Huntington's Disease in a Coloured Family

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SUMMARY

A South African Coloured (of mixed descent) family with Huntington's disease in which all four members of one sibship, ranging in age from 16 to 23 years, are affected, is described. One generation back, definitely two, and possibly three, members of a sibship of six were affected with the adult form.

The offspring of the one affected male all show some evidence of this condition, the age of onset being between 13 and 16 years. The offspring of the one female carrier who was definitely affected do not at this time appear to have been affected.

The literature concerning juvenile Huntington's disease, especially with regard to its clinical presentation, EEG, and air encephalographic findings, is reviewed and compared with the family described. The predominance of rigidity and akinesia in the juvenile form, as opposed to chorea, which is the main adult extrapyramidal manifestation, is stressed.

This is, to our knowledge, the first report of a Coloured (mixed descent) family's manifesting the clinical features of juvenile Huntington's disease.

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In 1872 George Huntington described an illness which was characterised by progressive dementia and involuntary choreiform movements,[1] and which was familial. The original family which he reported lived in Long Island, New York, and were descended from an Eastern English immigrant whose family was affected. The immigrant eloped to America, because his fiancée's parents would not allow their daughter to marry into a family which appeared to have inheritable lunacy. He also described the inheritance of this disease, which is that of an autosomal dominant gene with total penetrance.[2]

This disease has since been named after Huntington, and although he described it as occurring during early and middle adulthood, it has since been described in young and teenage children of affected parents.[3] The disease in children appears to have certain different manifestations as compared with the adult form. Thus, instead of chorea, the predominant extrapyramidal abnormalities are rigidity and akinesia. This condition appears to be very rare; Hansioto *et al.*,[4] who reviewed all the reports appearing in the Anglo-American literature between 1925 and 1968, found only 20 cases. To our knowledge, this is the first documentation of a South African Coloured (of mixed descent) family's manifesting the very rare juvenile form of Huntington's disease in 4 siblings, and the adult form in one of their aunts. The history obtained concerning the father is vague and inconclusive.

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THE FAMILY

Case 1

The proband, a 16-year-old girl, was admitted to hospital for control of major epileptic seizures. Over a 6-month period, her schoolteacher had noted a marked deterioration (which had begun 2 years previously) in her school performance and social behaviour. During that time, she became increasingly tense and withdrawn, was unable to concentrate in class, and her handwriting deteriorated from a neat and well-formed script to a large and irregular scrawl. She left school during 1971 without completing the fifth year of schooling.

Her mother focused our attention on the rest of the family. The father died at the age of 50 years, after a 5-year illness characterised by progressive dementia and involuntary choreiform-like movements. The 4 children had, between the ages of 14 and 16 years, manifested intellectual deterioration and voice changes; there had also been difficulty in walking and in making voluntary movements.

Examination revealed a tense, anxious teenage girl of low intelligence. Central nervous system examination revealed intact cranial nerves, no sensory deficiency and normal reflexes. There were mild intermittent choreiform movements of the hands and legs, which were present at rest, but which, on attempted movement, became so aggravated that she was unable to walk. Apart from the involuntary movements there were no motor abnormalities, and in particular, no rigidity. Her voice was high-pitched, dysarthric and dysphonic. Her tongue showed involuntary movements, especially when repeated activities were required. Speech was slurred, especially when she became excited. Her breath stream pulsed on exhalation. The rest of the physical examination was normal.

Laboratory investigations: Haemoglobin was 13,9 g/100 ml, haematocrit 38,9% and white cell count 6 500/mm^3, with a normal differential count. Lumbar puncture showed clear fluid, no cells, protein 13 mg/100 ml, sugar 57 mg/100 ml, chloride 118 mg/100 ml and Wassermann reaction was negative. Serum caeruloplasmin was found to be 48 mg/100 ml, and serum copper 96 μg/100 ml (normal 70 - 165). Urine chromatography showed no increase in urine amino acids.

Electro-encephalography revealed abnormal generalised sharp wave activity, with photic stimulation, on a normal background.

Air encephalography showed moderate enlargement of the lateral ventricles, with loss of convexity of the lateral walls and widening of superior lateral angles of the lateral ventricles. There was excess air in the sulci over the cerebral cortex, especially over the frontal poles.

Case 2

An 18-year-old brother of the proband was employed as a labourer, and had always held unskilled jobs since leaving school in his 10th year of schooling. The symptoms of his illness began when he was 14 years of age.

He appeared to have marked intellectual impairment. His general knowledge regarding everyday current events was negligible. There was marked bradykinesia, clumsiness, and dystonic posturing of his hands, arms and neck. Speech was slurred and dysphonic. He showed intermittent rigidity with cogwheeling, occasional involuntary facial movements, and minimal dysmetria and dysdiadochokinesis.

His face was blank and expressionless. He walked with a slow and unsteady gait, and associated arm-swinging movements were absent. The rest of the physical examination was normal.

Laboratory investigations: Haemoglobin was 15,9 g/100 ml, haematocrit 45%, and white cell count 7 000/mm^3 with a normal differential count. Lumbar puncture showed clear fluid, no cells, protein 27 mg/100 ml, sugar 62 mg/100 ml, and chloride 213 mg/100 ml. Wassermann reaction was negative. Serum caeruloplasmin was found to be 30 mg/100 ml and serum copper 85 μg/100 ml. Urine chromatography for amino acids was normal.

Electro-encephalogram: Extremely low voltage record with large portions showing no obvious rhythmicity, in particular no obvious alpha rhythm.

Air encephalography showed moderate dilatation of lateral ventricles, with loss of convexity of the lateral walls and widening of the superior lateral angles of the lateral ventricles. There was excess air over the sulci.

Case 3

A 22-year-old sister of the proband was 36 weeks pregnant at the time of examination and had one child aged 4 years. Symptoms of the disease were first noted when she was 15 years old.

She appeared to show mild intellectual impairment. There was mild unilateral rigidity with cogwheeling on the left, which was associated with left-sided loss of arm-swinging movements on walking. Speech was soft and slurred, but not as marked as that of her siblings. No involuntary movements were noted. There was no cerebellar dysfunction. The rest of the physical examination was normal.

Laboratory investigations: Haemoglobin was 17,6 g/100 ml, and white cell count 7 600/mm^3 with a normal differential count. Wassermann reaction was negative. Serum caeruloplasmin was found to be 30 mg/100 ml, and serum copper 80 μg/100 ml.

Electro-encephalogram: Extremely low voltage, but alpha activity was readily discernible.

Air encephalography showed widening of lateral ventricles, with loss of lateral wall convexity and widening of superior lateral angles of the lateral ventricles. Excess of air over sulci, especially in frontal areas, was noted.

Case 4

A 23-year-old brother of the proband was unemployed, and has been so since leaving school in his 12th year of schooling. His symptoms began when he was 16 years old, with intellectual impairment, manifested by a complete ignorance of everyday events.

He showed dystonic posturing, bilateral rigidity and cogwheeling, mild dysmetria and dysdiadochokinesis, slurred dysphonic speech, and slow, unsteady gait with absence of arm swinging. Reflexes were normal. The rest of the physical examination was also normal.

Laboratory investigations: Haemoglobin was 17,6 g/100 ml, white cell count 7 600/mm^3 with a normal differential count, and Wassermann reaction was negative. Serum caeruloplasmin was found to be 30 mg/100 ml, and serum copper 90 μg/100 ml.

Electro-encephalogram: Extremely low voltage, but alpha activity was readily discernible.

Case 5

A 52-year-old paternal aunt of the proband was a housewife with 9 children ranging in age from 12 to 27 years.

There were mild choreiform movements of hands and legs (she did not know how long these had been present), generalised hyper-reflexia, increased tone (greater in extension than flexion) and diminished arm-swinging movements on walking.

She appeared to have marked intellectual impairment. She recalled only 3 of 5 objects in a 5-minute memory retention test. She was able to repeat only 4 numbers forward and only 2 backwards. A test of simple arithmetic was executed with difficulty. She was slow and frequently incorrect. Her general knowledge was extremely poor. She did not know the capital of South Africa, nor in which province Johannesburg was situated. She knew there were four provinces in the Republic but could name only two.

Her children were not examined, but were observed at their daily activities around the house. They did not show any obvious bradykinesia, clumsiness, postural dystonia or grossly abnormal movements.

An older sister's daughter, granddaughter of the father of the proband, a schoolteacher, was interviewed. She described her 60-year-old grandmother, who lives in Pietermaritzburg, in the province of Natal, as being a frail, stooped lady, who walks with a small shuffling gait, 'trembles a lot', and 'doesn't always talk sense'.

DISCUSSION

The proband's father had, as described by his wife, a dementing illness associated with chorea, which appears to be compatible with a diagnosis of Huntington's chorea.

His younger sister would also appear to show the stigmata of this disease; and his 4 children seem to have, in varying degrees of severity, the juvenile form.

Further attempts to elucidate the family history were only partially successful. The family is originally from Pietermaritzburg, Natal, descended from a White ancestor three generations back from the proband. Information was gathered about the proband's grandparents, but was inconclusive and unsatisfactory. One of them must, however, have been affected, as it is unlikely that a mutation would arise spontaneously in two members of the same sibship (Fig. 1).

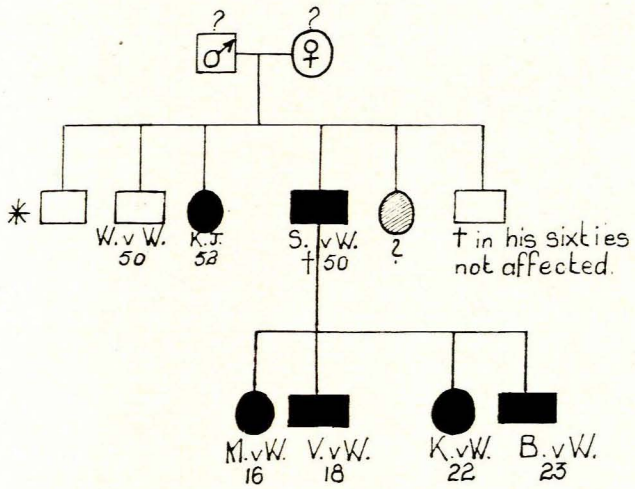

Fig. 1. Family pedigree.

*No definitive information available. Apparently not affected.

The aunt's presumed state of health has already been noted. The description as obtained was suggestive of involvement, but nothing more, hence the question mark in the pedigree (Fig. 1). She knew of nobody else in her immediate family similarly affected.

The clinical presentation of juvenile Huntington's disease has been well documented.[3-6] The condition has been described as beginning between the ages of 4 and 16 years, and the rate of progression appears to be variable though inexorable.

Features occurring most commonly are intellectual impairment, which is frequently the presenting symptom, cerebellar disorders, extrapyramidal signs such as either chorea or rigidity, speech disturbances, epilepsy (especially in the younger onset group),[4] and difficulties with extra-ocular muscle movements. Chorea and rigidity occurred either together or independently of one another, with rigidity being seen over-all more frequently than chorea. Rigidity occurring alone may, in the past, have led to the diagnosis of Huntington's disease being overlooked in children who presented with signs of Parkinsonism.

All of our 5 patients, 4 with juvenile Huntington's and 1 apparently with the adult form, showed some degree of mental impairment (Table I). Two members of the family displayed chorea alone. One had both chorea and rigidity, with rigidity being far more marked. Two of the family showed only features of Parkinsonism.

Three of our patients manifested cerebellar signs, which included ataxia, dysdiadochokinesis and dysmetria. Four showed dyslalia. Only the proband was epileptic, and none had difficulties of extra-ocular movement.

Abnormal EEG findings in Huntington's disease have been reviewed by Scott *et al.*[7] These include absence of any rhythmicity, and, especially, absence of any alpha activity in excess of 30 μV. This pattern is not pathognomonic of Huntington's disease, since it is found with other degenerative CNS conditions as well, but it is seen with great frequency in this disease. Only one of our patients had such a record.

The air encephalographic findings have been reviewed.[8] These include enlargement of lateral ventricles with widening of the body and temporal horns, loss of lateral wall convexity as a result of the caudate nucleus atrophy, and widening of superior lateral angles of the lateral ventricles. This angle is normally acute. It is formed by the junction

TABLE I. SUMMARY OF CLINICAL FINDINGS AND INVESTIGATIONS IN THE 5 PATIENTS EXAMINED

	Case 1	Case 2	Case 3	Case 4	Case 5*
Sex	F	M	F	M	F
Age	16 yrs	18 yrs	22 yrs	23 yrs	52 yrs
Age of onset	13 yrs	14 yrs	15 yrs	16 yrs	U
Chorea	+++	+	0	0	++
Rigidity or akinesia	0	+++	+	+++	0
Mental impairment	+++	+++	+	++	+++
Dyslalia	++	++	+	++	0
Cerebellar signs	?	++	0	++	0
Epilepsy	+	0	0	0	0
EEG	Sharp waves on photic stimulation	Irregular alpha	Normal	Low voltage, no alpha	Normal
Air encephalogram	Dilated lateral ventricles, excess air in sulci	Dilated lateral ventricles, excess air in sulci	NP	Dilated lateral ventricles, excess air in sulci	NP

Key: * = adult form; U = unknown; NP = not performed.

of the caudate nucleus below, and the corpus callosum above. Caudate atrophy would cause it to become opened, rounded, and more obtuse. Excess air in the sulci, especially over the frontal poles, indicative of cortical atrophy, has also been described. All our patients who had the air encephalography displayed the above features.

Barbeau[9] has described a sex preference in the mode of inheritance of juvenile Huntington's disease. He found that there was a statistically significant incidence of the juvenile form when the disease was inherited from the male. This might explain why, in our family, the disease appears to be so malignant in the offspring of the father described, whereas the children of case 5 show no gross disturbances of posture or movement at this stage.

Huntington's chorea is determined by a single dominantly inherited gene, and the 'juvenile' and adult forms of the disorder are manifestations of the same gene. In other words, the presence of juvenile and adult cases in a single kindred is the result of variation in clinical manifestation of the same gene, rather than a representation of separate genetic entities.

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