease. Clinicians should suspect it mainly in people of African ancestry who have typical clinical features of Huntington's disease but without the disease-causing CAG expansion in the huntingtin gene. Anderson *et al*[4] in a cross-sectional study compared 15 patients with Huntington's disease-like 2 with 13 patients with Huntington's disease, all of African ancestry. They were submitted to a video-recorded rating scale and evaluated by blinded experts. Raters could not distinguish the two diseases and had a high level of agreement. Patients with Huntington's disease-like 2 had presented earlier and had more prominent dysarthria and dystonia. In addition, they also had higher scores on the rating scale than in patients with Huntington's disease but not significantly so. In a systematic review of 69 cases of Huntington's disease-like 2,[5] there was a higher prevalence of parkinsonism (37%), less dysarthria and relatively preserved oculomotor function

Video 1 Proband with facial chorea with tongue movement impersistence, upper limb bradykinesia and delayed ocular movement initiation with slow saccades. The video also shows the proband's sister with generalised chorea.

when compared with cases of Huntington's disease. There might be two different phenotypes: (1) an earlier-onset parkinsonian form without overt oculomotor involvement and (2) a later-onset choreiform variant, with classical Huntington's disease phenotype and typical oculomotor involvement.

The diagnosis of Huntington's disease-like 2 is based on a positive family history, characteristic clinical features and finding an expansion of 40 or more repetitions of CTG trinucleotides in the junctophilin-3 (*JPH3*) gene (16q24.3). Affected people have CTG repeat expansions of 41–59 triplets (normal 6–27). MR scan of brain shows prominent atrophy of the caudate and cerebral cortex, similar to that in Huntington's disease.[2]

The clinical diagnosis of chorea may be challenging, given its broad differential diagnosis. As a general rule, acquired or sporadic causes of chorea present acutely or subacutely, whereas genetic causes tend to be more chronic. According to European studies, Huntington's disease is by far the most common genetic cause of chorea in adults, followed by *C9orf72* disease, and spinocerebellar ataxia type 17 (SCA17). However, in Latin America, particularly in Brazil where there is an important African ancestry, the most common genetic phenocopy of Huntington's disease is Huntington's disease-like 2.[3] Ethnicity can be an important diagnostic clue, since it occurs almost exclusively in people with African ancestry. Clinicians must distinguish it from chorea–acanthocytosis, which has a wide range of phenotypes including chorea, tics, dystonia, parkinsonism, seizures, peripheral neuropathy, psychiatric symptoms, muscle abnormalities and cardiac manifestations.[6] Note that a blinded, controlled study[7] did not confirm previous reports of acanthocytosis in Huntington's disease-like 2.

The treatment is symptomatic, as in Huntington's disease and other neurodegenerative disorders. Pharmacological agents that might suppress abnormal movements include tetrabenazine and its derivatives, and low-dose neuroleptic agents such as haloperidol. Antidepressants, antipsychotics and mood stabilisers (lithium, valproic acid, carbamazepine and lamotrigine) can improve psychiatric manifestations.[6]

In conclusion, Huntington's disease-like 2 should be sought in people with a Huntington's disease phenotype who test negative for the CAG expansion, and have African ancestry. This case shows that parkinsonism can be its presenting and most prominent feature, sometimes overshadowing the chorea. Being

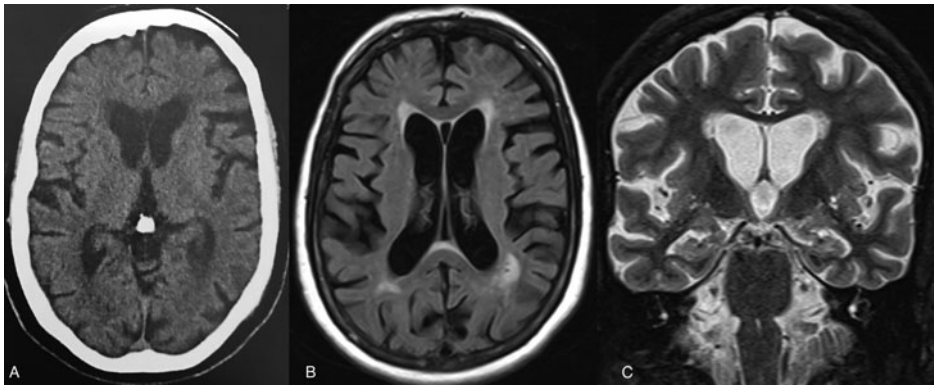

Figure 1 Diffuse cortical atrophy and caudate and lentiform nuclei atrophy with subsequent widening of the frontal horns of the lateral ventricle seen on (A) CT scan of head; (B) MR scan of brain axial FLAIR image and (C) MR scan of brain coronal T2-weighted image. FLAIR, fluid-attenuated inversion recovery.

a relatively new condition, it may be under-recognised and under-reported. The great similarity in phenotype between Huntington's disease-like 2 and Huntington's disease raises the question as to whether polyglutamine toxicity is indeed the main pathogenic mechanism of Huntington's disease.

Key points

- Huntington's disease-like 2, a phenocopy of Huntington's disease, should be sought in people with a Huntington's disease phenotype who test negative for the CAG expansion, and have African ancestry.
- The clinical phenotype is broad, characterised by chorea, psychiatric and cognitive features with oculomotor abnormalities; it can progress to parkinsonism, which sometimes can overshadow chorea.
- There appears to be two different phenotypes: an earlier-onset parkinsonian form without overt oculomotor involvement, and a later-onset choreiform variant, with classical Huntington's disease phenotype and typical oculomotor involvement.
- The diagnosis of Huntington's disease-like 2 is based on a positive family history, characteristic clinical features and finding an expansion of 40 or more repetitions of CTG trinucleotides in the junctophilin-3 (*JPH3*) gene.

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