



Huntington's disease: Genetic heterogeneity in black African patients

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Objective. Huntington's disease (HD) has been reported to occur rarely in black patients. A new genetic variant—Huntington's disease-like 2 (HDL2) – occurring more frequently in blacks, has recently been described. The absence of an expanded trinucleotide repeat at the chromosome 4 HD locus was previously regarded as a way of excluding classic HD. The objective of this paper is to describe a number of black patients with genetically proven HD and to review its occurrence in Africa.

Methods. Eleven black families (12 subjects), with genetically proven HD, are described: 9 from the Dr George Mukhari Hospital, and 2 from private practice in Tshwane.

Results. Chorea was present in all 12 patients and cognitive

decline in 9. Nine had an age of onset between 30 and 50 years. Six families exhibited expansion of the trinucleotide repeat at the chromosome 4, IT 15 gene (HD), and 5 a junctophilin (JPH3) trinucleotide expansion at chromosome 16 (HDL2). The HDL2 subtype showed a tendency towards a later age of onset.

Conclusions. The clinical presentation of the two genotypes (i.e. HD and HDL2) appears to be similar. The actual rate of occurrence of HD in blacks may require re-assessment. Considering the number of Huntington's chorea patients occurring in our area (Garankuwa), the possibility of clustering of the condition arises.

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George Huntington's description of Huntington's disease (HD) in 1872 (at the age of 22 years) remains the basic pillar of diagnosis: 'A hereditary chorea, tendency to insanity and suicide and its manifesting itself as a grave disease in adulthood'.¹ HD is a progressive autosomal dominant disorder, characterised by involuntary choreiform movements, psychiatric manifestations with cognitive decline and, rarely, a bradykinetic rigidity. A G8 HD probe developed in Boston for preclinical and prenatal screening of HD using molecular genetics was first acquired in South Africa in the late 1980s.² The disease has been shown to be due to an increased number of trinucleotide repeats in the IT 15 gene on chromosome 4p 16.3. Measurement of the CAG trinucleotide expansion has been found to be a highly sensitive and specific marker for the diagnosis of HD (sensitivity 98.8%; 95% confidence interval (CI) 97.7 - 99.4%; specificity 100%, 95% CI 95.2 - 100%).³ In view of the excellent sensitivity and specificity, it has been suggested that the absence of CAG repeats at chromosome 4 excludes the diagnosis of HD.⁴

Harper, in an article on the epidemiology of HD, suggested the presence of a separate mutation in people of black African origin.⁵ HD is considered rare among South African blacks, with an estimated prevalence rate of 1 per 10 million.⁶ However, this assessment was before genetic tests became available for the condition. Workers from Johns Hopkins Hospital in Baltimore, USA, have since demonstrated a repeat expansion mutation of CAG/CTG in the junctophilin-3 gene on chromosome 16q 23-24 associated with Huntington's disease-like 2 (HDL2) in 1 Moroccan and 4 African-American subjects.⁷ The present paper reports on the clinical and genetic features in 11 black African families and briefly reviews the literature on HD in blacks in Africa.

Methods

Eleven families (12 subjects) with genetically diagnosed HD were identified and described: 9 were seen at Dr George Mukhari Hospital (between January 2004 and December 2005) and 2 were from private practice in Tshwane, with 1 of the latter families seen between 2001 and 2002. The genetic tests were performed at the Division of Human Genetics, School of Pathology, National Health Laboratory Service (NHLS) and University of the Witwatersrand, Johannesburg. Every patient was assessed clinically by a qualified neurologist. A Mayo Mini Mental test⁸ was performed on 9 subjects. Some of the investigations included brain imaging, copper studies, thyroid functions, syphilis, HIV and other tests in selected patients. We also undertook a review of literature on the occurrence of HD in Africa.

Results

The clinical and genetic data are summarised in Table I. Six patients showed the clinical triad of an autosomal dominant

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Table I. Clinical and genetic data

Patients	DNA mutation	Age of onset*	Gender	Affected limbs (chorea)	Family history	Mental function (MMMS)
Patient 1	IT 15	44	F	All	+ve	27/38
Patient 2	JPH3	52	M	All	-ve	33/38
Patient 3	JPH3	46	M	All	-ve	Normal
Patient 4	JPH3	40	F	All	+ve	19/38
Patient 5	IT 15	50	M	All	-ve	23/38
Patient 6	IT 15	41	F	All	+ve	<20/38
Patient 7	IT 15	35	F	All	-ve	28/38
Patient 8	JPH3	52	M	All	Uncertain	Decreased cognition
Patient 9	IT 15	25	M	All	+ve	Normal
Patient 10 [†]	JPH3	64	F	All	+ve	23/38
Patient 11	JPH3	49	F	All	+ve	26/38
Patient 12	IT 15	40	M	All	+ve	27/38

*The average age of onset for HDL2 (JPH3) was 50.5 years, and that for HD (IT 15) 39 years.

[†]Patients 10 and 11 are mother and daughter, therefore 12 patients and 11 families.
MMMS = Mayo Mini Mental Score.

family history, chorea and dementia. Nine of the 12 subjects presented with a combination of chorea and dementia. Chorea affecting all 4 limbs was present in every subject. The facial and neck movements were not observed in 1. The dementia was of a moderate to severe degree, and no patient had a picture of bradykinetic rigidity. No history of mixed ancestry could be obtained.

Six patients had an IT 15 mutation on chromosome 4 (HD1), and another 6 had a JPH3 mutation (HDL2). Those patients with a JPH3 (HDL2) abnormality tended to have a later age of onset for the chorea (average age of onset 50.5 years compared with 39 years for the IT 15 mutation). There was otherwise no recognisable difference in clinical presentation between the patients with HD1 and those with HDL2. We were unable to obtain a positive family history in 4 patients, who were proven genetically to suffer from the condition (2 with HD1, and the other 2 with HDL2).

Discussion

The diagnosis of HD has rested mainly on the clinical triad of an autosomal dominant family history, a history of progressive chorea, and dementia (usually presenting in middle adult life).¹ The most consistent finding in our series was the presence of chorea which, because of its conspicuous nature, might have prompted the patients to seek medical attention. Two patients presented with normal cognitive function even though diagnosed positively on genetic testing (we expect that cognitive decline may develop with time). The ratio of the occurrence of HD and HDL2 was 1:1 among our patients. Although the numbers are small, they do suggest a higher

occurrence of the HDL2 variant in this population than has been generally held. However, further studies and a larger number of black patients will be necessary before we can make definitive conclusions. There seems to be no clear difference in clinical presentation between the two genotypes except that the age of onset of chorea in the HDL2-type patients showed a tendency to be later than in the HD subjects. None of our patients presented with a bradykinetic rigidity syndrome, as may be seen in the Westphal variant; however, larger numbers of black patients are needed for further investigations.

Having undertaken a detailed enquiry, we found that 4 patients had an apparently negative family history. *De novo* mutations in HD have rarely been described but do not appear to be a well-recognised phenomenon.^{9,10} It is more likely that information was missing in the patients' histories that may require further evaluation.

The discovery of a second genetic locus, resulting in HDL2,⁷ suggests the need for reassessment of the actual occurrence of HD in black patients, with its associated implications for informed genetic counselling. The junctophilin-3 (JPH3) gene encodes a protein thought to be involved in the formation of junctional membrane structures and in the regulation of intracellular calcium.¹¹

A synopsis of disease reports on clinical HD in South Africa appears in Table II. A report of a suspected patient with HD in a Zulu family appeared in 1962.¹² A doyen of South African neurology commented in 1973 that he had not encountered Huntington's chorea in black patients.¹³ The minimum prevalence of the disease in the coloured population was reported to be 3.5/100 000;¹⁴ 16% of these patients had an age



Table II. Clinical studies of Huntington's disease in South Africa

First author, year of publication	Number of patients (number of families)	Comments
Klintworth, ¹¹ 1962	(1)	
Cosnett, ¹³ 1973		HD in blacks not encountered
Saffer, ²⁶ 1974	5 (1)	Coloured family Juvenile Huntington's (JH)
Hayden, ¹⁴ 1977	26 (14)	Cape Coloured families High frequency (JH)
Glass, ¹⁶ 1979	2 (1)	Black family
Hayden, ²⁷ 1980		Social perspectives discussed
Hayden, ²² 1980	>200 (50)	Afrikaner population Progenitor 17th century
Hayden, ⁶ 1980	481	National survey
Hayden, ¹⁵ 1982	17	Children comprised 7.7% of patients in survey
Hayden, ¹⁷ 1982	157	Collected data on 328 deceased individuals
Joubert, ¹⁸ 1988	8 (4)	Black patients (2 childhood)

of onset <20 years. The incidence of juvenile HD was found to be higher in this group than in the white population, and in fact to be one of the highest in the world.^{14,15} In 1979, Glass and Saffer reported Huntington's chorea in a black family.¹⁶ The comment was made that the family was probably of mixed ancestry and, quoting the authors, 'The impression gained from

the literature that Huntington's chorea rarely occurs in Blacks is strengthened'. In a South African national survey reported in 1980,⁶ 481 persons, including only 11 blacks, were identified as having died of or been afflicted with the disorder at the time. A prevalence rate of 0.1 per million was estimated in the South African 'Negro' population – much lower than the estimate of 22 per million in the white and coloured groups.⁶ A subsequent national survey on HD identified only 3 black patients out of a population of 19 million.¹⁷ The 4 black families with HD reported by Joubert¹⁸ emanated from a similar Medunsa geographical drainage area as our present report. This link may possibly represent a form of clustering of patients, as was suggested to have occurred in Tanzania¹⁹ and also in a survey from Maryland, USA,²⁰ where 61 black patients with HD were recorded with a high point prevalence of 6.37/100 000. Ninety-eight black patients with HD were reported from South Carolina.²¹

HD was reported to be prevalent among the Afrikaner population of South Africa;²² the origin of the gene in that population has been traced over 14 generations from the present to the days of the first free burghers at the Cape of Good Hope in the late 17th century. Over 200 affected individuals in more than 50 supposedly unrelated families have been found to be ancestrally related through a common progenitor from that period.²²

A synopsis of clinical HD reports from the rest of Africa is shown in Table III. Scrimgeour and Simpson,²³ in a literature survey on HD in Africa, refer to reports from Kenya, Northern Tanzania, Nigeria, Togo, Zimbabwe and Ghana, and suggested that there could well be foci of the disease in Africa that were as yet unidentified for various reasons.

Table IV presents a summary of genetic studies on HD from Africa. Scrimgeour *et al.*²⁴ and Silber *et al.*²⁵ reported genetically confirmed HD patients in Africa. Heckmann *et al.*⁴ drew attention to the possible value of negative CAG trinucleotide testing on chromosome 4. Our paper supports the presence of a genetic heterogeneity involving two loci in patients with a

Table III. Clinical studies of Huntington's disease from the rest of Africa

First author, year of publication	Country	Number of patients (number of families)	Comments
Gordon, ²⁸ 1935	Kenya	1	'No family history'
Hutton, ²⁹ 1956	Uganda	1	'Typical example'
Harries, ³⁰ 1973	Kenya	(2)	Hereditary nature unclear
Samuels, ³¹ 1978	Rhodesia	4 (1)	
Scrimgeour, ¹⁹ 1981	Tanzania	2 (1)	Good literature review of Africa
Scrimgeour, ³² 1982	Tanzania	57 (23)	50 out of 57 potential choreics
Aiyesimoju, ³³ 1984	Nigeria	4	Review of 2.1 million patients over 25 years
Scrimgeour, ³⁴ 1992	Zimbabwe	13 (3)	



Table IV. Genetic studies of Huntington's disease from Africa

First author, year of publication	Country	Number of patients (number of families)	Comments
Silber, ²⁵ 1982	South Africa	(5)	Black. Expanded trinucleotide repeats
Hayden, ² 1987	South Africa		Discussion of impact of molecular genetics
Scrimgeour, ²⁴ 1995	Sudan	1 (1)	Genetic CAG repeat confirmation, first reported case in Sudan
Greenberg, ³⁵ 1991	South Africa	(10)	2 white, 4 coloured, 2 black
Kromberg, ³⁶ 1999	South Africa	30	Prenatal predictive testing
Kabore, ³⁷ 2000	Burkina Faso	4(2)	Separate mutations
Heckmann, ⁴ 2001	South Africa	3	Absence of CAG repeats Chromosome 4 against HD
Bardien, ³⁸ 2007	South Africa	(1)	HDL2 phenotype can differ from typical HD
Magazi, 2008 Present study	South Africa	12 (11)	Black families 6 HD1 5 HDL-2 Genetic heterogeneity

clinical HD phenotype, making it important to assess patients clinically and to test for both HD and HDL2 before making a diagnosis. Furthermore, HD is still reported less frequently in black patients than in white patients. There is a need to reassess the prevalence estimates now that definitive genetic testing is available.

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