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Tremor and Other Hyperkinetic Movements

Viewpoint

Update on the Non-Huntington's Disease Choreas with Comments on the Current Nomenclature

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Abstract

Chorea can be caused by a multitude of etiologies: neurodegenerative, pharmacological, structural, metabolic, and others. In absence of other apparent causes, exclusion of Huntington's disease is often a first step in the diagnostic process. There are a number of neurodegenerative disorders whose genetic etiology has been identified in the past decade. Molecular diagnosis has enabled genetic identification of disorder subtypes which were previously grouped together, such as the neurodegeneration with brain iron accumulation disorders and the neuroacanthocytosis syndromes, as well as identification of phenotypic outliers for recognized disorders. Correct molecular diagnosis is essential for genetic counseling and, hopefully, ultimately genetic therapies. In addition, there has recently been recognition of other disorders which can mimic neurodegenerative disorders, including paraneoplastic and prion disorders. This article focuses upon recent developments in the field but is not intended to provide an exhaustive review of all causes of chorea, which is available elsewhere. I also discuss the nomenclature of these disorders which has become somewhat unwieldy, but may ultimately be refined by association with the causative gene.

Keywords: Chorea, neurodegeneration with brain iron accumulation, neuroacanthocytosis

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Introduction

Chorea can be caused by a multitude of etiologies: neurodegenerative, pharmacological, structural, metabolic, and others. This article focuses upon recent developments in the field. I also discuss the nomenclature of these disorders, which has become somewhat unwieldy, but may ultimately be refined by association with the causative gene. This article is not intended to provide an exhaustive review of all causes of chorea, as this is available elsewhere.[1,2]

The identification in 1993 of the causative trinucleotide repeat expansion within the gene responsible for Huntington's disease (HD)[3] was the starting point for the recognition that there were other genetic causes of chorea. Prior to this, any patient with a progressive movement disorder and neuropsychiatric changes was given the diagnosis of HD, particularly if there was a positive family history. However, between 1%[4] and 12–15%[5,6] of patients thought to have HD were found to be negative for the HD mutation. The identification of the HD gene led to the search for other genes that could cause familial basal ganglia neurodegenerative syndromes. In addition, it became possible to make the diagnosis of HD in those with atypical features, such as late age of onset and the absence of a family history, who had previously been given the now-obsolete label of "senile chorea."

"Huntington's disease-like" disorders

The grammatically clumsy naming, involving an adjectival construct masquerading as a noun, of the Huntington's disease-like (HDL) disorders, commenced in 1998 with HDL1.[7] Although traditional requirements for being "HDL" should have been autosomal dominant (AD) inheritance, in addition to comprising a progressive hyperkinetic movement disorder and cognitive impairment, one of the four disorders with this unfortunate name demonstrated autosomal recessive inheritance (HDL3).

The term HDL1 was used to describe a family with a disorder characterized by personality changes starting in early–mid adulthood, followed by chorea, rigidity, dysarthria, myoclonus, and ataxia, and seizures.[7] Symptoms developed in three generations, demonstrating

AD inheritance. This disease was determined to be a prion disorder due to an octapeptide repeat.[8] Other families with this mutation have a different phenotype in which psychiatric features predominated over a variety of cerebellar, pyramidal or parkinsonian signs.[9]

HDL2 was reported initially as being due to a CAG repeat expansion, with AD inheritance and clinical features very similar to HD, in one family.[10] The mutation was subsequently identified as being a CTG/CAG trinucleotide repeat expansion located within a variably spliced exon, labeled 2A, between exon 1 and exon 2B of *junctophilin-3* (*JPH3*) on chromosome 16q24.3.[11] Unusually, neurodegeneration appears to be due to transcription of the antisense CAG repeat.[12] In addition, mRNA toxicity, in common with myotonic dystrophy 1 and some of the spinocerebellar ataxias (SCAs),[13] may play a significant role in pathogenesis.[12] Intriguingly, the latter feature may be shared with HD, and may offer insights into a common disease mechanism.

Only reported to date in subjects of black African ancestry, HDL2 has been found in many countries,[5,10,11,14–16] especially among black South Africans. Ten percent may have acanthocytes, resulting in the inclusion of this disorder with neuroacanthocytosis syndromes.[17]

The term HDL3 was given to five affected siblings with chorea, dystonia, dysarthria, cognitive impairment, and seizures.[18] Neuroimaging showed cortical and caudate nucleus atrophy. Although linkage localized the mutation to the vicinity of the HD gene, HD was excluded. No further cases have been reported with this disorder, nor has a causative gene been identified.

HDL4 was the term given to what transpired to be a familial phenotypic variation of SCA17:[19] 1% of a cohort of non-HD patients were found to have this mutation.[5] Although ataxia is a more typical presentation of SCA17, in some families there may be striking phenotypic homogeneity.[20]

Fortunately, no new disorders have been given an "HDL" name. In addition to being inelegant, the absence of the noun in the term, which most logically would be the repetitive "disease" ("Huntington's disease-like disease 2"), makes the name challenging to translate into other languages such as French or German, where the ending of the adjective should agree with the gender of the noun.

It is this author's hope that this terminology will be abandoned and the named HDL disorders given names related to their causative mutation. One option would be to follow the convention of the neurodegeneration with brain iron accumulation (NBIA) disorders, e.g. "junctophilin 3-associated neurodegeneration (J3AN)." Another alternative would be to adopt terminology similar to that for the neurodegenerative disorders characterized by abnormal protein accumulation, such as "tau-opathy" and "synuclein-opathy," hence "junctophilin-opathy." One distinction from these disorders is that in general this terminology has been used to refer to accumulation of the specified protein on neuropathological examination, rather than the causative mutation. Although neither of these options is much more elegant than "HDL," it is appealing to use nomenclature which is etiologically accurate, and has the additional advantage of not being dependent upon the clinical phenotype which may not be choreiform.

Other trinucleotide repeat disorders

In addition to HDL2 and SCA17, movement disorders can be seen in some of the other SCAs and dentatorubropallidoluysian atrophy (DRPLA). In some cases the typical cerebellar findings, such as abnormalities of eye movement and ataxia, are less prominent than the movement disorder. Parkinsonism, dystonia, and chorea are not infrequent in SCA3 (Machado–Joseph disease), the most common SCA in most populations. Patients with SCA1[21] and SCA2[22,23] may occasionally present with or develop chorea. There does not seem to be a relationship between size of the trinucleotide repeat expansion and the phenotype.

DRPLA was initially thought to be seen only in Japanese populations, but has occasionally been reported in Caucasian[24,25] or African-American[26] families. There are two typical phenotypes related to the age of onset, and thus in this case correlate with the size of the trinucleotide repeat expansion. In younger onset patients myoclonus and seizures are prominent, in addition to ataxia and dementia. In patients with age of onset older than 20 years, chorea and neuropsychiatric symptoms are typical, similar to HD.

Neuroacanthocytosis syndromes

The past decade has seen clarification of the clinically and genetically heterogeneous disorders given the term "neuroacanthocytosis." This term is still often used to refer to cases for which the more accurate term, especially if genetic or protein confirmation has been performed, is chorea-acanthocytosis (ChAc; also referred to as choreoacanthocytosis).

Following the seminal reports by Levine et al.,[27] and Critchley et al.,[28] in the 1960s, of a neurological disorder accompanied by acanthocytes with normal lipoproteins, the term "neuroacanthocytosis" was adopted, despite the potential for confusion with the disorders of lipoproteins (abetalipoproteinemia [Bassen–Kornzweig disease] and hypobetalipoproteinemia). The term "Levine–Critchley" syndrome was used initially by authors from Japan, where ChAc is more common.[29] The widely cited case series published by Hardie et al. in 1991[30] unfortunately perpetuated diagnostic confusion due to its genetic heterogeneity, but has subsequently been updated.[31] It has recently been confirmed that Critchley's original Kentucky kindred were indeed affected by ChAc.[32]

The identification of mutations in *VPS13A* (encoding for vacuolar protein sorting-associated protein 13A) as the cause, and the affected protein as chorein,[33–35] has facilitated precise diagnosis of ChAc.[36] Use of Western blotting to demonstrate absence of the protein has been useful in clinical practice.[37] Molecular conformation is challenging due to the large gene size and the many locations and natures of mutations,[38] but may be made easier with recent advances in genetic techniques.

As both acanthocytes[39–41] and chorea may be variable or absent at any point in a patient's clinical course, it has been suggested that the name "chorea-acanthocytosis" is inaccurate. As the affected protein has been named "chorein," a more appropriate term may be "chorein disease," "chorein-associated neurodegeneration," or "chorein-opathy,"

although I am reluctant to advocate for yet another change in nomenclature for a disorder whose taxonomy has already resulted in confusion.

Recognition of an association of the McLeod blood type[42,43] with various movement disorders, including chorea, parkinsonism, tics, and dystonia, has permitted molecular diagnosis of this X-linked neuroacanthocytosis syndrome (McLeod syndrome; MLS).[44–46] Although very rare, with fewer than a hundred published cases,[47] this diagnosis is important because of the potential complications of blood transfusion incompatibility and preventable cardiac complications.[44,48]

Potential diagnostic confusion may be caused by the observations of acanthocytes in HDL2[17] and in pantothenate kinase-associated neurodegeneration (PKAN).[49] Indeed, one of Hardie's original series was likely to have had this disorder (initially given the name hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa and pallidal degeneration [HARP][50]).

The mechanism for the production of acanthocytes is not known. In PKAN, it is likely that this is a result of impaired lipid synthesis; however, this hypothesis raises the question as to why acanthocytosis is not a universal finding in these patients.

Neurodegeneration with brain iron accumulation

This group of disorders is characterized by the finding on magnetic resonance imaging (MRI) of iron deposition primarily in the globus pallidus. Prior to the advent of MRI, the diagnosis was made only post mortem, on the basis of neuropathological findings. The disorders were described as "Hallervorden–Spatz disease" or "Hallervorden–Spatz syndrome" if atypical. Causative mutations in the *PANK2* gene were discovered,[51] and the term "pantothenate kinase-associated neurodegeneration" was proposed in light of the unethical nature of the work of Drs. Hallervorden and Spatz in Nazi Germany.[52,53] The prototypical NBIA disorder, PKAN, typically presents in childhood with dystonia, rather than chorea, in addition to other findings such as pigmentary retinal degeneration.[49] The disorder initially termed HARP was found to be allelic with PKAN.[50,54]

Adult onset of basal ganglia iron deposition is associated with chorea. A small number of families have been reported with autosomal dominant inheritance of mutations of ferritin light chain, responsible for iron transportation, resulting in neuroferritinopathy.[55–58] Autosomal recessive inheritance of mutations of ceruloplasmin,[59,60] a ferroxidase, results in chorea and dystonia, often orofacial, with the addition of ataxia. Symptomatic heteroplasmic carriers have been reported.[61] The pattern of basal ganglia iron deposition can be distinguished in the different disorders by distinctive patterns of iron and inflammation on neuroimaging.[62]

Childhood-onset NBIA disorders appear to be characterized by dystonia and parkinsonism, and include one phenotype of neuroaxonal dystrophy, due to mutations of *PLA2G6* (phospholipase-associated neurodegeneration; PLAN),[63–65] Kufor–Rakeb syndrome (PARK9; *ATP13A2* mutations),[66] and fatty acid hydroxylase-associated neurodegeneration (FAHN),[67] and a growing list of other disorders.

Benign hereditary chorea

Benign hereditary chorea is so called as it does not appear to be associated with a dementing process or severe neurological impairment. It has been associated with mutation of thyroid transcription factor 1 (*TITF-1*),[68–70] also known as *NKX2.1*. However, this mutation is not found in all families, and the disorder appears to be genetically[71] and possibly phenotypically[72] heterogeneous. Onset may be in childhood, and there is sometimes also mild ataxia. The chorea may respond to l-dopa.[73] Neuropathological findings are subtle and reflect alterations in a subset of striatal interneurons.[74] Subtle changes are reported on structural and functional neuroimaging.[75,76]

Mutations of the same gene have been reported to cause a multisystem disorder comprising congenital hypothyroidism, hypotonia, and pulmonary problems, in addition to chorea.[70,77–79] Differences in the size and nature of mutations may account for the varying severity in these two disorders.

Autoimmune disorders

An expanding number of paraneoplastic neurologic syndromes have been recognized. Although much less common than cerebellar and neuromuscular presentations, chorea has been reported in renal, small cell lung, breast, Hodgkin's and non-Hodgkin's lymphoma,[80–84] due to anti-CRMP-5/CV2[83,85] or, occasionally, anti-Hu[84] or anti-Yo[86] neuronal autoantibodies.

Although not technically choreiform in nature, the identification of the anti-*N*-methyl-D-aspartate (NMDA)-receptor antibody-related syndrome is mentioned here due to its apparent frequency and recent insights into its course and pathogenesis.[87–91] This disorder results in encephalopathy with complex, often stereotypic movements with components of dystonia and chorea. In some patients ovarian teratomas are identified, although in others the etiology remains obscure.[87] Importantly, some patients may recover after a prolonged disease course.

Prion diseases

Prion disease both inherited and sporadic may cause chorea,[92] rather than the more typical movement disorder presentation of myoclonus in a patient with progressive cognitive deterioration. In addition to HDL1[8] (discussed above), new variant Creutzfeldt–Jakob disease, related to bovine spongiform encephalopathy, can cause chorea and cognitive impairment which progress subacutely over months.[93,94]

Advances in therapies

Neurosurgical advances for other movement disorders appear to have benefited patients with the non-HD choreas, although at present it is challenging to accurately gauge success rates as cases with poor outcomes are less likely to be reported. There is a need to collate all cases receiving surgery for each of these rare diseases in order to provide general recommendations.

Case reports and small series have reported the effects of deep brain stimulation (DBS) or lesioning of the subthalamic nucleus (STN) or

globus palldus pars interna (GPi) in patients with chorea of various etiologies. Case reports of DBS of the GPi in "senile chorea"[95] have been promising, although in ChAc[96–98] and MLS[99] results are mixed. The benefits in these progressive disorders may be limited by ongoing neurodegeneration. The motor thalamus has also been proposed as a potentially promising site for DBS in "senile chorea"[95] and has been reported as being beneficial in a patient with ChAc.[96,99] The optimal site and frequency of stimulation for treatment of chorea remain to be identified.[99] Positive results following pallidotomy have been reported in DRPLA[100] and ChAc.[101]

The most significant advance in medical therapies in the USA has been the recent approval of tetrabenazine,[102,103] which depletes monoamines from presynaptic terminals.[104] However, the side effects of depression, parkinsonism, and impaired swallowing may be limiting,[105] and tetrabenazine should be used with care. Reserpine may also be useful with the same caveats.

As in HD, the newer atypical antipsychotics, including clozapine, quetiapine, aripiprazole, and ziprasidone have been a useful addition to the pharmacological armamentarium. Although parkinsonism and tardive dyskinesia can occasionally be seen with these agents, and sedation can be a significant problem, weight gain is rarely an issue in patients with neurodegenerative choreas, and thus these medications can be helpful.

Other agents with different mechanisms of action have been reported to give benefit in non-HD choreas, including levetiracetam,[106] possibly related to a membrane-stabilizing effect. However, caution should be employed, as some anticonvulsants, such as lamotrigine, have been reported to worsen involuntary movements in ChAc.[107] Glutamatergic NMDA-receptor antagonists such as amantadine and riluzole may reduce chorea in HD[108–112] and may be considered in non-HD choreas.

Neuroimaging

Although limited by the rarity and clinical heterogeneity of these disorders, quantitative neuroimaging has resulted in demonstration of specific features in some of the non-HD choreas, such as specific atrophy affecting the head of caudate nucleus in ChAc[113–115] and progression of neurodegeneration in MLS[44,116]

Studies of metabolism such as magnetic resonance spectroscopy are in their infancy, but may ultimately lead to additional insights into disease pathogenesis.[117]

Future needs

Despite recent advances with progress in molecular medicine, a significant number of subjects with chorea remains undiagnosed. The rarity of many of these disorders means that funding for research is limited, especially in the current climate. There is a need for an internationally accessible database of clinical descriptions, neuroimaging findings, other laboratory features, and tissue samples for all non-diagnosed subjects with chorea, with or without family history. This could be modeled upon the neuroacanthocytosis database (http://www.euro-hd.net/html/na/submodule/), which has been piggy-backed onto the European Huntington's disease database (http://euro-hd.net), with the addition of a centralized tissue bank. Such a resource could be used, for example, for genetic studies, for screening for serological and neuroimaging biomarkers, for searches for distinguishing phenotypic features, and would be a rewarding use of the technology now at our disposal.

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