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Huntington's disease and other choreas

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Abstract Chorea can have many causes, some hereditary and many sporadic in nature. The archetypal hereditary cause of chorea is Huntington's disease (HD). However, this condition often manifests as a mixed movement disorder, and some individuals with the Westphal variant may not display chorea at all. Moreover, since gene-specific testing has become available, we now know that in many cases of HD, particularly those with late onset, a positive family history may be lacking. In addition, dentatorubro-pallidoluysian atrophy (DRPLA), another dominantly inherited CAG repeat disease, can produce a similar clinical picture. In both conditions, the phenotype may vary according to repeat length, and anticipation and excess of paternal inheritance in younger-onset cases with longer repeat lengths are seen. Neuroacanthocytosis is probably genetically heterogenous, and many instances of "benign hereditary chorea" have been caused by other conditions. If it exists at all, this disorder is exceedingly rare. The principal causes of sporadic chorea include drugs, pregnancy, vascular disease, thyrotoxicosis, systemic lupus erythematosus (SLE) and the lupus anticoagulant syndrome, polycythaemia rubra vera, AIDS and both initial and recurrent Sydenham's chorea. The symptomatic treatment of chorea is unsatisfactory and, at least in HD, neuropsychiatric disturbance may be much more important for the family. Potential disease-modifying treatments such as anti-excitotoxins, antioxidants, free radical scavengers and neuronal grafting are now being explored in this condition.

Key words Chorea · Huntington's disease · Dentatorubro-pallidoluysian atrophy (DRPLA) · Neuroacanthocytosis · Benign hereditary chorea

Huntington's disease

Recent years have seen advances in the understanding of a number of causes of hereditary and sporadic choreas, although advances in treatment are so far lagging some way behind. The most important development, which took 11 years after linkage to the short arm of chromosome 4 was demonstrated [17], has been the discovery in 1993 [68] that Huntington's disease (HD) is one of a growing number of diseases of the central nervous system determined by expanded CAG trinucleotide repeats, the others so far identified being bulbospinal neuronopathy (BSMA), dentatorubro-pallidoluysian atrophy (DRPLA) and spinocerebellar ataxias (SCAs) 1–3, 6 and 7. These conditions are all (usually) adult-onset and show the phenomenon of anticipation, whereby the condition tends to start progressively earlier in succeeding generations.

HD is much the most important hereditary cause of chorea. Reported prevalence figures of living affected cases vary considerably. Usually this reflects the intensity and duration of case ascertainment efforts, but sometimes

it reflects founder effects. The true prevalence of the condition in Caucasian populations may reach as high as 10 per 100,000. Because many gene carriers are yet to develop symptoms, their prevalence is more than twice that of symptomatic cases. The number of people at 50% and 25% or higher risk of HD is 5 and 11 times the disease prevalence, respectively. Therefore the burden of HD in the population is considerable, albeit disproportionately borne by certain families. HD is uncommon in Finland, Japan, China and in black South Africans. However, the same expansion has been identified in affected cases from widely differing races and regions [29]. Mean age at onset of symptoms is 35–42 years, mean age at death 50–56 years and mean duration 15–17 years. However, HD can start at any age, from 2 years (or younger) to 92 years (or older). About 6% of cases have juvenile Huntington's disease [10] with onset earlier than 20 years of age. Many, but not all, of these patients have the Westphal variant characterised by an akinetic-rigid syndrome with dystonia, more severe intellectual decline, and frequently seizures and myoclonus. Disease duration was previously thought to be shorter among juvenile cases, but this is probably incorrect [54]. Ninety per cent of these cases have inherited their disease from an affected father and have unusually long CAG repeats. This is because CAG-repeat instability is greater in the successive meioses in spermatogenesis as opposed to oogenesis. At the other end of the spectrum, as many as 28% of cases of HD are late-onset, beginning after 50 years of age [39]. Late-onset disease is characterised by a milder clinical course and also milder pathological changes. Thus the patients may have mild slowly progressive chorea, normal eye movements and intellect, little overt neuropsychiatric change, and unless (and even if) subjected to meticulous neuropathological examination by an expert, even at autopsy their brains may be passed as normal. It is important to re-emphasize that there is no upper age limit for developing Huntington's disease: for example, one of us has made a new diagnosis of Huntington's disease at the age of 86 years in a patient specifically examined by a genetics nurse for signs of the disease 2 years previously (one child with clinical HD had been published [1] as a new mutation when the affected parent was 70 years old and normal). This underlines the point that whilst a positive or suspicious (early death, suicide) family history may raise the possibility of Huntington's disease in an antecedent family member, a negative family history, with parents even of proven paternity still unaffected in their eighties, still does not rule out the disease in their offspring. In counselling older subjects whose initial risk of HD was 50%, one can not only start to give a lower risk after they have passed a certain age, but equally importantly one can predict that even if they do develop HD it should take a milder disease course than the typical case. Senile chorea simply means chorea in an old person. Most such cases can now be shown to be caused by the HD mutation. However, we also now know that a minority of cases said to have senile chorea are not caused by the *HD* mutation [13, 59]. Cases with pathology different from that of HD have been reported by Friedman [12] and Steiger et al. [66]. Among patients with suspected HD who have been found to be negative for the HD CAG repeat expansion, a number with a dominant family history have been shown to have DRPLA (see below). Among cases with apparently sporadic Huntington's disease [8], an expanded *HD* gene was confirmed in the majority of those with typical clinical features (interestingly, these patients tended to be examples of late-onset disease). Among the remainder was a small but significant minority of individuals with a previous history of Sydenham's chorea that had recurred later in life [14].

The evolution of the neurological features of HD over time has been well documented. Chorea and eye-movement disturbance tend to be early features. The latter in its mildest form comprises gaze impersistence, distractibility and initiation defects [34], with a tendency to use head thrusts, and can progress through increased saccadic latency to a supranuclear gaze palsy. Often it is simply difficult to apparently gain full cooperation of the patient in examining oculomotricity, which may itself be a clue. In the Lake Maracaibo population in Venezuela, the families say that the disease enters through the eyes. As the disease progresses, underlying parkinsonism [46, 69] and dystonia become increasingly evident, and the chorea may sometimes even decline. Although neurologists are familiar with the early stages of the disease, since they are frequently involved in initial diagnosis, they commonly do not see individuals in the late stages of the disease. Moreover, one should recognise that not only do a minority of juveniles not have the Westphal variant, but a minority of older-onset patients present with an akinetic-rigid syndrome.

The brunt of HD pathology falls on the caudate (initially medial and tail) and putamen (initially and predominantly dorsal), the globus pallidus, and the cortex (mild neuronal loss in layers III, V and VI and to a lesser degree in layer IV). Vonsattel et al. [73] have graded striatal pathology in HD from 0 (no change) to 4 (95% loss of caudate volume with marked astrocytosis). Xuereb et al. [76] recently also demonstrated pathological HD repeat expansions in three histologically normal (grade 0) brains from patients with a clinical diagnosis of HD during life.

Genetically, HD is a true dominant condition, since homozygotes for the defective gene do not differ from heterozygotes [75]. The CAG repeat mutation gives rise to a gain-of-function, and the size of the mutant huntingtin protein is highly correlated with CAG repeat length. The precise cutt-off between normal and abnormal is a slightly grey zone, within which sits the question of intermediate alleles, which, although not in the accepted HD range, could expand to become so in offspring, or could even be themselves HD alleles associated with extremely late age of onset [40]. One method of repeat estimation included

an additional flanking CCG repeat usually consisting of 7 copies, but which could vary between 7 and 12. Using this method, CAG repeat length was estimated by subtracting 7, but this could potentially lead to false-positive results by overestimating CAG repeat length by up to 5, and was particularly important where this method suggested a CAG repeat length between 30 and 40. Therefore, the technically more demanding direct estimation of CAG repeat length is now usually undertaken. The exact number of repeats varies slightly between laboratories, but in most centres less than 32 CAG repeats would be considered normal, 32–39 intermediate and more than 39 abnormal [55]. Although long repeat lengths are particularly striking in juvenile cases, repeat length alone does not explain the whole of variation in age at onset, so that there is at least one other gene that determines this. Longevity of the unaffected parent also shows some correlation to the lateness of disease onset in the offspring [11].

The distribution of mutated huntingtin is, like that of the normal form, heterogeneous throughout the brain. One study found that it is not limited to vulnerable neurons in HD, supporting the hypothesis that the presence of mutated huntingtin in a neuron is not in itself sufficient to lead to neuronal death [15]. However, another study found that although neuronal staining for huntingtin was reduced in areas of the HD striatum depleted of medium-sized neurons, large striatal neurons, which are spared in HD, retained normal levels of huntingtin expression [57].

Recently, mice have been generated that are transgenic for the 5′ end of the human *HD* gene carrying $(CAG)_{115}$–$(CAG)_{150}$ repeat expansions [38]. These mice exhibit a progressive neurological phenotype including choreiform-like movements, involuntary stereotypic movements, tremor and epileptic seizures. Brains from these animals were consistently smaller than those of controls, but this reduction in size appeared to be uniform throughout all central nervous system (CNS) structures. Among human CAG repeat diseases, intranuclear inclusions containing ataxin-3 protein have recently been demonstrated in pathologically affected areas in SCA3 or Machado Joseph disease [45]. As long ago as 1979, Roizin et al. [53] reported the presence of nuclear inclusions in biopsies of cerebral cortex and caudate nucleus of patients with HD. It is of considerable interest that recently Davies et al. [7] have observed that the transgenic mice mentioned above also develop pronounced neuronal intranuclear inclusions, containing the proteins huntingtin and ubiquitin, prior to developing a neurological phenotype. Moreover, the localisation of these inclusions within the majority of striatal neurons, but not in the cholinergic or NADPH-diaphorase containing interneurons, parallels the pattern of cell death observed in HD.

A huntingtin-associated protein (HAP-1) [36] has been identified in rat and human that binds weakly to normal huntingtin (corresponding to 19–32 CAG repeats) and strongly to abnormal huntingtin (with positive correlation to the number of abnormal repeats). Unlike huntingtin itself, which is non-selectively expressed [33], HAP-1 is selectively expressed, maximally in caudate and cortex, which might explain the distribution of pathology in HD. In addition, it has been discovered that huntingtin [5] and also the abnormal gene products in DRPLA [5], SCA1 [28] and BSMA [28] bind to glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which is an essential enzyme for glycolysis, and there is evidence that longer polyglutamine tracts inhibit this enzyme more than shorter ones. Two other potential huntingtin-interacting proteins (HIP1 [23] and HIP2 [22]) have also been identified.

There is also some other evidence pointing to energy impairment in HD. One group [44] reported abnormalities in complex I of the mitochondrial respiratory chain in HD platelets, and another more recently found defective complex II, III and IV activity in HD caudate nucleus [16], but nor platelets; positron emission tomography (PET) scans have shown an early drop in striatal glucose metabolism [30], and some magnetic resonance spectroscopy (MRS) studies have indicated increased brain lactate levels [21, 27]. In animals, mitochondrial toxins such as MPP+, which blocks conversion of complex I, and 3-nitroproprionic acid (3-NP), which blocks the conversion of complex II, to co-enzyme Q, injected into striatum, can give rise to an indirect excitotoxic lesion that can be prevented by MK801 treatment, or by decortication. The slow chronic intraperitoneal administration of 3-NP to rats gives a striatal lesion with sparing of the same NADPH-positive neurons containing somatostatin and neuropeptide Y that are also spared in the human disease, and 3-NP can also cause a similar lesion in baboons.

A number of clinical trials in HD have been mounted to investigate whether putative antiexcitotoxic compounds, antioxidants [51], free radical scavengers or the administration of co-enzyme Q10 can influence signs, symptoms and progression of the disease. In addition, the ground work has been laid for surgical trials in HD. A small number of patients in the Good Samaritan Hospital in Los Angeles [31] and at the Hôpital Henri Mondor, near Paris, have received human fetal striatal grafts, and two patients in Boston have received fetal porcine striatal grafts, but it is still too early to expect any meaningful results. In addition, because the most striking effect of pallidotomy in Parkinson's disease is the reduction in levodopa-induced dyskinesias, often choreiform, two HD patients have undergone pallidotomy at Emory University in Atlanta with apparent early improvement in chorea but worsening of akinesia (M. deLong, personal communication).

An important prerequisite of all these potentially disease-modifying studies is the development of sound methodology for patient assessment. The Unified Huntington's Disease Rating Scale (UHDRS) [20], developed by the Huntington Study Group (HSG) in North America, has been designed and validated as a battery to measure aspects of disease progression, and an abbreviated version

has recently been published [61]. A more detailed Core Assessment Program for Intracerebral Transplantation in HD (CAPIT-HD) protocol [48] incorporating UHDRS, but also a number of additional neuropsychiatric measures to capture cognitive or behavioural changes in smaller numbers of individuals intensively studied, has been developed in Europe and is currently being revised in the light of experience with its use.

Until any disease-modifying treatment is available, one is restricted to considering the use of a range of medications to treat symptoms. These should be administered sparingly, and for specific indications. For severe troublesome chorea, it may be justifiable to try tetrabenazine or a neuroleptic such as sulpiride. However, both of these can worsen akinetic features and may make the patient feel drugged, and tetrabenazine can provoke depression, and neuroleptics tardive dyskinesia. A recent double-blind placebo-controlled trial of clozapine showed little beneficial effect [71]. It is important to assess early on whether the patient as a whole is better as a result of antidopaminergic treatment; if not, it should be stopped. Also consider whether a cosmetic result that pleases family or carers is being achieved at the expense of the patient's overall wellbeing. Neuroleptics may also be indicated for psychosis in HD, and occasionally for behavioural disorder, but the latter may be better managed without them; occasionally carbamazepine helps in this regard, and sometimes benzodiazepines help either chorea or behaviour or both.

Depression is common in HD, especially in the early to middle stages, when there is a high risk of suicide. It is eminently treatable and should respond to conventional or newer antidepressants as well as depression in any other context. Where obsessionality is also a prominent feature, clomipramine or a selective serotonin reuptake blocker (SSRI) may be particularly indicated. Levodopa and dopamine agonists do not help the akinetic-rigid syndrome of HD; nor do they provoke chorea in such patients. Sometimes amantadine or an anticholinergic can loosen the patient slightly to aid nursing care.

By the middle to late stages of HD, when patients often enter a long-term care facility, it is unfortunately the rule rather than the exception that they have accumulated a long list of medications, may of which are working against each other. For example, a patient may be taking tetrabenazine and haloperidol for chorea, plus procyclidine (which should make chorea worse) for drug-induced parkinsonism, plus amitriptyline for the depression caused by the tetrabenazine, etc. Such patients are usually greatly benefited by gradual reduction and rationalisation of their therapy. As Shoulson has said: "with neuroleptics you can help HD patients twice – once when you start them and again when you stop them!" [60].

Presymptomatic and antenatal exclusion testing have been greatly simplified now that a gene-specific test is available, and diagnosis can be definitely confirmed or excluded in most individual cases, although there remains some uncertainty if the repeat length is in the intermediate zone. Whilst diagnostic testing can be done on individuals at any age (with appropriate consent), presymptomatic testing can still only be offered to adults [3]. Where intervening unaffected parents-to-be wish to have the opportunity to terminate or continue a pregnancy depending on whether or not the foetus is "at risk", without altering their own perceived risk, the older linkage-based prenatal exclusion test can still be offered if the family structure is suitable [62]. Potential difficulties arise when such individuals want a gene-specific predictive test whilst their still unaffected parent may not wish to know their own gene status. The overall consensus view is that the right of the at-risk offspring to know their own genetic status should take precedence over the wish of the at-risk parent not to know. In theory, it is possible not to inform the latter, but this can pose major additional problems. Fortunately, there have not been too many major problems resulting from either positive or negative predictive test results, perhaps because of the caution and support with which testing has generally been introduced.

Dentatorubro-pallidoluysian atrophy (DRPLA)

This neurodegenerative disorder, first described by Titica and van Bogaert [70] and by Smith et al. [64] has been chiefly reported in Japan [42], where it is more common than HD. It is dominantly inherited, again owing to an unstable CAG trinucleotide repeat expansion (> 49 repeats) in a gene on chromosome 12p [25, 41]. Its phenotypic expression can vary widely, and originally attempts were made to categorise it into choreic, myoclonic and ataxic forms. Again anticipation, associated with paternal transmission, occurs. A small number of families have been described from outside Japan, particularly in one African-American family (the Haw River syndrome [4]), and one other white American [47] and five European [43, 74] families. All of these last five families had carried a diagnosis of HD until they were found to be negative for the HD expansion.

The pathological changes, as the name would suggest, usually involve degeneration in the dentate and red nuclei, the external pallidum and the subthalamic nucleus. Clinical features include varying combinations of chorea, myoclonus, dystonia or parkinsonism, cerebellar ataxia, epilepsy, psychosis and dementia and can vary widely both within and between families. Mean disease duration is about 11 or 12 years. Young-onset cases have the longest CAG repeat expansions and tend to present predominantly as progressive myoclonus epilepsy [26, 74].

Benign hereditary chorea

Benign hereditary chorea (BHC) is rare. Not only that, but its very existence as a discrete entity is questionable. About 20 families alleged to have this dominantly inherited condition (sometimes with variable penetrance), originally described by Haerer et al. in 1966 [18], have been published. Among them, 1 family turned out to have probable hereditary idiopathic dystonia [49, 58], 1 an ataxia telangiectasia variant [24, 50], and 1 HD [37]. In addition, at least 1 published family with hereditary alcohol-responsive myoclonic dystonia [32] had earlier been felt by one authority to have BHC [63]. These conditions, all more common than "BHC", should be considered and excluded before accepting the diagnosis in an individual with otherwise unexplained (usually) childhood-onset apparent chorea without dementia or other neurological abnormality.

Neuroacanthocytosis

Neuroacanthocytosis (NA) is a rare progressive neurological syndrome associated with acanthocytes in the peripheral blood, often accompanied by elevation of serum creatine phospokinase levels. Usually, it presents in the 3rd–5th decade, but the age of onset ranges from the 1st to the 7th decade. The most common manifestation is chorea, but dystonia, tics and vocalisations may occur, and an akinetic-rigid syndrome can develop as the disease progresses [19, 65]. Oromandibular dyskinesia is often conspicuous and may result in mutilation of lips and tongue or a characteristic feeding dystonia, with tongue protrusion forcing food back out of the mouth. Typically, tendon reflexes are reduced or lost owing to an axonal neuropathy, and amyotrophy, cognitive impairment, psychiatric features, personality change and seizures may occur [6, 19, 35]. In most cases, inheritance appears to be autosomal recessive, and recently the disease has been linked to chromosome 9q21 in 11 such families [56]. However, autosomal dominant inheritance has also been reported in a few cases [35], and there is an overlap with the X-linked McLeod syndrome (a distinct entity of acanthocytosis, weak expression of the Kell blood group system and neurological abnormality [19, 67]). This and the fact that there is male-to-female preponderance of 2 : 1 indicates that NA is a heterogeneous disorder.

Pathologically, there is atrophy of the caudate nucleus and striatum, but, in contrast to HD, the cerebral cortex, subthalamic nucleus, brain stem and cerebellum are unaffected [52]. Computed tomography (CT) may reveal cerebral and caudate atrophy, and non-specific focal lesions of striatum and caudate may be seen on MRI [19]. In contrast to a-β-lipoproteinaemia, which is a third neurological disorder associated with acanthocytosis in the peripheral blood [2], lipoproteins are normal. The diagnosis of NA is made by the finding of more than 3% of acanthocytes in a fresh thick wet blood film. However, the diagnosis may sometimes be missed if less than three blood films are examined before the diagnosis is dismissed.

Sporadic chorea

The list of conditions, both hereditary and non-genetic, in which chorea has been described, is enormous (see Shoulson's excellent review [60]). In patients with sporadic chorea, the following should initially be considered and excluded: chorea gravidarum, or caused by the contraceptive pill and possibly hormone replacement therapy (HRT); other drug-induced chorea, especially owing to anticholinergics, levodopa, neuroleptics and anticonvulsants; Sydenham's chorea (and recurrence thereof); SLE or the lupus anticoagulant syndrome; neuroacanthocytosis [19], thyrotoxicosis; polycythaemia rubra vera; other vascular chorea, often in the form of hemichorea or hemiballism. The last of these, although previously seen mostly in elderly people with hypertension and/or diabetes, may also be seen in younger people, in whom it is often not due to stroke but to other causes [9, 72], including toxoplasma abscess in HIV-infected subjects. Moreover, the lesion assumed to be responsible is not always demonstrated to be in the subthalamic nucleus itself.

Formerly, in an individual with sporadic chorea, if after a full history and examination the cause was not apparent, one requested most or all of: full blood count, fresh thick film for acanthocytes, creatine phosphokinase (CPK), erythrocyte sedimentation rate (ESR), thyroid function, antinuclear factor (ANF), lupus anticoagulant, antistreptolysin O (ASO) titre, anti-DNAaseB, biochemical screen and structural brain imaging. If no cause was found, HD was often considered as a possible diagnosis. Today, depending on the individual circumstances, if one is clinically suspicious of HD in someone with sporadic chorea, one may choose to consider genetic testing for HD (and, if negative, DRPLA) first, and proceed with other investigations only if this is negative.

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