Viewpoint

Update on the Non-Huntington’s Disease Chores 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.4 However, between 1% and 12–15% 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).7

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, demonstrations...
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 juncophilin-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.20 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. “juncophilin 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 “juncophilin-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 SCA121 and SCA222 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 Caucasian24,25 or African-American26 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 choreaacanthocytosis).

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 199130 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 nature of mutations,38 but may be made easier with recent advances in genetic techniques.

As both acanthocytes39–41 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 with various movement disorders, including chorea, parkinsonism, tics, and dystonia, has permitted molecular diagnosis of this X-linked neuroacanthocytosis syndrome (McLeod syndrome; MLS). 54–56 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 Dr. Hallervorden’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 postmortem, 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 neuroferritinopathies. 55–56 Autosomal recessive inheritance of mutations of ceruloplasmin, a ferroxidase, results in chorea and dystonia, often orofacial, with the addition of ataxia. Symptomatic heterozygous 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 dementiaing process or severe neurological impairment. It has been associated with mutation of thyroid transcription factor 1 (TTF-1), 68–70 also known as NX2.1. 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. 76, 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 lymphomas, 80–84 due to anti-CRMP-5/CV2 85 or, occasionally, anti-Hu 84 or anti-Yo 86 neuronal autoantibodies.

Although not technically choreiform in nature, the identification of the anti-V-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 stereotype 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, rather than the more typical movement disorder presentation of myoclonus in a patient with progressive cognitive deterioration. In addition to HDL18 (discussed above), new variant Creutzfeldt–Jakob disease, related to bovine spongiform encephalopathy, can cause chorea and cognitive impairment which progress subacutely over months. 87

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 pallidus pars interna (GPi) in patients with chorea of various etiologies. Case reports of DBS of the GPi in “senile chorea”105 have been promising, although in ChAc96–98 and MLS99 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”105 and has been reported as being beneficial in a patient with ChAc96,99. The optimal site and frequency of stimulation for treatment of chorea remain to be identified.104 Positive results following pallidotomy have been reported in DRPLA100 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 have been promising, although in ChAc96–98 and MLS99 results are mixed. Neuroimaging has resulted in demonstration of specific features in some of the non-HD choreas, such as specific disease pathogenesis.117

**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 ChAc113–115 and progression of neurodegeneration in MLS44,116. 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 undiagnosed 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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**References**

1. Walker RH. Differential diagnosis of chorea. *Curr Neurol Neurosci Rep* 2011; 11:385–395, http://dx.doi.org/10.1007/s11910-011-0202-2.
2. Walker RH. The differential diagnosis of chorea. 2011. Oxford University Press, New York, NY
3. Huntington Study Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell* 1993;72:971–983, http://dx.doi.org/10.1016/0092-8674(93)90585-E.
4. Andrew SE, Goldberg YP, Kremer B, et al. Huntington disease without cag expansion - phenocopies or errors in assignment. *Am J Hum Genet* 1994;54:852–863.
5. Stevanin G, Fujigasaki H, Lebre AS, et al. Huntington’s disease-like phenotype due to trinucleotide repeat expansions in the TBP and JPH3 genes. *Brain* 2003;126:1599–1603, http://dx.doi.org/10.1093/brain/awg155.
6. Vuillaume I, Meynieu P, Schraen-Maschke S, et al. Absence of unidentified CAG repeat expansion in patients with Huntington’s disease-like phenotype. *J Neurol Neurosurg Psychiatry* 2000;68:672–675, http://dx.doi.org/10.1136/jnnp.68.5.672.
7. Xiang F, Almqvist EW, Huq M, et al. A Huntington disease-like neurodegenerative disorder maps to chromosome 20p. *Am J Hum Genet* 1998;63:1431–1438.
8. Moore RC, Xiang F, Monaghan J, et al. Huntington disease phenocopy is a familial prion disease. *Am J Hum Genet* 2001;69:1385–1388.
9. Laplanche JL, Hachimi KH, Durieux I, et al. Prominent psychiatric features and early onset in an inherited prion disease with a new insertional mutation in the prion protein gene. *Brain* 1999;122:2375–2386, http://dx.doi.org/10.1093/brain/122.12.2375.
10. Margolis RL, O’Hearn E, Rosenblatt A, et al. A disorder similar to Huntington’s disease is associated with a novel CAG repeat expansion. *Ann Neurol* 2001;50:373–380.
11. Holmes SE, O’Hearn E, Rosenblatt A, et al. A repeat expansion in the gene encoding junctophilin-3 is associated with Huntington disease-like 2. *Nat Genet* 2001;29:377–378, http://dx.doi.org/10.1038/ng670.
12. Williams B, Rudnicki DD, Zhao J, et al. An antisense CAG repeat transcript at JPH3 locus mediates expanded polyglutamine protein toxicity in Huntington’s disease-like 2 mice. *Neuron* 2011;70:427–440, http://dx.doi.org/10.1016/j.neuron.2011.03.021.
13. Rudnicki DD, Holmes SE, Lin MW, et al. Huntington’s disease-like 2 is associated with CUG repeat-containing RNA foci. *Ann Neurol* 2007;61:272–282, http://dx.doi.org/10.1002/ana.21081.
14. Rodrigues GG, Walker RH, Brice A, et al. Huntington's disease-like 2 in Brazil—Report of 4 patients. *Mov Disord* 2008;23:2244–2247, http://dx.doi.org/10.1002/mds.22223.

15. Santos C, Wanderley H, Vedolin L, et al. Huntington disease-like 2: the first patient with apparent European ancestry. *Can J Neurol Sci* 2008;35:480–485, http://dx.doi.org/10.1016/j.cjns.2008.09.013.

16. Maagazi DS, Krause A, Bonev V, et al. Huntington's disease: genetic heterogeneity in black African patients. *S Afr Med J* 2008;99:200–203.

17. Walker RH, Rasmussen A, Ruthnicki D et al. Huntington's Disease-like 2 can present as chorea-acanthocytosis. *Neurology* 2003;61:1002–1004.

18. Kamboursi M, Bohleca S, Al Tahan A et al. Localization of the gene for a novel autosomal recessive neurodegenerative Huntington-like disorder to 4p15.3. *Am J Hum Genet* 2006;66:445–452.

19. Richfield EK, Vonsattel JP, Macdonald ME et al. Selective loss of striatal preprotachykinin neurons in a phenocopy of Huntington's disease. *Mov Disord* 2002;17:327–332, http://dx.doi.org/10.1002/mds.10032.

20. Schneider SA, van de Warrenburg BP, Hughes TD et al. Phenotypic homogeneity of the Huntington's disease-like presentation in a SCA17 family. *Neurology* 2006;67:1701–1703, http://dx.doi.org/10.1212/01.wnl.0000242740.01273.00.

21. Namekawa M, Takiyama Y, Ando Y et al. Chorriform movements in spinocerebellar ataxia type 1. *J Neurol Sci* 2001;187:103–106, http://dx.doi.org/10.1016/S0022-510X(01)00527-5.

22. Geschwind DH, Perlman S, Figueroa CP et al. The prevalence and wide clinical spectrum of the spinocerebellar ataxia type 2 trinucleotide repeat in patients with autosomal dominant cerebellar ataxia. *Am J Hum Genet* 2001;69:1245–1251, http://dx.doi.org/10.1086/321156.

23. Rottnek M, Riggio S, Byrne W et al. Schizophrenia in a patient with spinocerebellar ataxia 2: coincidence of two disorders or a neurodegenerative disease presenting with psychosis? *Am J Psychiatry* 2008;165:964–967.

24. Le B, I, Cauzadat A, Castelnovo G et al. Prevalence of dentatorubropallidoluysian atrophy in a large series of white patients with cerebellar ataxia. *Arch Neurol* 2003;60:1097–1099, http://dx.doi.org/10.1001/archneur.60.8.1097.

25. Wardle M, Majoneo E, Williams NM et al. Dentatorubral pallidoluysian atrophy in South Wales. *J Neurol Neurosurg Psychiatry* 2008;79:804–807, http://dx.doi.org/10.1136/jnnp.2007.128074.

26. Burke JR, Wingfield MS, Lewis KE et al. The Haw River Syndrome: Dentatorubropallidoluysian atrophy (DRPLA) in an African-American family. *Nat Genet* 1994;7:521–524, http://dx.doi.org/10.1038/ng0894-521.

27. Levine IM, Estes JW, Looney JM. Hereditary neurological disease with acanthocytosis. A new syndrome. *Arch Neurol* 1968;19:403–409, http://dx.doi.org/10.1001/archneur.1968.00480040060007.

28. Critchley EM, Clark DB, Wilder A. Acanthocytosis and neurological disorder without betalipoproteinemia. *Arch Neurol* 1968;15:134–140, http://dx.doi.org/10.1001/archneur.1968.00470320036004.

29. Hirose H. Neuroacanthocytosis in Japan—Review of the literature and cases. *Neuroacanthocytosis Syndromes II*, ed. Walker RH, Saito S, Danek A, Springer-Verlag, Berlin Heidelberg, 2008;75–84.

30. Hardie RJ, Pullen HW, Harding AE et al. Neuroacanthocytosis. A clinical, haematological and pathological study of 19 cases. *Brain* 1991;114:43–49.

31. Gandhi S, Hardie RJ, and Lees AJ. An update on the Hardie neuroacanthocytosis series. *Neuroacanthocytosis Syndromes II*, ed. Walker RH, Saito S, Danek A, Springer-Verlag, Berlin Heidelberg, Germany, 2008; 45–51.

32. Velayos-Baeza A, Holinski-Feder E, Nietzel B et al. Choreo-acanthocytosis genotype in Critchley's original Kentucky neuroacanthocytosis kindred. *Arch Neurol* 2011;68:1330–1333, http://dx.doi.org/10.1001/archneur.2011.239.

33. Ueno S, Maruki Y, Nakamura M et al. The gene encoding a newly discovered protein, chorein, is mutated in choreo-acanthocytosis. *Nat Genet* 2001;28:121–122, http://dx.doi.org/10.1038/ng8825.

34. Rampoldi L, Dobson-Stone C, Rubio JP et al. A conserved sorting-associated protein is mutant in choreo-acanthocytosis. *Nat Genet* 2001;28:119–120, http://dx.doi.org/10.1038/ng8821.

35. Velayos-Baeza A, Vettori A, Copley RR et al. Analysis of the human VPS13 gene family. *Genomics* 2004;84:536–549, http://dx.doi.org/10.1016/j.ygeno.2004.04.012.

36. Rampoldi L, Danek A, Monaco AP. Clinical features and molecular bases of neuroacanthocytosis. *J Mol Med* 2002;80:475–491.

37. Dobson-Stone C, Velayos-Baeza A, Filippone LA et al. Chorin detection for the diagnosis of choreo-acanthocytosis. *Ann Neurol* 2004;56:299–302, http://dx.doi.org/10.1002/ana.20200.

38. Dobson-Stone C, Danek A, Rampoldi L et al. Mutational spectrum of the CHAC gene in patients with choreo-acanthocytosis. *Eur J Hum Genet* 2002;10:773–781.

39. Sorrentino G, De Renzo A, Minnello S et al. Late appearance of acanthocytes during the course of choreo-acanthocytosis. *J Neurol Sci* 1999;163:175–178, http://dx.doi.org/10.1016/S0022-510X(99)000005-2.

40. Bayreuther C, Borg M. Choreo-acanthocytosis: a diagnosis not to be ruled out in absence of acanthocytes. *J Neurol* 2008;255:98.

41. Malandrini A, Fabrizi GM, Palmeri S et al. Choreo-acanthocytosis like phenotype without acanthocytes: clinicopathological case report. A contribution to the knowledge of the functional pathology of the caudate nucleus. *Acta Neuropathol (Berl)* 1999;86:651–658, http://dx.doi.org/10.1007/BF00294306.

42. Symmans WA, Shepherd CS, Marsh WL et al. Hereditary acanthocytosis associated with the McLeod phenotype of the Kell blood group system. *Br J Haematol* 1979;42:575–583.

43. Redman CM, Russo D, Lee S, Kelly K, and the McLeod syndrome. *Baillieres Best Pract Res Clin Haematol* 1999;12:621–635, http://dx.doi.org/10.1016/S0887-8979(99)00002-5.

44. Danek A, Rubio JP, Rampoldi L, et al. McLeod neuroacanthocytosis: genotype and phenotype. *Ann Neurol* 2001;50:755–764, http://dx.doi.org/10.1002/ana.11003.

45. Jung HH, Hergersberg M, Kneifel S et al. McLeod syndrome: a novel mutation, predominant psychiatric manifestations, and distinct striatal imaging findings. *Ann Neurol* 2001;49:384–392, http://dx.doi.org/10.1002/ana.76.

46. Danek A, Tison F, Rubio J, et al. The chorea of McLeod syndrome. *Mov Disord* 2001;16:882–889, http://dx.doi.org/10.1002/mds.1188.

47. Walker RH, Danek A, Uttner I, et al. McLeod phenotype without the McLeod syndrome. *Transfusion* 2006;46:299–305, http://dx.doi.org/10.1111/j.1537-2995.2007.01106.x.

48. Oechlin E, Kaup D, Jenni R, et al. Cardiac abnormalities in McLeod syndrome. *Int J Cardiol* 2009;132:130–132.
49. Hayflick SJ, Westaway SK, Levinson B, et al. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. *N Engl J Med* 2003; 348:35–40.

50. Orrell RW, Amroha PJ, Heald A et al. Acanthoeyctosis, retinitis pigmentosa, and pallidal degeneration: a report of three patients, including the second reported case with hypoprebetalipoproteinemia (HARP syndrome). *Neurology* 1995;45:487–492.

51. Zhou B, Westaway SK, Levinson B, et al. A novel pantothen kinase gene (PANK2) is defective in Hallervorden-Spatz syndrome. *Nat Genet* 2001;28:345–349, http://dx.doi.org/10.1038/ng572.

52. Shevell ML, Feifer J, Julius Hallervorden’s wartime activities: implications for science under dictatorship. *Pediatr Neurol* 2001;25:162–165, http://dx.doi.org/10.1016/S0887-8994(00)00243-5.

53. Shevell M. Hallervorden and history. *N Engl J Med* 2003;348:3–4.

54. Malandrin A, Cesaretti S, Muliani M, et al. Acanthoeyctosis, retinitis pigmentosa, pallidal degeneration. Report of two cases without serum lipid abnormalities. *J Neurol Sci* 2004;224:441–445, http://dx.doi.org/10.1016/mds.22435.

55. Curtis AR, Fey C, Morris CM, et al. Mutation in the gene encoding fibrinogen light polypeptide causes dominant adult-onset basal ganglia disease. *Nat Genet* 2001;28:330–334, http://dx.doi.org/10.1038/ng571.

56. Crompton DE, Chinnery PF, Bates D, et al. Spectrum of movement disorders in neuroferritinopathy. *Mov Disord* 2004;20:95–99, http://dx.doi.org/10.1002/mds.20284.

57. Mir P, Edwards MJ, Curtis AR, et al. Adult-onset generalized dystonia due to a mutation in the neuroferritinopathy gene. *Mov Disord* 2004;20:243–245, http://dx.doi.org/10.1002/mds.20280.

58. Kubota A, Hida A, Ichikawa Y, et al. A novel fibrinogen light chain gene mutation in a Japanese family with neuroferritinopathy: description of clinical features and implications for genotype-phenotype correlations. *Mov Disord* 2009;24:441–445, http://dx.doi.org/10.1002/mds.22435.

59. Xu X, Pin S, Gathinji M, et al. Aceruloplasminemia: an inherited neurodegenerative disease with impairment of iron homeostasis. *Ann N Y Acad Sci* 2004;1012:299–305, http://dx.doi.org/10.1196/annals.1306.024.

60. Miyajima H. Aceruloplasminemia, an iron metabolic disorder. *Neuropathology* 2003;23:345–350, http://dx.doi.org/10.1046/j.1440-1789.2003.00521.x.

61. McNeill A, Pandolfo M, Kuhn J, et al. The neurological presentation of ceruloplasmin gene mutations. *Eur Neurol* 2008;60:200–205, http://dx.doi.org/10.1159/000148691.

62. McNeill A, Birchall D, Hayflick SJ, et al. T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation. *Neurology* 2008;70:1614–1619, http://dx.doi.org/10.1212/01.wnl.0000310985.40011.d6.

63. Morgan NV, Westaway SK, Morton JE, et al. PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. *Nat Genet* 2006;38:752–754, http://dx.doi.org/10.1038/ng1826.

64. Gregory A, Westaway SK, Holm IE, et al. Neurodegeneration associated with genetic defects in phospholipase A2*. *Neurology* 2006;71:1402–1409, http://dx.doi.org/10.1212/01.wnl.0000327094.66726.28.

65. Mubaidin A, Roberts E, Hampshire D, et al. Karak syndrome: a novel degenerative disorder of the basal ganglia and cerebellum. *J Med Genet* 2003;40:543–546, http://dx.doi.org/10.1136/jmg.40.7.543.

66. Schneider SA, Paisan-Ruiz C, Quinn NP, et al. ATP13A2 mutations (PARK9) cause neurodegeneration with brain iron accumulation. *Mov Disord* 2010;25:979–984, http://dx.doi.org/10.1002/mds.22947.

67. Kruzer MC, Paisan-Ruiz C, Boddart N, et al. Defective FA2H leads to a novel form of neurodegeneration with brain iron accumulation (NBIA). *Ann Neurol* 2010;68:611–618, http://dx.doi.org/10.1002/ana.22122.

68. Breedveld GJ, van Dongen JW, Danesino C et al. Mutations in TTFL-1 are associated with benign hereditary chorea. *Hum Mol Genet* 2002;11:971–979, http://dx.doi.org/10.1093/hmg/11.8.971.

69. Mahajnah M, Inbar D, Steinmetz A et al. Benign hereditary chorea: clinical, neuroimaging, and genetic findings. *J Child Neurol* 2007;22:1231–1234, http://dx.doi.org/10.1177/08830730706261.

70. Devos D, Vuillaume I, De Beedeleveve A et al. New syndromic form of benign hereditary chorea is associated with a deletion of TTFL-1 and PAX-9 contiguous genes. *Mov Disord* 2006;21:2237–2240, http://dx.doi.org/10.1002/mds.21135.

71. Bauer P, Kreuz FR, Burk K, et al. Mutations in TTFL1 are not relevant to sporadic and familial chorea of unknown cause. *Mov Disord* 2006;21:1734–1737, http://dx.doi.org/10.1002/mds.21031.

72. Schrag A, Quinn NP, Bhatia KP et al. Benign hereditary chorea—Entity or syndrome? *Mov Disord* 2000;15:280–288, http://dx.doi.org/10.1002/1531-8257(200003)15:2<280::AID-MDS1011>3.0.CO;2-Q.

73. Asmus F, Horber V, Pohlenz J, et al. A novel TTFL-1 mutation causes benign hereditary chorea with response to levodopa. *Neurology* 2005;64:1952–1954, http://dx.doi.org/10.1212/01.wnl.0000166000.75046.CC.

74. Kleiner-Fisman G, Calingasan NY, Punt M, et al. Alterations of striatal neurons in benign hereditary chorea. *Mov Disord* 2005;20:1353–1357, http://dx.doi.org/10.1002/mds.20577.

75. Maccabelli G, Pichiechio A, Guala A, et al. Advanced magnetic resonance imaging in benign hereditary chorea: study of two familial cases. *Mov Disord* 2010;25:2670–2674, http://dx.doi.org/10.1002/mds.23281.

76. Salvatore E, Di Maio L, Filla A, et al. Benign hereditary chorea: clinical and neuroimaging features in an Italian family. *Mov Disord* 2010;25:1491–1496, http://dx.doi.org/10.1002/mds.23065.

77. Kruide H, Schutz B, Bierbemm H, et al. Choreoathetosis, hypothyroidism, and pulmonary alterations due to human NKKX2-1 haploinsufficiency. *J Clin Invest* 2002;109:475–480.

78. Ferrara AM, De Michele G, Salvatore E, et al. A novel NKKX2.1 mutation in a family with hypothyroidism and benign hereditary chorea. *Thyroid* 2008;18:1005–1009, http://dx.doi.org/10.1089/thy.2008.0095.

79. Willemsen MA, Breedveld GJ, Wouda S, et al. Brain-thyroid-hung syndrome: a patient with a severe multi-system disorder due to a de novo mutation in the thyroid transcription factor 1 gene. *Eur J Pediatr* 2005;164:28–30.

80. Kajjawa KA, Niemi VR, Tomasi MA, et al. Ballistic-choreic movements as the presenting feature of renal cancer. *Arch Neurol* 2001;58:1133–1135, http://dx.doi.org/10.1001/archneur.58.7.1133.

81. Tani T, Piao Y, Mori S, et al. Chorea resulting from paraneoplastic striatal eucapheilin. *J Neurol Neurosurg Psychiatry* 2000;69:512–515, http://dx.doi.org/10.1136/jnnp.69.4.512.

82. Batchelor TT, Platten M, Palmer-Toy DE, et al. Chorea as a paraneoplastic complication of Hodgkin’s disease. *J Neurooncol* 1998;36:185–190, http://dx.doi.org/10.1023/A:1005860103173.
83. Vernino S, Tuie R, Adler CH, et al. Paraneoplastic chorea associated with CRMP-3 neuronal antibody and lung carcinoma. *Ann Neurol* 2002;51:625–630, http://dx.doi.org/10.1002/ana.10178.

84. Dorban S, Gille M, Kessler R, et al. [Chorea-athetosis in the anti-Hu syndrome]. *Rev Neurol (Paris)* 2004;160:126–129, http://dx.doi.org/10.1016/S0035-3747(04)70863-2.

85. Honnorat J, Cartalat-Carel S, Ricard D, et al. Onco-neural antibodies and tumour type determine survival and neurological symptoms in paraneoplastic neurological syndromes with Hu or CV2/CRMP5 antibodies. *J Neurol Neurosurg Psychiatry* 2009;80:412–416, http://dx.doi.org/10.1136/jnnp.2007.138016.

86. Krolik-Salmon P, Andreadis G, Meyronet D, et al. Slow evolution of cerebellar degeneration and chorea in a man with anti-Yo antibodies. *Eur J Neurol* 2006;13:307–308.

87. Lanca N, Daenguwan T, Dalmau J, et al. Anti-N-methyl-D-aspartate receptor encephalitis: A newly recognized inflammatory brain disease in children. *Arthritis Rheum* 2011;63:2515–2522, http://dx.doi.org/10.1002/art.30437.

88. Dalmau J, Lancaster E, Martínez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;10:63–74, http://dx.doi.org/10.1016/S1474-4422(10)70253-2.

89. Hughes EG, Peng X, Gleichman AJ, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurovirol* 2010;30:5866–5875, http://dx.doi.org/10.1015/jjneurovirol.2010.10.001.

90. Vincent A, Bien CG. Anti-NMDA-receptor encephalitis: a cause of psychiatric, seizure, and movement disorders in young adults. *Lancet Neurol* 2008;7:106–107, http://dx.doi.org/10.1016/S1474-4422(08)70225-4.

91. Dalmau J, Tuzun E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007;61:25–36, http://dx.doi.org/10.1002/ana.21050.

92. Lahiri N, Mead S, Tabrizi SJ. Chorea in the prion diseases. In: Walker RH, ed. *Tremor and Other Hyperkinetic Movements*, Oxford University Press, New York, New York; 2011;188–205.

93. Bowen J, Mitchell T, Pearce R, et al. Chorea in new variant Creutzfeldt-Jacob disease. *Mov Disord* 2000;15:1284–1285, http://dx.doi.org/10.1002/mds.10427.

94. McKee D, Talbot P. Chorea acanthocytosis successfully treated with posteroventral pallidotomy. *Neurosurg Rev* 2005;28:168–172, http://dx.doi.org/10.1007/s00702-004-0097-4.

95. Wihl G, Volkmann J, Danek A, et al. Automatic striatal volumetry allows for identification of patients with chorea-ataactohytocytosis at single subject level. *J Neural Transm* 2008;115:23–31, http://dx.doi.org/10.1007/s00702-007-0035-6.

96. Ruip J, Ayerve J, Bader B, et al. Deep brain stimulation in chorea-acanthocytosis. *Mov Disord* 2009;24:1546–1547, http://dx.doi.org/10.1002/mds.22592.

97. Yarnali J, Nandi D, Bradley K, et al. Senile chorea treated by deep brain stimulation of the internal pallidum did not improve chorea in a patient with neuro-acanthocytosis. *Mov Disord* 2001;16:572–575, http://dx.doi.org/10.1002/mds.1109.

98. Ruiz PJ, Ayerve J, Bader B, et al. Deep brain stimulation in chorea acanthocytosis. *Mov Disord* 2002;17:204–207, http://dx.doi.org/10.1002/mds.1260.

99. Burbach P. Deep brain stimulation in neuroacanthocytosis. *Mov Disord* 2005;20:1618–1621.

100. Watanai M, Hashimoto T, Yamamoto K, et al. Pallidotomy for severe generalized chorea of juvenile-onset dentatorubral-pallidolysian atrophy. *Neurology* 2003;61:1452–1454.

101. Fujimoto Y, Itozaki E, Yokochi F, et al. [A case of chorea-acanthocytosis successfully treated with posteroventral pallidotomy]. *Ninsu Shinkeigaku* 1997;37:891–894.

102. Jankovic J, Orman J. Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. *Neurology* 1988;38:391–394.

103. Chatterjee A, Frucht SJ. Tetrabenazine in the treatment of severe pediatric chorea. *Mov Disord* 2003;18:703–706, http://dx.doi.org/10.1002/mds.10427.

104. Pearson SJ, Reynolds GP. Depletion of monoamine transmitters by tetrabenazine in brain tissue in Huntington’s disease. *Neuropharmacology* 1988;27:717–719, http://dx.doi.org/10.1016/0028-3908(88)90889-9.

105. Moss JH, Stewart DE. Iatrogenic parkinsonism in Huntington’s chorea. *Can J Psychiatry* 1986;31:865–866.

106. Lin FC, Wei LJ, Shih PY. Effect of levitiracetam on truncal tic in neuroacanthocytosis. *Acta Neurol Taiwan* 2006;15:38–42.

107. Al-Asmi A, Jansen AG, Badhwar A, et al. Familial temporal lobe epilepsy as a presenting feature of choreoacanthocytosis. *Epilepsia* 2005;46:1256–1263, http://dx.doi.org/10.1111/j.1528-1167.2005.05894.x.

108. Lucetti C, Del Dotto P, Gambaccini G, et al. IV amantadine improves chorea in Huntington’s disease: an acute randomized, controlled study. *Neurology* 2003;60:1995–1997.

109. Verhagen ML, Morris MJ, Farmer C, et al. Huntington’s disease: a randomized, controlled trial using the NMDA-antagonist amantadine. *Neurology* 2002;59:694–699.

110. O’suilleabhain P, Dewey RB Jr. A randomized trial of amantadine in Huntington disease. *Arch Neurol* 2003;60:996–998, http://dx.doi.org/10.1001/archneur.60.7.996.

111. Rosas HD, Korfoshez WJ, Jenkins BG, et al. Riluzole therapy in Huntington’s disease (HD). *Mov Disord* 1999;14:326–330, http://dx.doi.org/10.1002/mds.1331.

112. Seppi K, Mueller J, Bodner T, et al. Riluzole in Huntington’s disease (HD): an open label study with one year follow up. *J Neurol* 2001;248:866–869.

113. Henkel K, Danek A, Graffman J, et al. Head of the caudate nucleus is most vulnerable in chorea-acanthocytosis: a voxel-based morphometry study. *Mov Disord* 2006;21:1728–1731, http://dx.doi.org/10.1002/mds.21046.

114. Huppertz HJ, Kroll-Seger J, Danek A, et al. Automatic striatal volumetry allows for identification of patients with chorea-acanthocytosis at single subject level. *J Neural Transm* 2008;115:1393–1400, http://dx.doi.org/10.1007/s00702-008-0094-8.

115. Walterfang M, Looi JC, Styner M, et al. Shape alterations in the striatum in chorea-acanthocytosis. *Psychiatry Res* 2011;192:29–36, http://dx.doi.org/10.1016/j.psychres.2010.10.006.

116. Valko PO, Hanggi J, Meyer M et al. Evolution of striatal degeneration in McLeod syndrome. *Eur J Neurol* 2010;17:612–618.

117. Ismailogullari S, Caglayan AO, Bader B et al. Magnetic resonance spectroscopy in two siblings with chorea-acanthocytosis. *Mov Disord* 2010;25:2094–2097, http://dx.doi.org/10.1002/mds.23365.