Late onset levodopa responsive Huntington’s disease with minimal chorea masquerading as Parkinson plus syndrome

I Reuter, M T M Hu, T C Andrews, D J Brooks, C Clough, K Ray Chaudhuri

Abstract

Huntington’s disease is characterised by hyperkinetic movements, mainly chorea, cognitive dysfunction, and psychiatric abnormalities. Non-dopa responsive parkinsonism occurs in the later stages of choreic disease or as the predominant feature of juvenile patients (Westphal variant). Late onset Huntington’s disease presenting as levodopa responsive parkinsonism is rare. A series of four patients with late onset Huntington’s disease presenting as levodopa responsive parkinsonism and cardiovascular dysautonomia, initially misdiagnosed as multiple system atrophy (MSA) in three patients, is reported. Levodopa treatment did not unmask significant chorea. These cases suggest the presence of a distinct phenotypic variant of Huntington’s disease to be added to the differential diagnosis of other akinetic rigid syndromes.

Case reports

CASE 1

A 63 year old right handed white man with a presumptive diagnosis of MSA was referred for tertiary opinion. He gave a 3 year history of slowly progressive ataxic gait, falls, abnormal posturing of his right arm, and slurred speech. On examination, he had a dominantly axial hypokinetic rigid syndrome with a wide based gait, impaired postural reflexes, and a tendency to fall backwards. Dystonic posturing of his right arm and mild chorea of the left fingers were noted and rigidity was more marked in the right upper limb. He had mild difficulties on routine cognitive testing and eye movements showed a saccadic pursuit movement but no supranuclear gaze palsy. There were no pyramidal signs. Family history was that of “probable Parkinson’s disease” in a paternal aunt and “tremor” in a maternal aunt. He had mild urinary frequency but sphincter electromyography (SEMG) studies were highly abnormal. Neuropsychometry showed a verbal IQ of 81 and performance IQ of 76, with an
Late onset Huntington’s disease

A 52 year old white left handed woman was referred because of a 5 year history of increasing slowness and difficulty in walking. She had a family history of movement disorders including chorea and one sister was known to have parkinsonism, later diagnosed as Huntington’s disease. On examination, she had an akinetic rigid syndrome with frequent gait freezing and reduced left arm swing with dystonic posturing of the left hand. She had reduced saccadic and pursuit upgaze but no supranuclear downgaze paresis, impersistence of tongue protrusion, or chorea. The initial diagnosis was thought to be a variant of akinetic rigid syndrome. Levodopa therapy at a dose of 600 mg produced moderate benefit but unmasked slight chorea of her face and limbs after therapy for 1 year. Neuropsychometry showed a verbal IQ of 90 and a performance IQ of 95 with an estimated IQ of 94. Other tests were rated as average. A genetic test for Huntington’s disease was positive (table). Levodopa therapy had to be discontinued because of dyskinesias and decreased response with time.

CASE 2
A 67 year old right handed white man was referred with a 6 year history of slowness of manual dexterity and gait. He and his carer denied history of cognitive decline, falls, or urinary difficulties although there was erec-tile dysfunction. His father was thought to have Parkinson’s disease and family history was otherwise negative. On examination, he had a bradykinesia dominant akinetic rigid syndrome with a left sided emphasis and impaired postural reflexes. In addition, there was a right laterocollicis and dystonic posturing of his left hand. Eye movements showed breaking up of smooth pursuit but no supranuclear gaze palsy or impersistence of tongue protrusion. A levodopa challenge test was strongly positive with greater than 40% improvement in KCHPDRS and he was thought to have Parkinson’s disease or the parkinsonian variant of MSA (MSA-P). Neuropsychometry showed a verbal IQ of 105 and a performance IQ of 93 with an estimated IQ of 95. All other neuropsychological testing was rated at the average level with no significant impairment. Brain MRI showed abnormal enhancement at the striatal region. Genetic tests performed because of family history of parkinsonism and dystonia at onset of illness was negative for DRPLA but positive for Huntington’s disease (table). At 2 year follow up the patient continues to be dopa responsive (levodopa dose 800 mg) with mild progression of clinical signs (table).

CASE 3
A 52 year old white left handed woman was referred because of a 5 year history of increasing slowness and difficulty in walking. She had a family history of movement disorders including chorea and one sister was known to have parkinsonism, later diagnosed as Huntington’s disease. On examination, she had an akinetic rigid syndrome with frequent gait freezing and reduced left arm swing with dystonic posturing of the left hand. She had reduced saccadic and pursuit upgaze but no supranuclear downgaze paresis, impersistence of tongue protrusion, or chorea. The initial diagnosis was thought to be a variant of akinetic rigid syndrome. Levodopa therapy at a dose of 600 mg produced moderate benefit but unmasked slight chorea of her face and limbs after therapy for 1 year. Neuropsychometry showed a verbal IQ of 90 and a performance IQ of 95 with an estimated IQ of 94. Other tests were rated as average. A genetic test for Huntington’s disease was positive (table). Levodopa therapy had to be discontinued because of dyskinesias and decreased response with time.

CASE 4
A 68 year old white man presented with a 4 year history of unsteady gait and swallowing difficulties. There was history of parkinsonism, epilepsy, motor neuron disease, and narcolepsy in the family. On examination, he had mild asymmetric parkinsonism with global hyporeflexia, extensor plantar responses, heel-toe ataxia, dystonia of lower limbs, but normal eye movements. There was a mild dysdiadochokinesis. The differential diagnoses included spinocerebellar ataxia, MSA, and other hereditary degenerative akinetic rigid syndromes. Levodopa therapy (300 mg) improved bradykinesia and rigidity and the patient continues with 400 mg of levodopa at 2 year follow up. Formal neuropsychometry could not be performed but a mini mental state examination documented a score of 25/30. Brain MRI showed generalised cerebral and caudate atrophy. A genetic test for Huntington’s disease was positive (table). In all patients the following tests were normal or negative: an autoantibody and acanthocyte screen, thyroid function tests, vitamin B12/folate concentrations, angiotensin converting enzymes, lysosomal enzymes, urinary organic and amino acids, slit lamp examination of eye, and serum copper and ceruloplasmin (case 3).

Autonomic signs and symptoms were evident in all patients and included mild but significant systolic postural hypotension in three patients (figure). Additionally, urinary frequency was present in patients 1 and 4 and
Reuter, Hu, Andrews, et al showed supranormal D2 receptor binding in reduced dopamine release. The caudate D2 receptors had reduced caudate and putamen suggesting early Huntington’s disease. Patients receptor binding in this patient was reduced, PET was performed in patients 1, 2, and 3. Patient 1 had a striatal fluorodopa uptake within the normal range and patient 2 demonstrated markedly reduced and asymmetric fluorodopa uptake in the putamen (right more affected than the left) with relative caudate sparing.11Vraclopride PET studies in patient 2 showed supranormal D2 receptor binding in the right putamen suggesting an up regulation of postsynaptic D2 receptors in response to reduced dopamine release. The caudate D2 receptor binding in this patient was reduced, suggesting early Huntington’s disease. Patients 1 and 3 had reduced caudate and putamen11V raclopride binding.

Discussion
This series of four patients illustrates that (a) levodopa responsive parkinsonism may be a presenting feature of late onset Huntington’s disease; (b) these patients may be misdiagnosed as MSA or atypical akinetic rigid syndromes; (c) dysautonomia may complicate clinical diagnosis in favour of MSA; and (d) a family history of “Parkinson’s disease” may be a misleading clue in these cases.

We think that this is the first report of a series of patients with Huntington’s disease presenting with a moderately levodopa responsive parkinsonism, mild dysautonomia, and a family history of parkinsonism. Other atypical features include the late age of onset of disease (56.75 years), asymmetric parkinsonism, absence of eye or tongue movement abnormalities seen in Huntington’s disease, abnormal sphincter EMG in one patient, lack of appreciable limb chorea and cognitive abnormalities, and mild dysautonomia manifest as postural hypotension, urinary frequency, and hyperhidrosis. Reports of such patients are extremely rare although recently two such patients have been described and one of these, reported on by Racette and Perlmutter,7 had a family history of a tremor disorder. Rigid and akinetic forms of Huntington’s disease were also reported by Bittenbender and Quadfasel, who described four “rigid” cases of Huntington’s disease and reviewed the literature on this subject.7 The mean age of onset of disease in these cases was 15.2 years, suggesting that these were of juvenile onset and thus different from our patient group. While reviewing the literature, these authors documented 64 cases of rigid Huntington’s disease with varying combinations of chorea, family history, cognitive impairment, and a mean age of onset of 22.2 years.5

The clinical phenotype and the unusual family histories in our patients led to misdiagnosis of these cases as MSA (patients 1, 2, and 4); supported by an abnormal sphincter EMG in patient 1, query Parkinson’s disease (patient 2), and an atypical akinetic-rigid syndrome (patient 3). These diagnoses were further supported by a positive levodopa response without unmasking chorea (a feature used to test for Huntington’s disease before genetic testing), cardiovascular dysautonomia particularly postural hypotension, the presence of early falls and cranio cervical and limb dystonias, and a lack of chorea and appreciable cognitive dysfunction. The diagnosis of Huntington’s disease was suspected on the basis of the atypical signs described above and the fact that MSA is rarely familial. There was a family history of Huntington’s disease in one patient (patient 3). However, a high index of suspicion is required as otherwise our patients could have been included in a familial Parkinson’s disease or MSA study or clinical trial.

In choreic and asymptomatic carriers of the Huntington’s disease gene, workers have reported a selective depletion of enkephalin immunoreactive terminals (colocalised in the indirect D2 expressing external striatopallidal pathway).12 However, in patients with akinetic-rigid Huntington’s disease a near total loss of both indirect and direct striatopallidal fibres containing encephalin as well as GABA and substance P have been reported.12 Studies using PET have shown that reduced striatal glucose metabolism and dopamine receptor binding occurs in symptomatic patients in Huntington’s disease and reduction of striatal D1 and D2 receptor binding in about 50% of at risk asymptomatic adults and mutation carriers.12 In our series, patient 1 had normal striatal fluorodopa uptake thus ruling out concurrent Parkinson’s disease whereas in patient 2, fluorodopa uptake in the putamen was reduced in an asymmetric fashion with relative sparing of caudate as seen in Parkinson’s disease. However, in this patient, caudate D2 binding was reduced suggesting early Huntington’s disease. Although the possibility of coexistent Parkinson’s disease in this patient exists, clinically this is unlikely as there was early postural reflex impairment, laterocollis, and dystonia at the onset of disease. Furthermore, we have reported postmortem findings on another patient with late onset Huntington’s disease with levodopa responsive parkinsonism and chorea who did not have Lewy bodies.18 This also suggests that the levodopa responsiveness in Huntington’s disease is unlikely to be due to concurrent Parkinson’s disease. The issue of dopa responsiveness and parkinsonism as the presenting feature in late onset Huntington’s disease is also unusual and merits discussion.
Late onset Huntington’s disease

Although both cases reported by Trosch and LeWitt8 and Racette and Perlmutter9 were levodopa responsive, the first responded only to large doses while in the second follow up information after 1 year is not available. Our patients (except patient 3) continue to derive benefit from a moderate dose of levodopa (mean dose 533.3 (SD 52) mg) at 2 year follow up. Benefit from levodopa in Huntington’s disease has previously only been reported in the juvenile hypokinetic-rigid variant.17 A recent11C D TBZ PET study has shown that striatal vesicular monoamine transporter type 2 (VMAT2) binding is markedly reduced in the posterior putamen of patients with akinetic rigid Huntington’s disease.16 This would indicate that the nigrostriatal pathway is additionally involved in akinetic rigid Huntington’s disease. The beneficial effect of levodopa in these patients with Huntington’s disease may reflect facilitation of neurotransmission through a damaged nigrostriatal pathway.

All our patients had small expansions of CAG repeats in IT15 (42–46, normal <38), as did the patient reported on by Racette and Perlmutter.9 Patients with juvenile onset parkinsonian Huntington’s disease tend to have CAG repeats in excess of 60, which correlates with a rapidly progressive course of Huntington’s disease, by contrast with slow progression seen in our patients. It may be speculated that the small CAG repeat expansion in our patients accounts for their slowly progressive disease.

In conclusion, we have described a distinct variant of Huntington’s disease with the following features:

1. Late onset parkinsonism with moderate and persistent dopa responsiveness at 2 year follow up, without inducing chorea.

2. Minimal or absent chorea or significant cognitive, eye and tongue movement abnormalities.

3. Family history of “parkinsonism” or other movement disorders.

(4) Mild cardiovascular dysautonomia.

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8 Trosch RM, LeWitt PA. Westphal variant Huntington’s disease masquerading as MSA. Mov Disord 1996;11(suppl 2):181.


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