

Huntington Disease: Report of First Case Documented in Malaysia

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Summary

Huntington disease has not previously been recorded in Malaysia. We report the first case in a local patient with a positive family history. The implications of diagnosing this disease will be discussed.

Key Word: Huntington disease

Introduction

Huntington disease (HD), described by George Huntington in 1872, is a genetic disorder which is characterised by involuntary movements and dementia beginning in midlife, with unrelenting progress to complete disability and death within 15 - 20 years¹. It has hitherto not been described in Malaysia. We report the first documented case of HD, a patient originating from Hutan Melintang in the West Malaysian state of Perak.

Case Report

A 40-year-old Malay man presented with a ten-year history of involuntary movements and two years of deterioration in cognitive function.

The involuntary movements began in the right upper limb, followed sequentially by the left upper limb, left lower limb and finally the head and neck. The movements occurred during wakefulness and were absent in sleep. They were described as jerky and non-purposeful. His gait assumed a dance-like character.

Impairment of cognitive function was gradual with poor memory for recent events and deteriorating intellect. He had been unable to work as a machine operator for the last three months. There was no history of drug abuse or prior administration of neuroleptic agents.

His maternal grandfather suffered from a dementing illness and died at the age of 25. His mother also died of a similar illness at the age of 25, as did her two sisters, at ages 28 and 16 respectively. His parents' marriage was not consanguineous. None of his living siblings (three brothers and one sister) was affected. The patient had seven children aged 17 years to two months, all of whom were well.

Physical examination showed choreo-athetoid movements of both upper and lower limbs and a jerky almost rhythmic dance-like gait. He had darting movements of the tongue and jerky, pecking bird-like movements of the head and neck. The tone, power and reflexes were normal. There was no cranial nerve palsy. Examination of the other systems was unremarkable.

CASE REPORT

Mental function testing revealed impaired short-term memory with preservation of remote memory. Concentration was poor and he was unable to perform the serial sevens test. There was no abnormal thought content.

Blood counts and sedimentation rate were normal and acanthocytosis was not demonstrated. Routine laboratory tests, including liver function tests, were normal, as were chest radiography and electrocardiogram. Thyroid function tests were normal. Screening for connective tissue disease was negative. The 24-hour urine copper was $0.1 \mu\text{mol/l}$ (normal 0.2-1.5) and serum copper was $11.4 \mu\text{mol/l}$ (normal 11-22). No Kayser-Fleischer ring was noted on slit-lamp examination. The cerebrospinal fluid was normal. Computed tomography of the brain is shown in Figure 1.

The patient was commenced on haloperidol 1.5 mg t.d.s. and benzhexol hydrochloride 2 mg t.d.s., with significant symptomatic relief.

Discussion

HD has been most extensively described in Caucasian

populations, where the prevalence is five to 10 per 100,000. In non-Caucasians it is believed to be less common, although documentation has been much less complete. In the Lake Maracaibo region of Venezuela, a unique focal concentration of HD has contributed enormously to the eventual identification of its gene locus.

It has often been suggested that in Oriental and African patients, the gene may have originated from Caucasian sources. In mainland China, it has been postulated that HD originated from Caucasian visitors in the 19th century², and in Zimbabwe, from Portuguese colonists from Mozambique, or other European visitors³.

It would therefore be expected that HD might occur among the multiracial population of Malaysia, in particular, those of Portuguese descent in the state of Melaka. However, to date, no case has been reported. Our patient is not known to have non-Malay ancestors. The family traces its origins to Indonesia. However, their village is close to the site of the assassination of the British Resident James Birch.

HD has long been recognised to be due to a monohybrid autosomal gene mutation transmitted by Mendelian dominant inheritance with complete penetrance. This patient's initial history suggested that only his mother was similarly afflicted. However, repeated interview of his relatives yielded a pedigree which included three other cases (Fig. 2), demonstrating an autosomal dominant mode of inheritance. This illustrates the need for detailed information gathering in order to establish the diagnosis of genetic disorders.

With the use of "reverse genetics" (now called positional cloning), the gene responsible for HD has been mapped to the distal portion of the short arm of chromosome 4 (4p16.3), 4 centiMorgans distal to the D4S10 marker. The HD gene has recently been isolated, and is named *it15*⁴. It is large gene of 100 kilobases containing 67 exons. The disease is due to a mutation consisting of an expansion of a CAG trinucleotide repeat sequence which is longer than normal in virtually all patients with HD. The messenger RNA codes for a predicted protein product

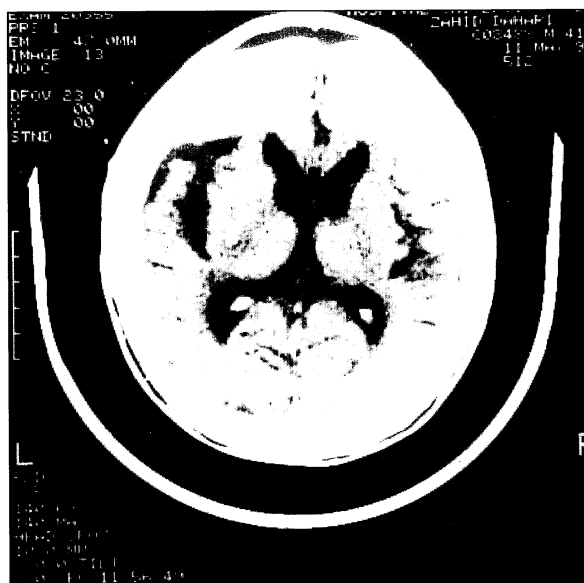


Fig. 1: CT brain scan showing (1) loss of convexity of the caudate nucleus on both sides and (2) marked cerebral atrophy and hydrocephalus

of molecular weight 348 kilodaltons. Now termed *huntingtin*, its function is as yet unknown.

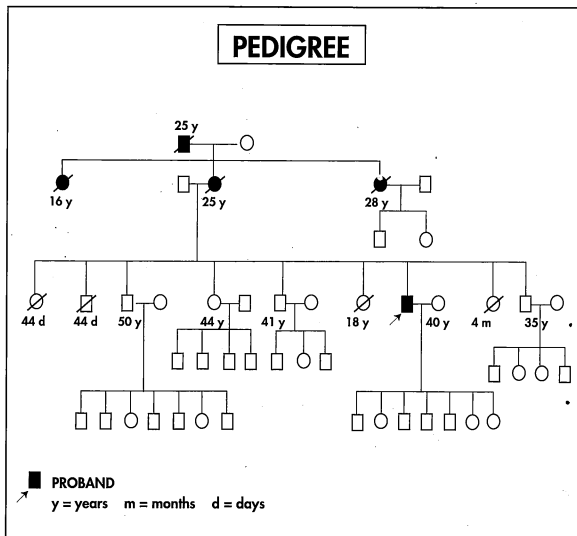


Fig. 2: Pedigree study of the patient's family

Spontaneous mutation is extremely rare in HD. To date, two cases have been proven by mutation analysis⁴. In apparently sporadic cases, incorrect paternity or illegitimacy should be suspected. Unrecognised mild disease in a parent is a much less likely cause.

Vertical transmission of HD is seen through three generations of this patient's family. It has yet to appear among his five siblings. They are, however, still young enough to be at risk of developing the disease, as 28 per cent of cases begin after the age of 50. It should be noted that the age of onset is variable even among members of the same family.

The ages at onset of HD and at death appear to have been younger in the previous two generations (Fig. 2). Onset before the age of 15 has been found in three to five per cent of cases. Disease of childhood onset is likely to progress rapidly. It is now known that the length of the trinucleotide repeat is inversely related to the age of onset⁴.

Cases of early onset are in most instances transmitted

by the father. This indeed was the case with the patient's mother and her two sisters. The molecular mechanism has been elucidated: paternally transmitted cases have a larger number of CAG repeats. Our patient, who inherited the disease from his mother, is therefore expected to progress more slowly. Paternal transmission is also associated with expansion of the repeat sequence. The p(CAG)_n sequence is particularly unstable in HD sperm. This provides a molecular basis for the phenomenon of *anticipation*, the tendency for autosomal dominant diseases to be progressively more severe in succeeding generations.

Although the characteristic movement disorder of HD is reflected in its previous name of *Huntington's chorea*, the initial signs may be subtle emotional and psychological manifestations. In early onset disease, these are likely to precede chorea and intellectual loss by many years. Our patient's movement disorder preceded cognitive impairment by about eight years.

Neuropathological damage is most severe in the striatum (caudate nucleus and putamen), where decreased glucose metabolism has been shown by positron emission tomography. This patient's CT scan demonstrated clear-cut loss of volume of the caudate nuclei indicative of atrophy. In addition, diffuse cerebral atrophy with hydrocephalus ex vacuole was already evident.

The identification of the gene mutation will provide a diagnostic test for HD, hitherto not possible with the linked DNA markers previously used. It should be realised, however, that the availability of mutation testing has serious ethical and social implications which must be anticipated⁵.

Conclusion

The gene for HD exists in Malaysia. This diagnosis should be considered when presenile dementia and choreiform movements are encountered in the setting of a positive family history. It will soon be possible to obtain molecular diagnosis in suspected cases. This will be important when treatment is eventually developed for this tragic neurologic disease.

CASE REPORT

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