Huntington's disease of early onset or juvenile Huntington's disease

Neil Gordon

The presentation of juvenile Huntington's disease can cause diagnostic difficulties. The genetics and pathogenesis of the condition are discussed. The diagnosis will depend on the symptoms raising suspicions and the exclusion of other disorders, especially by genetic studies.

Huntington's disease usually manifests itself in middle-aged adults, and most patients are asymptomatic during childhood. It shows a consistency of age of onset within families, in the sex of the transmitting parent, and of particular interest in anticipation of onset when it comes to successive generations (Myers et al, 1982). Also, there is evidence that the time interval between the first appearance of signs in the transmitting parent and the birth of the subsequently affected child has been shown to influence the age of onset of the disease. If parents at risk do plan to have children it may be better for them to plan their families early as the older the child if a parent becomes affected the easier it may be for that child to cope with the resulting distress. This can also apply if adoption is being considered (Brackenridge, 1978).

However, if the disease manifests itself in childhood there can be considerable difficulties in diagnosis as there can be marked variations in symptoms compared to those of adults, which are well reviewed by Kirkwood et al (2001), and this can cause serious problems in management. They divided the disease into six stages:

1. Involuntary movements
2. Mental and emotional symptoms, including sadness, depression, and difficulties with relationships
3. Clumsiness, lack of motivation, sexual problems and paranoia
4. Behavioural and cognitive symptoms, including unsteadiness and difficulty in walking, changes in sleep patterns, delusions, hallucinations, and intellectual decline and memory loss
5. Speech difficulty and weight loss
6. Loss of bladder and bowel control.

Dr Neil Gordon is retired Paediatric Neurologist, Royal Manchester Children's Hospitals

Correspondence c/o Hospital Medicine

At any age the disease is relentlessly progressive, which may be a result of dysfunctional feedback control involving the main output of the basal ganglia which modulates the action of the thalamus relaying sensory information to the cortex (Brooks et al, 1987). The recorded prevalence of early onset among patients with Huntington's disease varies between 1% and 10% (Levy et al, 1999). An early onset can occur among twins (Brackenridge, 1982).

Females have a somewhat poorer prognosis than males, and those displaying rigidity tended to have a shorter course of the illness than those with hyperkinetic movements, chorea and athetoid posturing. However, patients who began to dement within 2 years of onset succumbed much sooner than those who developed dementia later (Osborne et al, 1982a).

THE GENETICS OF HUNTINGTON'S DISEASE

Huntington's disease is an autosomal dominant inherited disorder with complete penetrance. The gene is located on chromosome 4p16.3, and when the onset is in childhood the affected child is about four times as likely to have inherited the disease from the father than the mother. In a review of 157 patients with the condition in South Africa it was found that 17 had a juvenile onset and in 13 of these the father had been the affected parent. It was suggested that this might be because of a modifying gene being closely linked to the gene for Huntington's disease (Hayden and Beighton, 1982).

Another example of this is given by Navarrete et al (1994), who reported the history of two siblings. They both presented at the age of 8 years with evidence of dementia and muscular rigidity, and their father and paternal grandfather suffered from Huntington's disease.

This apparent contradiction of Mendelian genetics, with inheritance from their fathers and with age of onset decreasing, has been explained by the amplification of an expanded CAG trinucleotide repeat.

An apparent correlation between repeat length and the age of onset of the disease has been observed with the largest trinucleotide repeats found in juvenile onset cases; patients presenting with atypical movement disorders, such as ataxia, dystonia or rigidity, rather than chorea, also have larger CAG expansions (Squiteri et al, 2000). The (CAG)n repeat appears to be located within the coding sequence of a predicted –348 kd protein that is widely expressed but unrelated to any known gene. Thus, the Huntington disease mutation involves an unstable DNA segment, similar to those described in other conditions such as the fragile X syndrome, acting in the context of a novel 4p16.3 gene to produce a dominant phenotype. The research group (Huntington's Disease Collaborative Research Group, 1995) who carried out these studies considered that the most likely cause of the disorder was the effect of the trinucleotide repeat expansion, either at the mRNA or protein level, on the expression and/or structure of the protein product of the IT15 gene, which they named huntingtin. This gene, containing the polymorphic trinucleotide that is expanded and unstable on Huntington's disease chromosomes, was isolated using cloned trapped exons from the target area (Lenti and Bianchini, 1993).

If the affected parent is the father the symptoms in the affected child may be of earlier onset (Reik et al, 1993). Studies have shown no significant correlation between methylation and age at onset, although there was one between the age of the patient and demethylation at D4S95, a locus tightly linked to the Huntington's disease gene. This may be related to the loss of methyl groups in DNA with age. The tendency for older fathers to have affected offspring with early onset disease may be consistent with a genetic imprinting mechanism involving DNA methylation (Farrer et al, 1992). These factors of age of onset and imprinting may interact to produce a major change in gene expression, that is, the early onset rigid variant (Ridley et al, 1991), although Clarke and Bundy (1990) considered this to be unlikely.

THE PATHOGENESIS OF HUNTINGTON'S DISEASE

The pathophysiology of this disease is unknown, but a favoured hypothesis suggests that toxicity arises from the cleavage and accumulation of amino-terminal fragments containing an expanded polyglutamine region. Dyer and McMurray (2001), in their work on huntingtin protein from the human brain, transgenic animals and cells, found that mutant huntingtin protein was more resistant to proteolysis than the normal variety. The N-terminal cleavage fragments they observed arose from the processing of such normal protein, sequestered by the full-length mutant protein.

Their results support a model in which inhibition of proteolysis on the mutant protein leads to aggregation and toxicity through the sequestering of important targets, including normal huntingtin protein. All this may result in the loss of the normal functions of huntingtin protein, and suggests that the aggregation and sequestration may be the primary event in the pathology of Huntington's disease.

Studies on patients with adult onset have shown that nuclear inclusions formed by N-terminal mutant huntingtin are more prevalent in the cortex than in the striatum, suggesting that these inclusions may have only a minor role in striatal degeneration. However, it was found that, in affected adults, the huntingtin protein appeared in dystrophic axons within the cortex, striatum, pallidum and the corticostriatal pathways, which may lead to defects in axonal transport by mutant huntingtin protein interactions, or its aggregation, or both (Sapp et al, 1999). If so, this may have implications for treatment in the future with efforts to accelerate the turnover of mutant huntingtin or to inhibit aggregate formation (Frankish, 2001), perhaps by the prevention of cleavage of these proteins (Wellington et al, 2000).

Also it may be that the cause lies in the cellular effects of the CAG expansions that encode the polyglutamine segments in expressed proteins (Tobin and Signer, 2000).

DIAGNOSIS

Symptoms and signs

The early onset of Huntington's disease can easily be overlooked, especially if there is no family history, and the diagnosis can present difficulties (Woldag et al, 1997). The juvenile variant can present as early as the first decade, and in one instance was reported in an infant aged 20 months with a severe behaviour disorder, who died aged 52 months. The computed tomography (CT) scan and neuropathology, especially of the basal ganglia, were compatible with a diagnosis of Huntington's disease, but there was no family history although evidence of this might appear at a later date (Haslam et al, 1983).

It usually presents with intellectual deterioration and difficulty in concentration, resulting in failure at school; and in adults it has been confirmed that several years before typical motor signs develop there can indeed be evidence of dementia and certain subtle disorders of motor function such as impaired rapid alternating movements (Kirkwood et al, 1999, 2000; Paulsen et al, 2001). The preclinical cognitive impairment can manifest itself as a deficit in tasks requiring optimal scheduling and sequencing of responses. This could be related to loss of dopamine receptor binding in the striatum (Lawrence et al, 1998a) and it has been suggested that this can result in a common deficit in inhibitory control regulated by striatofrontal mechanisms (Lawrence et al, 1998b).

At any age the intellectual deterioration is likely to be a major factor in reducing functional capacity (Mayeux et al, 1986).

Personality changes, anxiety and depression are often present, and to illustrate this, Foldager and Roijen (1996) record the history of a girl of 12 years of age who presented with a severe psychosis, progressive difficulty in speaking and mental deterioration, but no other physical signs; but scanning showed a similar picture to that shown among adults with this disease. Her father suffered from Huntington's disease, and committed suicide.

Extrapyramidal rigidity, tremor, dysarthria and sometimes cerebellar signs may be more characteristic than chorea in the juvenile type (Karagöl et al, 1995; Levy et al, 1999). This is a reason for referring to the condition as Huntington's disease rather than Huntington's chorea, although isolated chorea can occur (Osborne et al, 1982a) and it should not be regarded as a separate entity, but as a variant of Huntington's disease (Siesling et al, 1997). Apart from the rigidity and paucity of movement there may be staring of the eyes with impairment of rapid eye saccades (Morris and Pauson, 1970).

Family history

Another feature which may help is the increased frequency of seizures and myoclonus among affected children which are rare in adults (Haeberle et al, 2001). Seri et al (2001) have reported such a patient whose myoclonus responded to treatment with high doses of piracetam. The duration of the illness is very variable, and ranges from 2 to 38 years. Also symptoms can occur in a child before appearing in the affected parent, usually the father.

Affected siblings develop the disease early, often in the first decade; and siblings of patients with an onset before the age of 10 years who are unaffected by the age of 25 years have only an 8% chance of developing the disease compared with 50% chance in unselected at risk individuals of the same age (Osborne et al, 1982b). A study of very early onset Huntington's disease has shown that at least 38% of gene-carrying siblings also develop symptoms before the age of 10 years, thus improving the genetic risk for those who remain healthy. Clarke and Bundy (1990) considered the presence of early onset Huntington's disease among these siblings was most likely the result of a mutation during spermatogenesis, and that two mechanisms may contribute to the early onset: a modification by many genes and an epigenetic mechanism occurring when transmission is through a series of males.

Neuroradiology and ultrasound

The magnetic resonance imaging (MRI) scan shows striatal atrophy with better definition than the CT scan. The shrinking of the head of the caudate nucleus results in loss of the usual bulge on the inferolateral borders of the frontal horns of the lateral ventricles, and may also show hyper- or hypo-intense signal changes in the striatum. Hyperintensity of the striatum is seldom present in the hyperkinetic form of this disease but tends to be typical of those with rigidity and of those with an early onset (Reik et al, 1993). Transcranial ultrasound can show abnormalities in the substantia nigra, and less often in the caudate nucleus and lentiform nuclei. These findings do not necessarily correspond to the neuropathological ones (Becker and Berg, 2001).

Differential diagnosis

Other causes of chorea and other types of motor disorder will have to be considered in the differential diagnosis, particularly if there is a positive family history as is the case with benign hereditary chorea of early onset. This condition is in most instances transmitted in an autosomal dominant manner with diminished penetrance. It is non-progressive with a tendency to improve (Deonna and Voumard, 1979; Sleigh and Lindenbaum, 1981), and must be differentiated from Huntington's disease and Sydenham's chorea (Haerer et al, 1967). In the former CT and MRI scans may be normal, but single positron emission CT and positron emission tomography scans show abnormalities in the caudate nuclei. In contrast to Huntington's disease electrophysiological tests showed no abnormalities, suggesting an absence of cortical

dysfunction (Stapert et al, 1985). Also there will be no expansion of CAG repeats on the Huntington gene (Meszaros et al, 1996).

Other conditions in the differential diagnosis include neuroaxonal dystrophy, dystonia musculorum deformans, Wilson's disease, Tay–Sachs disease, Hallervorden–Spatz syndrome, familial benign chorea, metachromatic leukodystrophy, Lesch–Nyhan syndrome, familial basal ganglia calcification and post-encephalitic conditions (Rasmussen et al, 2000). The differentiation from Huntington's disease can be firmly established by finding that there are a normal number of CAG trinucleotide repeats on the relevant gene, and not an increase to between 35 and 121 copies (Hageman et al, 1996). A benign recessively inherited choreo-athetosis has also been reported. It is non-progressive, and the onset is in infancy (Nutting et al, 1969).

CONCLUSIONS

When diagnosing motor disorders in childhood the possibility of juvenile Huntington's disease has to be considered. There may well be no family history as the parent who is the carrier, usually the father, may not have yet manifested the condition. The discovery of the responsible gene has led to a number of advances in the understanding of the condition, and the differences that can occur with different ages of onset. Patients with juvenile Huntington's disease show the greatest genetic defects with the longest CAG repeats, but in spite of this cognitive state is slightly better preserved than among those with adult onset. This may be a result of the disability being conditioned more by motor deficits, especially rigidity, and by disorders of prefrontal functions rather than by global cognitive ones. This relative cognitive preservation suggests that younger patients may benefit from continuous educational support (Gómez-Tortosa et al, 1998).

An important development is the introduction of a gene test which can be used to corroborate the diagnosis. Nance et al (1997) warn against using this test in the evaluation of at-risk children with incomplete or atypical symptom profiles or no family history, as the results may well be normal or unrelated to the patient's symptoms. Genetic studies have also raised the possibility of effective treatment with the discovery of the huntingtin protein. Drugs which prevent cleavage of certain proteins may be developed which would help to halt the otherwise relentless progression of this disease. HM

Conflict of interest: none.

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KEY POINTS

- Huntington's disease can occur during childhood.
- Inheritance can be affected by the sex of the parent.
- There is improved understanding of the cause of the disease.
- Diagnosis is difficult but must be differentiated from other motor disorders.
- Genetic studies may lead to effective treatment.

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