SHORT REPORT

Levodopa responsive parkinsonism in an adult with Huntington's disease

Brad A Racette, Joel S Perlmutter

Abstract

A patient is reported on with Huntington's disease who, as an adult, first developed severe parkinsonism with bradykinesia, rigidity, postural instability and festinating gait. His clinical signs were similar to those of the Westphal variant of Huntington's disease except that he also had resting tremor and a supranuclear gaze palsy. Magnetic resonance imaging showed caudate and putamen atrophy. Genetic analysis disclosed 49 triple CAG repeats in allele 1 and 17 in allele 2 confirming the diagnosis of Huntington's disease. Treatment with levodopa produced substantial functional motor improvement with a 17 point reduction in the unified Parkinson's disease rating scale (UPDRS) motor subscale including reduction of tremor, bradykinesia, and postural instability. This is the first report of a patient with adult onset Huntington's disease with parkinsonism responsive to levodopa.

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Department of Neurology and Neurologic Surgery (Neurology)
B A Racette
J S Perlmutter

Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, MO 63110, USA
J S Perlmutter

Correspondence to:
Dr Joel S Perlmutter, Campus Box 8225, 4525 Scott Avenue, St Louis, MO 63110, USA. Telephone 001 314 362 6908; fax 001 314 362 0168.

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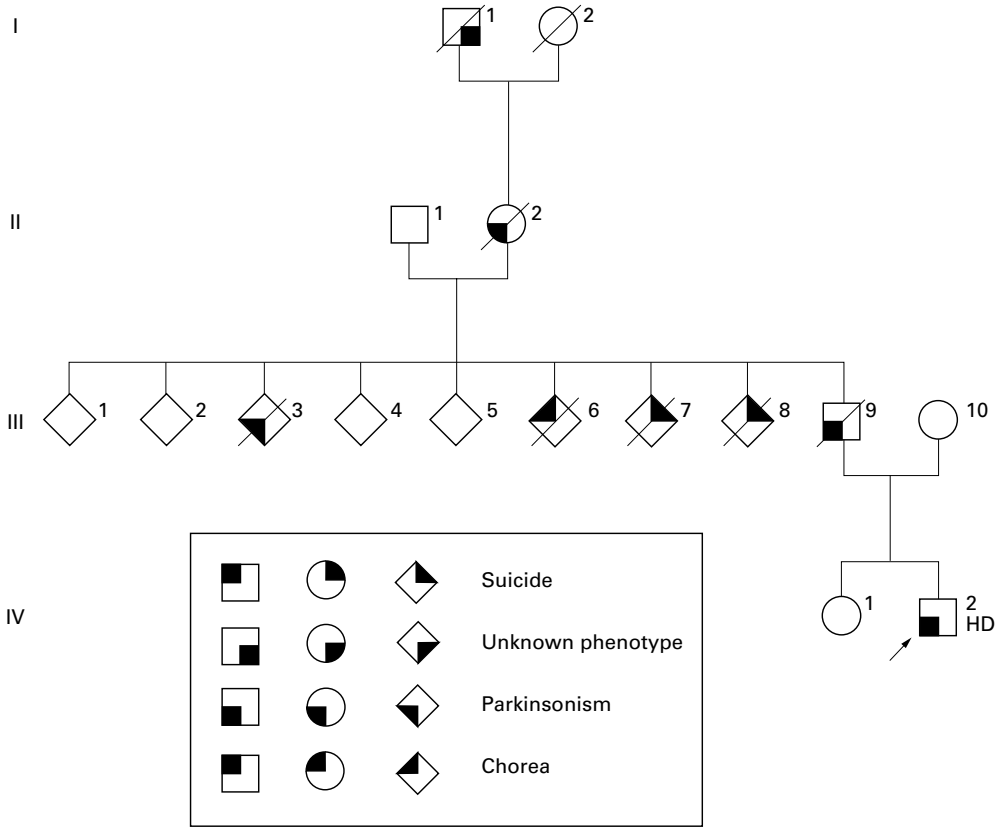
The initial manifestations of Huntington's disease typically include dementia, psychiatric disturbance, and chorea.[1] Alternatively, bradykinesia and rigidity may be the first feature; this is the most common presentation in childhood onset Huntington's disease. This "Westphal" variant accounts for 85% of childhood onset Huntington's disease whereas only 6% of patients with adult onset Huntington's disease have these initial manifestations.[2] Levodopa may provide symptomatic benefit in the childhood onset Westphal variant[3] but the response in patients with adult onset has not been described. We now report that levodopa provided symptomatic benefit in a patient with the adult onset Westphal variant of Huntington's disease.

Case report

A 38 year old right handed white man had a main complaint of shaking of his arms. Four years earlier he had noted the gradual onset of resting tremor in both upper limbs that spread to his lower limbs within one year. One year later, he developed difficulty with walking, freezing, and had subsequent loss of balance. He became stiffer and slower requiring maximal assistance to walk. Speech became softer and more difficult to understand, and he developed occasional dysphagia. He denied cognitive impairment or mood disturbance. He had no other medical problems, and no history of encephalitis, toxin exposure, or neuroleptic use. His father, paternal uncle, and paternal grandmother had similar symptoms with akinesia and rigidity beginning after the age of 40. None of the "affected" family members had genetic testing before they died and none of the asymptomatic relatives agreed to examination. The phenotype of his mother's grandfather was unknown except that he died of a "neurological problem." The figure shows the pedigree.

General examination disclosed multiple cigar burns on his limbs but was otherwise normal. He was awake, alert, oriented to person, place, and time but was mildly inattentive. He could register three of three objects but recalled none of three at 5 minutes. Speech was severely dysarthric and hypophonic but language was normal. He was unable to volitionally look left or up with either eye but was able to look down and to the right with slow smooth pursuits. He had preserved oculocephalics. There were no Kayser-Fleischer rings. He had marked facial masking. He had difficulty opening his mouth to command and could barely protrude his tongue. While lying in bed, he held his arms flexed and legs extended. He had normal strength but severe rigidity and bradykinesia in all four limbs. His right big toe was dorsiflexed at rest and with action. Reflexes were symmetrically brisk in his upper and lower limbs with sustained clonus at the knees and ankles. Plantar reflexes were extensor bilaterally. He had a 3 Hz large amplitude flexion-extension rest tremor in both upper limbs that persisted with action. He had excessive flexion of the upper limbs while standing and circumducted both legs while walking. He had severe postural instability and would fall spontaneously when not assisted. The UPDRS motor subscale before treatment was 83 out of a possible 108.

Brain MRI demonstrated marked caudate and putamen atrophy as well as mild diffuse cortical atrophy. Genetic testing for Hunting-



Pedigree. Squares indicate men and circles indicate women. Subjects in the third generation are represented as diamonds to protect anonymity. Diagonal lines represent deceased family members.

ton's disease showed heterozygosity of the CAG repeat region on 4p16.3 with a normal allele of 17 trinucleotide repeats and an abnormal allele of 49 repeats. Genetic testing for the Machado-Joseph/spinocerebellar ataxia 3 gene disclosed normal allele lengths (20 and 21 CAG repeats). Levodopa/carbidopa (200 mg/50 mg) provided symptomatic improvement with a 17 point reduction on the unified Parkinson's disease rating scale (UPDRS) motor subscale including improvement in tremor, finger and hand dexterity, postural stability, and rising from a chair. While taking levodopa he could rise from a chair independently and walk to the bathroom without assistance for the first time in 2 years. He could feed himself but still required assistance for dressing and bathing. Clinical improvement continued to increase with doses of levodopa up to 800 mg a day but there was no additional benefit at higher doses. He had no untoward effects from levodopa. He refused a trial of medication withdrawal. He maintained benefit for at least 1 year and did not develop fluctuations of his parkinsonian symptoms throughout the day. He was subsequently lost to follow up.

Discussion

We report on a patient with Huntington's disease with adult onset of manifestations similar to the Westphal variant but he also had rest tremor, supranuclear gaze palsy, and mild dementia. To our knowledge, this is the first description of response to levodopa in a patient with an adult onset with these features. Levodopa provided meaningful improvements in quality of life including improvements in gait and postural instability, as identified on the UPDRS motor subscale. Genetic testing and MRI were consistent with Huntington's disease but other diseases may have coexisted. Coexistent idiopathic Parkinson's disease is possible but the relative symmetry of signs and young onset makes this less likely. Parkinsonism with rest tremor and response to levodopa does not necessarily indicate idiopathic Parkinson's disease.[4 5] Two large series of patients presenting with presumed Parkinson's disease based on clinical criteria showed only 76% accuracy when followed up to necropsy. Over half of their patients with non-idiopathic Parkinson's disease had a "good" response to levodopa. The main confounding diagnoses included progressive supranuclear palsy, multiple systems atrophy, Alzheimer's disease, vascular disease, drug induced parkinsonism, and substantia nigra degeneration without Lewy bodies. Our patient has features inconsistent with idiopathic Parkinson's disease such as corticospinal tract signs, supranuclear gaze palsy, and relatively symmetric onset; however, Huntington's disease should be considered in patients with atypical parkinsonism, regardless of response to levodopa.

The mechanism of action of levodopa for relief of parkinsonian symptoms in Huntington's disease is unclear. Albin *et al* found loss of striatal neurons projecting to the globus pallidus externa, globus pallidus interna, and substantia nigra in akinetic rigid Huntington's

disease[6] with no reduction of neurons containing tyrosine hydroxylase in the substantia nigra whereas those patients with Huntington's disease with chorea had relative preservation of projections to the globus pallidus interna. As nigrostriatal neurons containing dopamine were presumably preserved, they argued that the additional degeneration of the direct pathway may underlie the parkinsonian Huntington's disease phenotype. It would be tempting to pose that the mechanism of action of levodopa is to partially restore activity of striatal projection neurons to the globus pallidus interna but we have no data to support this notion.

Levodopa has been used for diagnostic testing and symptomatic treatment in Huntington's disease. Klawans and Paulson suggested that dopa induced chorea in presymptomatic subjects could indicate increased likelihood of carrying the abnormal gene and subsequent development of Huntington's disease.[7] The lack of accuracy of this test and subsequent development of genetic testing have eliminated this as a reasonable alternative. Most attempts to treat chorea in Huntington's disease with levodopa were unsuccessful or caused an exacerbation of the chorea[8]; although a few adults with chorea as their primary motor manifestation of Huntington's disease had symptomatic benefit from levodopa. Patients with juvenile onset Huntington's disease had the most consistent symptomatic response to levodopa with reduction of parkinsonian manifestations.[3] Based on the experience with our patient, levodopa may provide symptomatic benefit to patients with adult onset Huntington's disease with prominent parkinsonism.

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