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Non-HD-Chorea: An Expanding Universe

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Search Strategy and Selection Criteria

We searched for original clinical studies and reviews in MEDLINE (via PubMed), Web of Science, Google Scholar, Lilacs published between August 18, 2019, and August 18 2024, in the English, French, German, Spanish, and Portuguese languages. We used the terms Huntington Disease-Like 1, Huntington Disease-Like 2, Huntington Disease-Like 3, Spinocerebellar Ataxia 2, Spinocerebellar Ataxia 12, Spinocerebellar Ataxia 17, Dentatorubral-pallidoluysian atrophy, Friedreich Ataxia, C9ORF72, Neuroacanthocytosis, VPS13A, McLeod Syndrome, Neurodegeneration with Brain Iron Accumulation, Sydenham's Chorea, Hemiballism-Hemichorea, Diabetic Striatopathy, Non-Ketotic Hyperosmolar Hyperglycaemia Chorea, Systemic Lupus Erythematosus, Primary Antiphospholipid Antibody Syndrome, Auto-Immune Chorea, Paraneoplastic Chorea, Wilson Disease, Chorein, SLC6A1, PDE10A, frontotemporal dementia, VCP, UBQLN2, anti-IGLON5 syndrome, anti-NMDAR encephalitis, anti-LHI1 antibodies, inherited prion disease, CACNA1A, neuroferritinopathy, aceruloplasminemia.

We searched for publications in the past years, but did not exclude older publications that were the original studies and were commonly referenced and highly regarded.

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Summary

The main aim of this article is to provide a practical diagnostic approach to phenocopies of Huntington disease (HD). These are defined as conditions characterized by a phenotype similar to HD but with no pathogenic repeat expansion in the *HTT* gene. Their frequency ranges from 2% to 40% depending on ethnicity and geographic location. The most frequent genetic causes are Huntington Disease-like 2/*JHP3*, followed by spinocerebellar ataxia genes (SCA17/*TBP,* SCA12*/PPP2R2B and SCA3/ATXN3, CACNA1A),* and frontotemporal dementia genes (*C9orf72,* and *VCP)*. There is current recognition that a growing number of acquired causes can mimic HD. Autoimmune causes such as primary antiphospholipid syndrome, paraneoplastic chorea, and anti-IGLON5 antibodies, as well as stroke, and diabetes mellitus type 2 complications are the leading acquired causes of HD phenocopies. Finally, we provide practical recommendations on how to approach HD phenocopies considering age at onset, ethnicity, and geographic location of individuals.

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Introduction

Chorea is a movement disorder characterized by a continuous and random flow of muscle contractions resulting in a dance-like appearance.[1] Huntington disease (HD) is the most common cause of genetic chorea in adults[1], due to a CAG repeat expansion above 36 repeats in the *HTT* gene. The aim of this article is to provide a review of the diagnostic and management approach of adult patients with chorea but without expansions in *HTT*.

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HD Phenocopies – Definition and Epidemiology

The clinical hallmark of HD in adults is the triad of movement disorders, particularly chorea, behavioral disturbances and cognitive changes[1]. Individuals who present with these clinical features but do not carry an expansion in the *HTT* gene are defined as HD phenocopies or HD-like syndromes (HDL).[2] Box 1 contains the causes of HD phenocopies usually reported in the literature.[2–4] In a previous review, the authors list causes of HD phenocopies such as: spinocerebellar ataxia 17 (1·1%), *HDL2/JPH3* (0·7%), Friedreich ataxia (0·35%), and inherited prion disease (0·24%).[3] However, the etiology of HD phenocopies is more complex and varied than previously thought. At the National Hospital for Neurology and Neurosurgery, London, there is a high proportion (63·5%) of negative diagnostic HD tests without sequencing strategies[4], with a final diagnosis being reached in just 3% of individuals.[3] In this sample, *C9orf72* expansions were the most frequently identified cause of phenocopies, found in ten (1·95%) out of 514 individuals[4], but this was not reproduced in other centers. The most likely explanation for the predominance of *C9orf72* mutations was that they are almost exclusively present in Caucasians.[5] Interestingly, in a series of Caucasian individuals with HD phenocopies from Sweden, there was no case of *C9orf72*, although the number of patients was smaller (73) than in the British cohort.[6] The identified causes were SCA17/TBP (2 patients) and inherited prion diseases/*PRNP* (1), *SGCE*-myoclonic-dystonia 11/*SGCE* (1), and benign hereditary chorea/NKX2-1 (1). This means that no definite genetic diagnosis was made in 93% of the subjects. A study performed in South Africa showed a strikingly distinct picture with 153/301 (50·8%) subjects with the HD phenotype carrying an expansion in *HTT*. Among whites, the proportion increased to 62% (106/171) and decreased to just 36% (47/130) among blacks.[7] In contrast, expansions in HDL2/*JPH3* were exclusively found in 20 of 83 (24%) of black South African descent. In a cohort studied in Paris[8], the investigators enrolled 226 patients with an HD phenotype, of whom 28 (12·4%) were phenocopies. In the first-row screening they identified three individuals with expansions in HDL2/*JPH3* and, interestingly, one with antiphospholipid syndrome and another one with B12 deficiency. The second tier of screening, a custom-made 63-gene panel, identified mutations in the following genes: *CACNA1A* in two individuals, and one each in chorea-acanthocytosis/*VPS13A,* and dementia genes: *VCP*, and *UBQLN2*. This means that 18 (64·3%) of the HD phenocopies of the French cohort remained undiagnosed.

Investigators from India reported a higher proportion of 159 individuals with an HD phenotype (65/41%) without expansions in *HTT*. There was also a small number of etiological diagnoses of phenocopies: SCA17/*TBP* in 5/65 (7·7%) and SCA12/*PPP2R2B* in 2/65 (3·1%).[9] Interestingly, this confirms that in ethnically distinct groups coding or noncoding expansions in ataxia genes

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are frequently involved in HD phenocopies. These findings reflect that SCA17/*TBP* expansions are more common in Asia, with SCA12/*PPP2R2B* expansions being particularly frequent in the Agarwal community of India.[10,11] In a Brazilian study, of 104 enrolled subjects with the HD phenotype, phenocopies were found in 10·6% of individuals. The majority, 54·6%, of phenocopies remained undiagnosed. The defined etiologies were HDL2/*JPH3* and SCA genes (respectively, 36·4% and 9% of phenocopies).[12]

HD phenocopies account for 15% (10·6%-63·5%) of individuals with an HD phenotype.[4,7–19,12] In a compilation of 177 reported cases since 2016, an etiological diagnosis was reached in 25 (14·1%) of subjects although the range varied greatly among different series. In Sweden, a diagnosis was made in 5/73 (6·8%) in contrast with 5/11 (45·4%) in Brazil[6,12], whereas in India and France the numbers were 10·7% and 28·5% respectively.[8,9] Several factors explain the discrepancies in established diagnoses among different series. The quality of the clinical and laboratory description is relevant. Although the features of HD can be quite variable, there are findings that, when present, cast doubt about its presence although do not rule out the diagnosis (Box 2). Of note, the lack of family history does not rule out HD. Ethnicity of the individual plays a major role in the etiology of HD phenocopies. In addition to the already mentioned importance of HDL2/*JPH3* in individuals with African ancestry, FTLD/*C9orf72* expansions in Caucasian subjects, SCA12/*PPP2R2B* in the Agarwal community in India, SCA17/TBP in Asia, dentatorubral-pallidolluysian atrophy (DRPLA/*ATN1*) is a condition that must be considered in individuals with Japanese or Portuguese background.[13,14]

Foremost of all factors impacting the diagnosis of HD phenocopies is how comprehensive is the work up for alternative causes. Box 3 highlights the most common causes of acquired chorea. As it is now apparent that acquired causes may result in HD phenocopies, the investigation of these individuals must rule them out. The growing number of recognized genetic causes of chorea in adults requires an ever more in-depth search using genome sequencing for underlying mutations combined with non-conventional methods aimed at identifying expansions.

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Acquired Causes of HD Phenocopies

Paraneoplastic Chorea

Most patients with paraneoplastic chorea experience a sudden onset of the movement disorder in association with other motor phenomena such as ocular motility disturbances, oromandibular dystonia, cerebellar ataxia, and spasticity. Non-motor findings are also common. Importantly, in many paraneoplastic syndromes the underlying neoplasm may only be detected many years after the onset of the movement disorder.[15] When there are significant behavioral problems, MRI imaging of the brain may show findings suggestive of limbic encephalitis such as temporal mesial FLAIR hyperintensity or atrophy of the anterior temporal lobe (Fig. 1). Small cell lung cancer, breast cancer, and thymoma are the most common neoplasms. The antibodies more commonly associated with this condition are anti-CV2/CRMP5, anti-HU, Ma-2, and anti-CASPR2.[16,17]. More recently, the association between paraneoplastic chorea with antibody against phosphodiesterase 10A (PDE10A) has been described. Brain MRI can show fluid-attenuated inversion recovery/T2 basal ganglia hyperintensities.[18]

Systemic Lupus Erythematosus (SLE)

SLE is a rare systemic autoimmune condition, more often seen in young females. In a consecutive series of patients with SLE, 98% of them were found to have neuropsychiatric lupus.[19] Consistent with other series[20], the most common finding was a dysexecutive syndrome whereas movement disorders (chorea, myoclonus, and parkinsonism) were observed in just 1·5% of individuals. Behavioral problems may also occur in SLE. In up to one third of affected cases, SLE-associated chorea has onset before the appearance of additional systemic findings. Recurrent thrombosis and/or pregnancy complications may be seen in individuals who do not meet criteria for SLE, but have positive antiphospholipid antibodies and are therefore classified as having primary antiphospholipid antibody syndrome.[21] In either case, the clinical picture of movement disorder, cognitive and behavioral disorder may resemble HD, but besides being negative for the *HTT*-expansion, other features that allow distinguishing them from HD include the subacute onset of symptoms, lack of ocular motility abnormalities; brain neuroimaging with normal size of the basal ganglia and presence of small vessel deep seated ischemic lesions; inflammatory cerebrospinal fluid (CSF); and positive serum antibodies (anticardiolipin, lupus anticoagulant, and/or anti-β2-glycoprotein 1).

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Anti-IgLON5 Disease

This condition was originally described in 2014 with eight patients presenting with a variable combination of sleep disturbances, bulbar dysfunction, cognitive decline, parkinsonism with severe gait disturbance, ophthalmoparesis and chorea.[22] The brain of individuals with this antibody-associated condition who came to post-mortem often, but not always, shows the presence of three- and four-repeat hyperphosphorylated tau.[23,24] A retrospective review of 72 patients showed that chorea was the most common (33%) movement disorder after gait disturbance (72%), but it usually occurs in combination with other movement disorders. Thirty-one (43%) have a combination of gait instability or ataxia associated with craniofacial dyskinesias or generalized chorea.[25] This and the presence of a prominent sleep disorder and bulbar dysfunctions as well as the lack of family history, and the normal size of the basal ganglia on MRI[25] allow one to differentiate it from HD, and positive IgLON-5 antibodies in the serum and CSF establish the diagnosis.

Other Autoimmune Conditions

Anti-NMDA receptor antibodies encephalitis is a condition produced by antibodies against the GluN1 subunit of this receptor. It is characterized by behavioral disorders, cognitive impairment, and dyskinesias. Although described only relatively recently[26], it is the first or second most common cause of sporadic encephalitis worldwide, particularly in children, with an estimated incidence of 1·5 per million population of year.[27,28] Recent data of a series of 70 patients shows that the incidence varies depending on the ethnicity of the individuals: the age-standardized and sex-standardized incidence of anti-NMDAR encephalitis per one million person-years was significantly higher in non-white (2·02-2·94) compared with white persons (0·40).[29] The clinical picture can resemble HD but there are marked clinical differences. It is usually a condition of individuals in the first three decades of life, no family history, sudden onset and a rather stereotyped sequence of events. It first starts with psychiatric abnormalities (in general, agitation and psychosis), followed by a combination of decreased level of awareness, dysautonomia, seizures, catatonia, and hyperkinesias. The latter, usually located in the cranial area, are variably described as oromandibular dystonia, stereotypies, or chorea.[30] This acute phase is followed by a prolonged recovery period with remission of those features and prominent dysexecutive function.[27] At least one third of individuals have an underlying neoplasm, particularly ovarian teratomas. Once more ethnicity matters, since 58% of Black female patients have this tumor.[29] MRI of the brain may show typical findings of limbic encephalitis, caudate atrophy is absent. Onset

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after age 40 years is uncommon but when it occurs, the clinical features tend to be different from the typical presentation. In a series of 577 patients, adult onset was more likely to have a predominantly cognitive and psychiatric presentation with psychosis and memory impairment.[31] A study of 111 patients with a psychiatric presentation showed that 9% of individuals lacked any associated neurological feature.[31] A review of 23 subjects with onset after age 65 years showed behavioral and cognitive changes in 95·7% of individuals and lack of movement disorders in 65·2%.[32] Overall, the clinical and imaging findings are readily distinguishable from HD and the presence of CSF antibodies confirms the diagnosis of anti-NMDA receptor encephalitis.

Anti-leucine-rich glioma inactivated 1 (LGI1) antibody encephalitis, an autoimmune disease that typically occurs in the elderly, is not commonly associated with an underlying neoplasm. The usual sequence of events is the occurrence of faciobrachial dystonic seizures followed by limbic encephalitis. The former is characterized by sudden contractions of the hemiface, flexion and elevation of the ipsilateral upper limb. Neuroimaging of the brain is either normal or shows non-specific white matter changes. Prompt recognition followed by immunotherapy results in remission of the disease.[33,34] However, there are reports showing that the clinical features can be broader than previously described. In a recent prospective assessment of 42 individuals, other clinical features previously not commonly recognized were sleep myoclonus (63%), insomnia (58%), REM-sleep behavior disorder (50%), and focal onset seizures (29%). Surprisingly, the classical faciobrachial dystonic seizures were present in just 38% of the individuals.[35] Patients may have a more protracted clinical course despite immunotherapy, increasing the potential for differential diagnosis with HD.[34,35]

Sydenham's chorea (SC), one of the major manifestations of rheumatic fever (RF), typically occurs in childhood (mean age of onset is 8 years), affecting more girls than boys. There is a global decline of the incidence of SC, even in areas where it used to be prevalent (Africa, India, Latin America and Turkey). Its clinical features include chorea, decreased muscle tone, behavioral changes and non-neurological findings, particularly carditis. The usual clinical course is characterized by sudden onset of behavioral changes, followed by chorea and remission.[1,36] In principle, this clinical picture does not lead to diagnostic difficulties with HD whose juvenile variant (Westphal) is characterized by a rigid-akinetic presentation lacking chorea.[37] Nevertheless, up to 20% of SC individuals who are followed up consecutively are left with persistent chorea into adulthood, dysexecutive syndrome, and abnormalities of ocular motility.[38] Additionally, recurrence or *de novo* chorea can occur later in life in patients with a history of RF, especially during pregnancy or use of oral contraceptives. The diagnosis of SC relies primarily on clinical grounds, although it is supported by the presence of valvular lesions on echocardiogram.[36]

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Table 1 summarizes the clinical findings of the most common acquired causes of HD phenocopies.

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Genetic Causes of HD Phenocopies

Autosomal Dominant Diseases

FTLD/*C9orf72* GGGGCC Expansion

The hexanucleotide (GGGGCC) expansion was first reported in 2011. It is the most common genetic cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS)[39,40] although rarely seen in non-Caucasian individuals.[5] Since the original description it has become clear that it is associated with a myriad of movement disorders. A study of 40 patients showed that 17 had a movement disorder, of whom 2 had no additional feature.[41] The median age of onset was 58 years and the most common phenomenon was tremor resembling essential tremor or parkinsonism, followed by myoclonus and cervical dystonia. Executive dysfunction was identified in 10 of 14 individuals. Motor neuron disease was present in 5 of the 17 patients with movement disorders. There was no family history of FTD and/or ALS in 35% of patients. No individual had basal ganglia atrophy. The adult-onset, autosomal dominant combination of hyperkinetic and/or hypokinetic movement disorders and frontal lobe-type cognitive decline makes *C9orf72* expansion a credible differential diagnosis for HD in Caucasian patients. Normal basal ganglia on neuroimaging and the eventual presence of motor neuron disease are red flags for the diagnosis of HD.

HDL2/*JPH3*

This disease, caused by an expanded CTG repeat of 40 or more in the *JPH3* gene[42], has been exclusively reported in individuals with African ancestry. The movement disorder, cognitive, behavioral and radiological features of HDL2 are truly indistinguishable from HD.[43,44] In the past, there were reports of the presence of acanthocytes in HDL2/*JPH3*, but more recent studies have not supported this claim.[45] A blind comparison of motor, behavioral and cognitive features of 13 HD individuals and 15 HDL2 subjects failed to identify demographic and clinical differences except for slightly earlier onset of significant dysarthria and dystonia in HDL2. Experienced investigators were not able to distinguish between the two diseases.[46] It must be highlighted that in many communities the significant degree of ethnic admixture makes skin colour an unreliable marker of ethnicity.[47] The practical consequence is the need to rule out HDL2/*JPH3* as cause of HD phenocopy in areas with present or past significant African presence.

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DRPLA/*ATN1*

Dentatorubral-pallidoluysian atrophy (DRPLA) is a condition caused by 49 or more CAG repeats in the *ATN1* gene.[48] It has a prevalence of 18·5/100.000 in Japan.[49] There are reports of rare patients with DRPLA outside Japan, but these are usually in individuals with a Japanese background. In Portugal, DRPLA is the second most common cause of autosomal dominant ataxia, accounting for 11·2% of families.[50] There are also reports of families with DRPLA in Brazil, a country that received a significant number of Japanese individuals.[51] The clinical features of DRPLA depend on the size of the expansion and age of onset.[52] The juvenile onset form is usually characterized by the phenotype of progressive myoclonic epilepsy. In contrast, patients with age of onset after 40 (late-onset) often present with chorea, cognitive decline, and cerebellar ataxia. If the disease onset occurs between 20 and 40, the clinical symptoms manifest as intermediate between juvenile- and late-onset.[53] In both cases, the phenotype can overlap with HD. Pure ataxia, a differential diagnosis of other SCAs, is more common in smaller (49-55) repeats.[52] On neuroimaging, patients have cerebellum and brainstem atrophy.

SCA17/*TBP*

SCA17/*TBP*, also known as HDL4 is a condition caused by a polyglutamine-encoding CAG/CAA repeat expansion within the TATA box-binding protein (*TBP*) gene.[54] A recent review of 346 patients led to the proposal of new cutoff values: 41-45 expanded repeats result in reduced penetrance, whereas full penetrance is found with repeats above 46.[55] Interestingly, *TBP* intermediate alleles alone are not responsible for disease expression unless associated with other genes, the most common being variants in *STUB1*, the gene associated with SCA48.[56] SCA17/*TBP* is more commonly seen in Asia and Germany. Pure parkinsonism is more frequently found in individuals with reduced penetrance who rarely display chorea. Ataxia variably combined with chorea, dystonia, myoclonus, slow saccadic eye movements, behavioral changes and cognitive decline is more commonly seen in subjects with more than 46 repeats.[55] MRI of the brain in SCA17 more commonly shows cerebellar and global cerebral atrophy.[57] Notably, focal basal ganglia atrophy has not been reported in ATX-*TBP*. The possible diagnosis of SCA17 as a cause of the HD phenotype should be entertained in individuals with chorea combined with ataxia, normal basal ganglia volume, and cerebellar atrophy on MRI of the brain.

SCA12/*PPP2R2B*

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SCA12 was originally described in a German family with age of onset ranging from 8 to 55 years, initially presenting with upper limb tremor, ataxia, slow saccades and, in some patients, dementia. It is related to a non-coding CAG expansion above 69 in the *PPP2R2B* gene.[9,58] This disease is particularly common among the Agarwal community in India, where it accounts for 57·3% of all SCA cases.[59] Less common clinical presentations include tongue protrusion and feeding dystonia[60], a progressive supranuclear palsy-like phenotype[61], myoclonus[62], and as an HD phenocopy.[7,62] Neuropsychological assessment of 30 individuals showed that all had executive dysfunction.[63] The most common findings on MRI of the brain were cerebellar or cerebral atrophy. Interestingly, normal MRI was found in 3/49 individuals.[62] The diagnosis of SCA12/*PPP2R2B* as a cause of HD phenocopy must be considered in individuals of Indian background who present with chorea associated with prominent tremor and neuroimaging with cerebellar atrophy.

Rarer Causes

The *CACNA1A* gene encodes a subunit of the voltage-gated $Ca_V2.1$ (P/Q-type) Ca^{2+} channel.[64] It was first described in association with episodic ataxia type 2 and familial hemiplegic migraine.[65] SCA6 is caused by an CAG expansion of 22 or more repeats in *CACNA1A*.[64] A study of 47 individuals with pathogenic or likely pathogenic variants of *CACNA1A* shows a heterogenous phenotype: developmental delay (96%), behavioral (especially autism) and psychiatric disorders (86%), ataxia (75%), ocular motility problems (56%), epilepsy (55%), hemiplegic migraine (36%), and episodic ataxia type 2 (32%).[64,66] There are also reports of mutations of this gene associated with focal or generalized dystonia.[67,68] In the French cohort of HD phenocopies, the authors found two cases associated with *CACNA1A* mutations.[8] Cerebellar atrophy is the characteristic neuroimaging abnormality of these individuals.[69]

Mutations in the valosin-containing protein (*VCP*) gene result in a multisystem proteinopathy with heterogeneous clinical features. A retrospective, multicenter international study of 255 patients found the following syndromes associated with *VCP* gene mutations: myopathy (50%), Paget's disease of bone (28·2%), dysautonomia (21·4%), and fronto-temporal dementia (14·3%).[70] There is one published case of HD phenocopy related to a *VCP* gene mutation.[6]

Huntington's Disease Like Type 1 (HDL1) is a rare prion disease caused by extra repeats of the octapeptide region (Pro-His-Gly-Gly-Gly-Trp-Gly-Gln) in the prion protein (PrP) gene (*PRNP*). Although first identified in 2001, it has been diagnosed in just four families.[71,72] The clinical picture is very heterogeneous, occasionally resembling HD when it presents with dementia, psychiatric symptoms, chorea and rigid-akinetic syndrome.

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Neuroferritinopathy is a rare adult-onset autosomal dominant disease caused by mutations in the ferritin light chain gene (*FTL*). First described in northern England, it has since been recognized in France, Italy, Japan, South Korea and China.[73] Around their fourth decade patients develop a combination of chorea, dystonia, dysarthria, parkinsonism, gait issues, and cognitive decline.[74] Patients characteristically have widespread brain iron accumulation. Serum ferritin levels are usually low. Importantly, iron chelation has been shown to partially reverse iron deposition and improve or stabilize the manifestations of the disease.[75,76]

Autosomal Recessive Diseases

Chorea-Acanthocytosis (VPS13A Disease)/*VPS13A*

The term neuroacanthocytosis (Levine-Critchley syndrome) was used in the past to describe a group of disorders characterized by movement disorders combined with acanthocytosis. Chorea-acanthocytosis, McLeod Syndrome, HDL2/*JPH3* and pantothenate kinase associated neurodegeneration (PKAN). The latter two were excluded from the neuroacanthocytosis umbrella because acanthocytes are not part of the clinical picture and their underlying mechanism is completely distinct from chorea-acanthocytosis[77] As McLeod Syndrome is an X-linked condition, it will be described later in this article.

Chorea-acanthocytosis is a rare disorder, present in all continents, with an estimated prevalence of 1/1.000.000.[77-79] The onset of the condition is usually in the third decade of life. Most patients initially develop a mild degree of chorea, although other movement disorders occur, such as self-mutilating oromandibular dystonia with biting of the lips and/or tongue as well as lingual dystonic protrusion triggered by feeding. Prominent psychiatric disturbances, particularly severe obsessive-compulsive disorder and impulsivity, also often occur. Many patients display a whiplash-like cervical dyskinesia that in severe cases also involves the trunk. Initially thought to be specific to chorea-acanthocytosis[80], it also occurs in HD.[81] Later in the course of the disease, patients can become parkinsonian. Neuroimaging shows atrophy of the head of the caudate and other areas of the basal ganglia. The clinical differential diagnosis with HD is helped by the relative preservation of cognition and eye movements as well as the presence of temporal lobe epilepsy, peripheral neuropathy and cardiopathy. Elevated serum CPK levels and more than 10% of acanthocytes on blood smear also support the diagnosis of chorea-acanthocytosis. Importantly, it is often necessary to perform osmotic shock to induce their presence.[82] Chorea-acanthocytosis is caused by mutations in the gene *VPS13A*.[83] There is a growing use of the nomenclature '*VPS13A* disease' to replace the more clinically-oriented chorea-acanthocytosis.[77]

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Friedreich Ataxia

The classical form of Friedreich Ataxia (FA), a condition caused by homozygous intronic expansions of GAA repeats of the frataxin gene, has a clinical picture that it is readily distinguishable from HD: onset in the first two decades of life, progressive course of limb and axial ataxia, nystagmus, dysarthria, loss of deep tendon reflexes, Babinski sign, normal cognition, no hyperkinetic phenomena and non-neurological features such as scoliosis, myocardial hypertrophy, and diabetes mellitus. Neuroimaging shows atrophy of the cervical spinal cord and normal cerebellum.[84-86] There is no difference between late onset (between 25 and 40 years) and very late onset (after 40 years) FA patients. In contrast, in comparison with 180 typical FA subjects, patients with later onset frequently presented with spastic paraparesis.[87] The lack of chorea and other hyperkinetic phenomena in large cohorts of individuals with FA raises the question if it can truly be a diagnostic consideration in HD phenocopies. One possibility is that severe dysmetria may eventually be misinterpreted as chorea.

Huntington Disease Like Type 3 (HDL3)

This condition, described in just one Saudi Arabian family in 2000, is related to chromosome 4p15.3 although the gene has not been described.[88] In the first decade of life patients develop cognitive decline, corticospinal tract dysfunction and hyperkinetic movement disorders (chorea and dystonia). Brain imaging shows global atrophy.[89] Despite the name HDL3, the clinical features are so dissimilar from HD, that it might not be a truly HD phenocopy.

Aceruloplasminemia

Aceruloplasminemia is a rare disease caused by biallelic mutations in the *CP* gene which encodes ceruloplasmin. There are over 100 cases described in the literature, mostly from Japan.[90] Loss of function of ceruloplasmin leads to brain and systemic iron accumulation and explain the classical triad of the disease, namely a combination of neurological symptoms (including chorea and facial dyskinesias, dystonia, parkinsonism, cognitive decline and neuropsychiatric symptoms), diabetes mellitus, and asymptomatic retinal degeneration.[91] Onset is after 50 years of age. Ceruloplasmin is very low (<2µg/dL) or undetected. There is a characteristic microcytic anemia with low serum iron in combination with elevated ferritin. MRI shows widespread brain iron accumulation involving

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the basal ganglia and cortex. Iron deposition can also be detected in the liver with MRI or biopsy. Iron chelation has been reported to improve neurologic symptoms, anemia and diabetes.[92,93]

X-Linked Diseases

McLeod Syndrome/*XK*

McLeod Syndrome is caused by mutations of the *XK* gene that result in absent or dysfunctional *XK* erythrocyte antigen. As *XK* is linked to the Kell protein in the erythrocyte membrane, the Kell antigen is significantly reduced.[94] This decrease is a useful diagnostic marker. McLeod syndrome and chorea-acanthocytosis share clinical and radiological features as well as the presence of circulating blood acanthocytes, although a later age at onset, more severe cardiopathy, splenomegaly, and myopathy suggest the former.[77,95] The remarkable clinical similarity between McLeod Syndrome and chorea-acanthocytosis is probably related to the close topographic relationship between the *VPS13A* and *XK* proteins.[77,94]

ALS/*UBQLN2*

Dominant X-linked mutations of the *UBQLN2* gene are part of the genetic causes of ALS and ALS/Frontotemporal Dementia.[96] There is one report describing a HD phenocopy caused by mutation in this gene.[8]

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Practical Approach to HD Phenocopies

The first step of how to approach HD phenocopies involves a careful and detailed description of the clinical picture as well as family history. Although often neglected in discussions of HD phenocopies, there is enough data to support the notion that autoimmune and other acquired conditions, many of them amenable to effective treatment, can mimic HD (Figure 2).[8] The second step is therefore to rule out acquired causes of chorea. Table 1 summarizes clinical findings suggestive of the main acquired causes of HD phenocopies, whereas Box 4 contains the recommended workup for these conditions.

Once an acquired cause is ruled out, the next step is to investigate potential underlying genetic causes. There is a growing tendency to use broader approaches since there are bioinformatic tools for the detection of coding expansions in short-read genome sequencing and even in exome sequencing. For non-coding expansions long-read genomes are indicated. There are, however, novel tools applied to short-read genome data that can detect repeat expansions either in a targeted manner or at the genome-wide level.[97]

The clinician should choose tests based on a combination of clinical and laboratory features, ethnicity and geography as shown in Figures 3 and 4. It is worth mentioning that the available information on the relationship between ethnicity and etiology is most likely incomplete due to the limited number of studies performed in non-Caucasian populations. Although there are no data on chorea to illuminate this issue, it is possible to speculate based on the information available for other phenomena. In dystonia, the broader the testing, the greater the diagnostic yield: a strategy based on target gene identifies possibly pathogenic variants in fewer than 20% of cases in early-onset and familial form of dystonia. In contrast, broader approaches increase this figure to 34%.[98] One related and relevant question is the cost-benefit of these different methodologies. It is necessary to be cautious while applying information from other fields of medicine, but it is well demonstrated that broader approaches are more cost effective in oncology.[99,100] Finally, clinicians need to be aware that, despite the comprehensive contemporary approach to the investigation of underlying causes of HD phenocopies, most patients will remain without an etiological diagnosis. In a review of 1559 published cases of HD phenocopies until 2016, etiology was determined in just 2·1%[89]. Numbers have improved since then: an etiological diagnosis was reached in 25 (14·1%) of 177 cases reported subsequently, although the range varied greatly among different series (6·8% to 45·4%).[6,8,9,12] This significant variation is mostly accounted for by the differences in size of the cohorts and the methodology used to identify the underlying causes. Despite these issues, there are relevant reasons to try to identify the etiology of HD phenocopies:

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some individuals have treatable acquired conditions; and the information allows genetic counselling to be carried out.

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Conclusions

HD phenocopies, also known as HDL diseases, account for 15·6% (10·6%-63·5%) of individuals with the HD phenotype.[4,7–9,12] The search for an underlying etiology must be informed by clinical features, ethnicity and geography, and broad non-targeted genetic approaches, using exome/genome sequencing when autoimmune causes are ruled out. It is expected that more comprehensive work-up, as well as the use of new genetic bioinformatic tools will increase the number of individuals with defined diagnoses.

Authors Contribution

FC developed the concept of this review, did the literate search and drafted the manuscript. DM and RM prepared the figures. All authors were involved in subsequent editing of the manuscript and are in agreement with its final content.

Conflicts of interests

FC: received honoraria from Torrent. Past-President of the International Parkinson and Movement Disorders Society.

DM: received honoraria from Abbvie, Boston Scientific and Teva Pharmaceuticals

RM: received honoraria from Boston Scientific.

JC: no conflicts to declare

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WP: unpaid leadership in the Austrian PD Society, Austrian Society for Neurology.

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