Huntington’s chorea

Report of 3 cases and review of the literature

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SUMMARY Three cases of Huntington’s chorea with onset before age 10 years are reported. Each child presented with rigidity and indistinct speech, and there was progressive deterioration. Necropsy examination confirmed the diagnosis in 2 of them. A review of reports showed a further 43 cases with onset before age 10 years. The rigid variety of disease was seen most often, but isolated chorea and isolated progressive mental deterioration occurred. Fits were common but occurred late and were often difficult to control. Dysarthria was common and occurred early. The duration of illness was very variable and ranged from 2 to 38 years. Symptoms can occur in a child before appearing in the affected parent who is most likely to be the father. Affected siblings develop the disease early, often in the first decade. Siblings of patients with onset before age 10 years who are unaffected by age 25 years had only an 8% chance of developing the disease, compared with a 50% chance in unselected at risk individuals of the same age.

Huntington’s chorea (HC) is a disease which is more common in adults than in children. The cardinal features of the disease were first documented by George Huntington in 1872\(^1\) and consist of the dominant inheritance of a progressive disease with gradual onset of chorea or a tendency to insanity and suicide, or both of these, which manifest themselves in adult life. We report 3 patients in whom the onset was in the first decade of life, and review the clinical and genetic features of a further 43 cases gleaned from reports.

Case reports

Case 1. This white girl had been born after a normal pregnancy at term by normal delivery; birthweight was 3.37 kg. Her early development had been normal. The mother and a 4-year-old sister are both well. There was a family history of HC affecting our patient’s father (onset at age 32 years, still alive), paternal grandmother (onset at age 28, died aged 32 years), the grandmother’s sister, and one of her two children. The father was examined and the diagnosis confirmed.

The patient was referred by her general practitioner just before her fifth birthday because of continual falling and stiffness. She had always been slightly clumsy, but during the previous year she had fallen more often, and had made little effort to save herself. Six months earlier she had been referred for speech therapy because of hesitant, indistinct speech. On examination she was withdrawn. Her speech was indistinct and monosyllabic. There was no chorea or ataxia. Her muscle tone was normal when relaxed but increased intermittently. Her gait was generally normal but she walked at times in a stooped position like an elderly person.

By age 6 years, her speech was more hesitant and she had reverted to the frequent use of short monosyllables. She preferred to crawl when indoors, but she was able to walk although falling frequently. She was occasionally incontinent of urine and had developed temper tantrums. Her appetite had deteriorated and she had difficulty in swallowing solids and liquids, managing best with a straw. She was no longer able to dress herself. She was still making slow progress with reading but was unable to write as clearly as previously. On examination at this stage she had developed evidence of chorea affecting her upper limbs and fingers. Her speech was dysarthric and hesitant becoming quieter as the phase progressed. She had developed pronounced cogwheel rigidity with decreased tendon reflexes. Her gait was still stooping but was more hesitant and there was a paucity of associated movement similar to that of Parkinson’s disease. Her eye movements showed a limitation of rapid following, most pronounced vertically. Her electroencephalogram (EEG) was very abnormal with paroxysmal bilaterally synchronous spike and slow-wave complexes of
maximal amplitude over the occipital areas. Computerised tomography (CT) (Fig. 1) showed atrophy of the caudate nucleus and small cortical sulci. Haloperidol had a temporary effect in improving the speed and clarity of her speech. A subsequent trial of baclofen had no effect, although she had 2 grand-mal fits for the first time.

Case 2. This white girl had been born at 41 weeks after a normal pregnancy. The second stage had been prolonged but the delivery was normal; she weighed 3.52 kg. There had been no neonatal problems. Her early development was normal. Her father had developed HC while in his twenties and he is now aged 48 years. She has one 21-year-old brother and one 18-year-old sister; both are well. The two paternal uncles and one paternal aunt all developed HC and their father had died in his fifties of HC. His mother had died at age 70 with ‘chorea’.

On starting school the patient had been referred to a child psychiatrist by the school health service. During the previous year she had begun to fall and had been unable to join in games at school. She had become quiet and withdrawn and had developed temper tantrums. Her IQ showed a performance level of 92 with an overall score of 71, showing that the verbal score was very low. An EEG was within normal limits. During the next 5 years her condition gradually deteriorated. Her speech became more indistinct and her writing more spidery. She tired easily and developed a peculiar gait which was said to be like that of her father. At age 10 years she had an immobile facies and she stooped. She laughed inappropriately and had dysarthric speech. She had visible choreic movements and a plastic rigidity of her limbs. The reflexes were sluggish and the plantar responses extensor. Her EEG at this age was still normal. She was sent to a special school for handicapped children at age 12 because of her physical handicap, and she had lost the ability to walk by age 13. She died at 14 years.

Necropsy examination showed a thin wasted body. The skull and dura were normal. The brain weighed 1000 g. There was a suggestion of cortical atrophy affecting all lobes but the cortex was not unduly thin. The corpus striatum was severely atrophic and the caudate nucleus consisted only of a narrow rim of a brownish tissue alongside the lateral ventricle. The putamen was also reduced to a quarter of its normal size. The globus pallidus was shrunken but not as severely as the caudate and the putamen. The thalamus and other central grey structures were normal. Histological sections confirmed very severe cell loss in the caudate and putamen, with almost total disappearance of small neurones while a few large nerve cells remained. There was considerable proliferation of glial cells but glial fibres were not prominent except in the subependymal region of the caudate nucleus.

Case 3. This white boy had been born by normal delivery at term after a normal pregnancy; he weighed 3.80 kg. There were no neonatal problems. His early development had been normal. His father and paternal grandmother were diagnosed as having HC after he presented although the father’s symptoms developed before those of his son. He was referred by the school health service at age 6 years 4 months because of a 12-month history of lack of progress at school. He had developed an unusual gait with his right arm flexed at the elbow while his hand lay apparently useless by the side of his chest. He would use his left hand to open a door and his right one to close it. He had become clumsy and his efforts at co-ordination had not improved.

On examination his gait was as described and he seemed terrified of falling. His speech was dysarthric and hesitant. The right leg was weak and the reflexes in this leg were increased and the plantar response was extensor.

An EEG showed a very irregular record. There was a 9 cycle per second posterior rhythm with much random intermediate slow activity. There were frequent spiked discharges independently in post-central leads on both sides. There was no obvious asymmetry. At age 9 years he and his brother developed a viral meningitis, after which he developed status epilepticus and died.

The brain was examined at necropsy by the late
Dr Norman at the Burden Neuropathological Laboratory. He reported 'this confirms HC showing all the classical features just like the adult, except that the cortex does not seem to be much affected. There is considerable atrophy of the caudate nucleus and putamen'.

**Review of reports**

A review of reports in English showed a further 43 children with symptoms of HC before age 10 years.\(^3\)\textsuperscript{-23} Cases were accepted if there was a family history of dominant inheritance of symptoms of HC. The earliest reported case was in 1880,\(^3\) eight years after Huntington's original report.

**Type of disease.** It is well known that there is a clinical variant of HC in which the predominant sign is rigidity; this is particularly common among those affected early. This rigid variety is often called the juvenile or Westphal variant.\(^23\) Of the 46 patients, 26 clearly had the rigid variant. Three had a mixed disease with rigidity and chorea, and 9 had a predominantly choreic illness. In 3 cases details were lacking and in 3 others behavioural problems were the major cause of illness. A further 2 children presented with non-specific progressive mental deterioration.

**Fits.** Fits are often mentioned as being common in children with HC. Of the 46 children, 13 had grand-mal fits only, one child had grand-mal with petit-mal, 7 had grand-mal and myoclonic or astatic fits, and one had myoclonic or astatic fits only. Two children had photosensitive fits, one of whom also had myoclonic or astatic fits. Five patients had not had fits, and fits were not mentioned in 17 cases.

**Speech.** Speech defects are common, and in 33 of the 46 patients a speech disorder was mentioned. Dysarthria occurred in 30 cases, slow or hesitant speech in 7, and monosyllabic speech in 7 cases. One patient had a stammer.

**Duration and age of onset.** The age at onset ranged from 3 to 9 years and was equally distributed throughout these ages (Fig. 2). The duration of illness ranged between 1 and 25 years in the 25 children known to be alive at the time of reporting with a mean of 5\(\frac{1}{2}\) years (Fig. 3). The duration of illness in the 19 children known to have died ranged from 2 to 38 years with a mean of 9-3 years (Fig. 4). Thus although the duration of illness is generally shorter than in an adult, it is unpredictable and one child who was affected at age 8 lived long enough to bear an affected child and was still alive at age 33 years.\(^17\)

There was a report of a child affected before the parent developed signs and symptoms of the disease.\(^9\) This phenomenon can occur even in patients presenting as adults.\(^4\) A more frequent occurrence is the presentation of a child with neurological symptoms before the disease had been diagnosed in a symptomatic parent. This occurred in Case 3.

**Affected parents.** The 46 affected children came from 32 families and they all appeared in the same
generation except for the one case already mentioned. There were therefore 33 affected parents (27 fathers and 6 mothers). The difference if compared with the sex ratio of affected children (23 males and 23 females) is highly significant (using Yates's correction, $\chi^2 = 7.06$, P is less than 0.01).

The age at onset in the affected parent was known in 19 instances and the mean age was 28.1 years (with a standard deviation (SD) of 9.1 years). Although the numbers are small, the mean age at onset in the 14 affected fathers was 32 years (with an SD of 6.4 years), while for the 5 affected mothers it was 16.5 years (with an SD of 5.2 years). The fathers had an average of 3.4 children and the mothers an average of 2 children.

**Siblings.** It is important for genetic counselling to know what happens to the siblings of affected children. Data were lacking in one family, so 31 families were analysed. There was a total of 103 children born to 32 affected parents. Forty-eight of these 103 are known to have been affected at the time of reporting and this is close to the expected figure of 50% for any dominantly inherited disease. Only 3 of the affected siblings developed symptoms after the first decade: one at 14, one at 24, and one at 26 years. There were 13 affected siblings of probands who developed symptoms before age 10 years. These data show an 8% chance of a 25-year-old unaffected sibling of a proband with onset before age 10 years ever developing the disease compared with the nearly 50% risk in unselected at risk individuals of the same age.

**Discussion**

The diagnosis of HC is straightforward in the child of a known affected parent. Normal parents do not rule out the diagnosis which is difficult to make if the family history is covert. Chorea is not obligatory even before death and some authors have suggested a new name—Huntington's disease. Dementia, rigidity, and psychiatric symptoms may each be the predominant feature. Severe behavioural disorders may be caused by the social problems surrounding these families, or may be a feature of the disease.

Sydenham's chorea has been reported as occurring during the childhood of some adults who later developed HC. Isolated chorea in the child of an affected or at risk adult may therefore not be due to HC. A CT scan showing caudate atrophy is not diagnostic in isolation but must be supported by a family history of HC and clinical signs. It has been suggested that caudate atrophy shown by CT scan may precede symptoms in adults but this is not yet proved. Each of our 3 patients had a positive family history and typical signs and symptoms, and the diagnosis was confirmed by necropsy examination in 2 of them and by the CT scan in the third. The lesion is similar to that found in the adult. Investigations in our 3 children did not show any other disease.

Fits occurred in more than 80% of those cases in whom it was mentioned and in 50% of the total, but at least one family was revealed because of the fits. The fits generally occurred late in the course of the disease and were often difficult to control. This may be related to the type of seizure since myoclonic or astatic fits were common. Speech defects are equally common but occur early, frequently being the presenting symptom. Ocular signs have not been reported previously in children but are a well-known feature in adults. Voluntary and reflex rapid eye movements are impaired while slow ocular following movements are preserved. Such voluntary movements were impaired in Case 1 but were not noted in the other 2 cases.

As in adults the duration of illness is unpredictable for the individual, but it tends to be shorter in childhood. The predominance of affected fathers is highly significant and had been noted previously. It has been suggested that there is a sex-linked factor in the inheritance of Huntington's chorea, but this may partly be owing to a sampling error. Our data show that early onset fathers have more offspring than early onset mothers. There may also be a tendency for very early onset females not to procreate: this would cause an even higher incidence of affected fathers. This effect has not been found in adults with onset before age 30 years. The earlier age at onset in affected mothers compared with affected fathers suggests that the factors influencing age at onset are more dominant if the affected parent is male.

The data presented here suggest that affected siblings of children with onset of HC before age 10 years have a very early onset too, often before 10 years of age. The data might be biased by the more frequent reporting of families in whom all affected children presented early, but the occurrence of 2 affected children born of an affected father by different wives confirms age at onset as an inherited factor. It has been previously noted that the age at onset varies less within families than between them and that the average age at onset is earlier the earlier the onset in the affected parent.

Since writing this report the sister of Case 1, now aged 5 years, has developed signs of HC.

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References


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