Late onset of Huntington's disease

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SUMMARY Twenty-five patients with late-onset Huntington's disease were studied; motor impairment appeared at age 50 years or later. The average age at onset of chorea was 57·5 years, with an average age at diagnosis of 63·1 years. Approximately 25% of persons affected by Huntington's disease exhibit late onset. A preponderance of maternal transmission was noted in late-onset Huntington's disease. The clinical features resembled those of mid-life onset Huntington's disease but progressed more slowly. Neuropathological evaluation of two cases reveal less severe neuronal atrophy than for mid-life onset disease.

Huntington's disease, a progressive disorder characterised by dementia and chorea inherited as an autosomal dominant disorder, displays striking variability in clinical manifestations and age at which first symptoms appear. It usually begins in mid-life, between ages 21 and 50, with an average age at onset of 41 years.[1–3] Chorea and cognitive impairment slowly worsen for 15 to 20 years and death most commonly results from intercurrent infection at an average age of 54 years.[4]

The expression of Huntington's disease is influenced by the sex of the affected parent. A preponderance of paternal transmission has been reported for cases with onset before age 21.[5–10] In contrast, among cases of late onset (first symptoms at age 50 or later), more cases may inherit the gene from an affected mother than from an affected father.[11 12]

Early onset is associated with the rigid-type or Westphal variant of Huntington's disease. Among 70 cases of rigid Huntington's disease, Bittenbender and Quadfasel[13] found a mean age at onset of 22·2 years. The rare juvenile form of Huntington's disease with onset between ages 4 and 10 (2% of all cases), is characterised by rigidity, bradykinesia, seizures and mental retardation and the duration

appears to be shorter than for mid-life onset Huntington's disease.[14 15] Huntington's disease in adolescence (ages 10 to 20, 4% of all cases) more closely resembles the mid-life onset form.

Although cases of late-onset have been mentioned since 1916[1 16 17] the frequency of the manifestation of Huntington's disease late in life has not been widely appreciated. We report 68 cases of late-onset Huntington's disease.

Methods

One hundred and eleven individuals were examined with the diagnosis of Huntington's disease confirmed by neurological evaluation. One hundred and one family histories were collected through interviews and medical record review as previously described.[12] In each family the proband was diagnosed as having Huntington's disease by a neurologist.

Onset of Huntington's disease for this study was defined as the age at manifestation of movement disorder (combinations of gait or handwriting disturbance, subtle twitches, frequent accidents, dropping objects, or incoordination which evolved into unequivocal impairment). Although several patients had exhibited mild affective disorder and suspected dementia prior to motor onset, impaired motor function was emphasised in defining onset because behavioural changes in Huntington's disease may be substantially influenced by family and employment stability.[18 19] Information about sex, dates and places of birth and death, causes of death, and number of children was collected for all family members. Age at onset of chorea and psychiatric symptoms, and age at diagnosis were documented whenever possible.

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Table 1

	Physical Disability Scale		Independence Scale
100	Normal, no disease evident	100	No special care needed.
90	Onset-minimal signs, slight facial or extremity movement disorders.	90	No physical care needed if difficult tasks are avoided.
80	Normal daily activity with effort, gait disturbance, stumbling, slurred speech.	80	Pre-disease level of employment changes or ends, cannot perform hh chores to pre-disease level, may need help with finances.
70	Limited activity, occasional falls, overt chorea; less speech with dysarthria, occasional swallowing difficulty.	70	Self care maintained for bathing, limited hh duties (cooking and use of knives), driving terminates, unable to manage finances.
60	Can be left alone for short periods of time, several falls, can walk up to 1 block outside home.	60	Needs minor assistance in dressing, toileting, bathing. Food must be cut for patient.
50	Needs assistance in walking, ambulation limited to home; difficulty communicating and swallowing.	50	24 hour supervision appropriate. Assistance required for bathing, eating, toileting.
40	Limited ability to walk assisted, single word utterances.	40	Chronic care facility needed. Limited self feeding, liquified diet.
30	Confined to wheel chair, unintelligible speech, frequent choking.	30	Patient provides minimal assistance in own feeding, bathing, toileting.
20	Completely bedridden, anarthria.	20	No self care, must be fed.
10	Fixed posture requiring total care—gastrotomy, catheterization.	10	Tube feeding, total bed care.

Disability rating = mean of Physical Disability and Independence Scales

Twenty-five persons with late-onset Huntington's disease were examined by one of three physicians affiliated with the Centre (DS, EB, or JM) who recorded the results of a standard neurological evaluation. An assessment of disability was made by averaging the patient's ratings on a Physical Disability Scale and an Independence Scale (table 1) assigned at the time of examination. In addition, a rating of (−) not present, (+) suspected, or (++) definitely present was made for the symptoms of depression, euphoria, anxiety, apathy, angry/assaultive behaviour, paranoia, hallucinations, sleep disturbance, suicidal ideation, cognitive impairment, swallowing difficulty, speech difficulty, bladder incontinence and bowel incontinence. The presence of each of the above was assessed by clinical observation at the time of the neurological evaluation and through inquiry of the patient and accompanying family members. Gait disturbance, plantar response, tendon reflexes, chorea, ankle clonus, rigidity and seizures were also recorded.

Statistical analysis was made by Pearson correlation, nonparametric correlation using Kendall's tau, analysis of variance and chi square.

Results

I. Population description

One hundred and one apparently unrelated pedigrees containing 3717 individuals were collected from families having members diagnosed with Huntington's disease. Five hundred and twenty-two living or deceased individuals affected by Huntington's disease were identified in the family histories.

Onset age of symptoms was ascertained for 243 of these affected individuals with a mean age of 40·95 years and a range from 4 to 75 years. Sixty-eight persons (28%) had onset after age 50. The sex of the affected parent was identified for 206 of these 243; 102 inherited the Huntington's disease gene from an affected father and 104 from an affected mother. The average age at onset for the 37 persons for whom the affected parent was not identified was 49·47 years. The age at death was ascertained for 111 of the Huntington's disease patients with an average of 56·7 years. Offspring of mothers affected by Huntington's disease had a later average onset age ($\bar{x}$ = 43·47) than offspring of affected fathers ($\bar{x}$ = 35·13, p < 0·0001).

The 68 late-onset cases came from 46 apparently unrelated families. One family had six late-onset individuals, another had five, three families had three cases, and seven families had two late-onset members. The mean age at onset of the 68 late-onset cases was 56·2 years. There was a nearly equal sex distribution among the late-onset cases with 33 men and 35 women. As previously reported,[11] the affected parent was identified for 43 of the late-onset patients; thirteen inherited the Huntington's disease gene from an affected father and 32 from an affected mother. The mean onset of the late onset cases of maternal descent was 58·3 and the mean onset of the mothers was 52·0 years. Of the remaining 25 for whom the affected parent could not be identified, 21 had affected siblings or offspring and two were adopted. Huntington's disease was confirmed by necropsy for one of the adopted patients. The other two had no family history of Huntington's disease.

Twenty-five of the 111 Huntington's disease patients examined at the Centre exhibited initial symptoms at age 50 or later. Twelve men and thirteen women were examined (table 2). The average age of onset for this group was 57·5 years with an average age at diagnosis of 63·1 years and an average age at last examination of 67·8 years.

II. Motor system

The age at onset was designated as the age at which

Table 2   Late onset Huntington's Disease, ranked by duration of illness (N =25)

Case	1	2	3	4	5	6	7	8	9	10	11	12	13
Age at examination	55	56	57	61	67	70	70	64	59	67	70	59	68
Age at diagnosis	55	53	54	56	66	68	66	63	58	60	66	57	61
Age at onset	53	51	52	56	62	65	65	58	52	60	62	50	59
Duration	2	5	5	5	5	5	5	6	7	7	8	9	9
Disability rating	95	80	90	75	70	95	70	95	85	50	70	90	30
Sex	M	M	F	M	M	M	F	M	M	F	M	F	F
Depression	++	++	—	++	—	—	—	++	++	+	—	++	+
Euphoria	—	—	—	—	—	—	—	—	+	—	—	—	—
Anxiety	+	++	—	++	+	—	—	++	—	++	—	++	—
Apathy	—	++	+	++	—	—	—	+	—	++	—	++	—
Angry/assaultive	++	—	++	++	—	—	—	++	+	—	—	—	++
Paranoia	++	—	++	++	—	—	—	+	—	—	—	—	—
Hallucinations	—	—	—	—	—	—	—	—	—	—	—	—	—
Sleep disturbance	—	++	++	++	—	—	—	—	—	+	—	—	—
Suicide attempts	—	—	—	+	—	—	—	—	—	—	—	—	—
Dementia	+	+	++	++	++	+	++	+	++	++	++	++	++
Speech difficulty	—	—	—	+	++	+	++	+	+	++	++	+	++
Swallowing difficulty	—	—	—	—	+	—	—	—	++	+	+	—	++
Bladder incontinence	—	—	+	—	+	—	—	—	—	—	—	—	++
Bowel incontinence	—	—	—	—	+	—	—	+	—	—	—	—	++
Gait Disturbance	—	—	+	—	+	—	+	—	—	++	+	+	++
Non ambulatory	—	—	—	—	—	—	—	—	—	—	—	—	++
Institutionalised/ nursing home*	—	—	—	—	+	—	+	—	—	—	—	—	++

(—) Not present (+) Suspected *(+) Short duration (++) Definite

motor impairment was initially noted by patient and family. Some patients reported signs of cognitive impairment or depression before chorea but the diagnosis of Huntington's disease was not made on the basis of these symptoms alone. All of the 25 diagnosed patients had chorea and hypotonia. Eighteen had gait disturbance and 15 had dysphagia. These two symptoms gradually became more prominent and were correlated with duration of illness (t = 0·53, p < 0·001; t = 0·49, p < 0·002 respectively). Six patients were nonambulatory after symptoms for 9 to 17 years. Speech was intelligible for all patients although dysarthria became apparent shortly after onset. The length of illness did not correlate with bladder or bowel incontinence.

III. Mental and Affective Status

All 25 examined patients had evidence of cognitive impairment. Five patients had neuropsychological testing and two continued to perform at average levels but exhibited memory impairment and complained of a decline in intellectual ability (patient No 2 WAIS IQ = 68; No 7 WAIS IQ = 64; No 9 WAIS IQ = 106; No 11 WAIS IQ = 73; No 17 WAIS IQ = 100).

Depression was more likely to be noted early in the illness and was negatively correlated with duration of illness (t = −0·39, p < 0·01). Anxiety, while not significantly inversely correlated with duration (t = −0·23, p < 0·09), was correlated with depression (t = 0·40, p < 0·02). Apathy also correlated with depression (t = 0·37, p < 0·03). The presence of angry or assaultive behaviour was unrelated to

the duration of the illness and was not significantly more common among men. Paranoia correlated with angry/assaultive behaviour (t = 0·67, p < 0·001). Less than half of the group exhibited depression, anxiety or apathy.

Although depressive reaction with anxiety was present in six patients, no psychiatric disorders required hospital care. Four patients with depression responded to treatment with tricyclic drugs, and two patients with angry or assaultive behaviour were responsive to neuroleptics.

Five patients had sleep disturbance and three of these five were also depressed. One patient with depression and sleep disturbance was found to have sleep apnoea.

IV. Course of the illness

The average disability rating for the 25 examined patients was 64·4 (see table 1). The disability ratings of patients with late-onset Huntington's disease showed a gradual fall-off in functional status. However, prolonged maintenance of a particular rating level suggested that, for some patients, the illness remained stable for several years. Fourteen patients had disability ratings of 70 or more after a mean duration of 7½ years. These people continued to maintain self-care for bathing and household duties.

The disability rating was made on the basis of observed and reported functional status. An inter-rater reliability measure for fourteen persons examined by two of us (DSS and JBM) produced a Spearman correlation of 0·83 (p < 0·0003). The rating was significantly inversely correlated to dura-

14	15	16	17	18	19	20	21	22	23	24	25	Total
68	61	62	76	71	70	68	71	77	82	87	80	x̄ = 67·8
67	52	56	74	66	57	55	68	77	80	83	59	x̄ = 63·1
58	50	51	65	58	55	52	54	60	65	70	55	x̄ = 57·5
10	11	11	11	13	15	16	17	17	17	17	25	x̄ = 10·3
60	25	30	80	50	80	20	45	80	50	40	45	x̄ = 64·4
F	F	M	F	M	F	M	F	M	F	F	F	12M/13F
—	+	+	—	+	—	—	—	—	—	—	—	11
—	—	—	—	—	—	—	—	—	—	—	—	1
—	—	—	—	—	++	+	—	—	+	—	—	10
+	—	—	—	—	—	+	—	—	—	—	—	8
—	—	+	—	++	—	++	+	—	—	—	—	10
—	—	—	—	—	—	+	—	—	—	—	—	5
—	—	—	—	—	—	+	—	—	—	—	—	1
—	—	—	—	—	—	—	—	—	—	++	—	5
—	—	—	—	—	—	—	—	—	—	—	—	1
++	++	++	++	++	++	++	++	++	++	++	++	25
++	++	++	+	++	++	++	++	+	++	++	++	22
—	++	++	++	+	—	++	++	—	++	++	++	15
++	—	+	—	+	—	++	+	—	—	++	—	9
+	—	+	—	+	—	++	—	—	—	++	—	8
++	++	++	—	+	+	++	++	+	++	++	++	18
—	++	++	—	—	—	++	++	—	—	++	—	6
—	++	++	—	—	—	++	—	—	+	++	+	9

tion of disease (r = −0·54, p < 0·003). The disability rating was also significantly inversely correlated with cognitive impairment, swallowing difficulty, bladder and bowel incontinence, gait disturbance and institutionalisation, but did not correlate with depression, anxiety, apathy, angry/assaultive behaviour, paranoia or sleep disturbance.

Three of the 25 examined patients died after the evaluation, with symptoms for 13, 17 and 25 years. The causes of death were choking, a ruptured abdominal aneurysm and congestive heart failure.

V. Computed tomography (CT) and neuropathology
CT showed frontal horn to inter-caudate ratios of less than 2·0 for all nine patients tested (Nos 2, 3, 7, 11, 17, 18, 19, 22, 24) consistent with caudate atrophy seen in Huntington's disease.[20]

Postmortem examinations were performed on two cases. In one (patient No 22) changes of Alzheimer's disease (large numbers of neuritic plaques and neurofibrillary tangles in virtually all areas of the cerebral cortex) were noted in addition to those of Huntington's disease. In the other (No 18), there were several small haemorrhagic cerebral infarctions in addition to signs of Huntington's disease. The first case had minimal atrophy of the head of the caudate but the second did not show caudate atrophy on gross examination. In both cases mild neuronal loss and gliosis in the caudate nucleus were indicative of Huntington's disease. CT scan in both cases had revealed caudate nucleus atrophy.

Discussion

Approximately 25% of persons affected by Hun-

tington's disease exhibit initial signs of chorea at age 50 or later and half of these will not come to medical attention until after age 60. Senile chorea and Alzheimer's disease must be considered in the differential diagnosis of late-onset Huntington's disease. The diagnosis of senile chorea has been made when chorea occurs late in life without a family history.[21] Senile chorea without dementia has been reported,[22] but we concur with the view that senile chorea is often Huntington's disease with an obscured family history.[23 24]

A rating scale for degree of physical disability and independence in function was designed to assess stage of disease. This scale, in contrast to the previously reported scale of functional assessment,[25] evaluates late stages of disease occurring after chronic hospitalisation. Rating of disability correlates significantly with time since onset.

The clinical features of late-onset Huntington's disease resemble those of midlife onset but the illness is more slowly progressive and less functionally debilitating. Evidence of decline in cognitive function was found for all cases; however, persons with above average intelligence prior to onset continued to perform in the average range in formal testing. Slowly progressive chorea and cognitive impairment are the hallmarks. In late-onset Huntington's disease, symptoms may appear to plateau or progress very slowly over several years. The most common symptoms in our 25 examined late-onset cases were mild to moderate chorea and cognitive impairment (100% of the cases), dysarthria (88%) and gait disturbance (72%). The moderate aspect of the chorea in late-onset Huntington's disease often allows the patient to stay at home, with minimal nursing sup-

port, to remain ambulatory, and to maintain activities of daily living for many years.

We found minimal changes on neuropathologic evaluation of two cases, suggesting that neuronal loss was less severe than in cases of early or midlife onset. Although these two cases died of causes other than those usually associated with Huntington's disease, they nevertheless experienced prolonged illness. These data suggest that the pathology of late-onset Huntington's disease may be less likely to reflect the morphologic changes usually associated with Huntington's disease. Neuropathologic features of Alzheimer's disease were found in one case in addition to those for Huntington's disease.

The preponderance of affected mothers for this population has been previously reported.[12] A maternally transmitted factor such as a cytoplasmic organelle or a maternal intrauterine modification have been proposed to account for the effect of the sex of the affected parent upon onset age in the offspring. These late onset offspring of affected women had an older mean onset age than did their mothers, suggesting a maternally transmitted factor which delays onset in Huntington's disease. The collection of family history may be more difficult in late-onset cases because members of prior generations are more likely to have been late-onset and to have died before experiencing impairment. This emphasises the importance of evaluating siblings in pursuing a family history for the diagnosis of Huntington's disease.

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