The non-Huntington disease choreas

Five new things

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Abstract

Purpose of review: Chorea can be due to a wide variety of causes. In this review, I provide updates on several recently identified genetic and autoimmune causes of chorea, and review evidence supporting the use of deep brain stimulation in chorea. **Recent findings:** New genes that may cause chorea include *ADCY5* (encoding for adenylate cyclase 5) *C9ORF72* (in addition to amyotrophic lateral sclerosis and frontotemporal dementia), and those responsible for the neurodegeneration with brain iron accumulation disorders. Novel autoantibodies are increasingly being identified as associated with a variety of neurologic syndromes, including chorea, in both paraneoplastic and non-paraneoplastic settings. Deep brain stimulation can be a useful intervention in patients with chorea who do not respond to oral medications, whether due to neurodegenerative or nondegenerative causes. **Summary:** New causes of chorea continue to be identified. Correct diagnosis is essential for prognostication and treatment. *Neurol Clin Pract* 2016;6:150-156

Chorea can have many etiologies, including structural, genetic, metabolic, pharmacologic, and autoimmune causes¹ (figure). While Huntington disease (HD) is the prototypic autosomal dominantly inherited chorea, it has been apparent since the identification of a locus for huntingtin that a similar presentation can be due to mutations of other genes. While patients with these disorders comprise a relatively small number of cases with chorea, molecular diagnosis is essential for genetic counseling and prediction of disease course. Despite recent advances, a large percentage, 90% in some studies, of patients with HD phenocopies remain undiagnosed. It should be noted that the diagnosis of senile chorea is obsolete.

Mutations in the gene encoding for adenylate cyclase 5 (*ADCY5*) have recently been identified as the cause of a non-neurodegenerative autosomal dominant movement disorder. Patients can be cognitively impaired, but this does not progress. The phenotype can be variable, and may include families labeled with benign hereditary chorea.

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Figure An algorithm for the approach to chorea

(A) The initial approach by age. (B) The approach to the child with chorea in whom Sydenham chorea has been excluded. (C) The approach to the adult with chorea in whom Huntington disease (HD) has been excluded. CJD = Creutzfeldt-Jakob disease; CPK = creatine phosphokinase; DRPLA = dentatorubral-pallidoluysian atrophy; LFT = liver function test; NBIA = neurodegeneration with brain iron accumulation; PKAN = pantothenate kinase-associated neurodegeneration; PLAN = phospholipase-associated neurodegeneration; SCA = spinocerebellar ataxia. Adapted from Hermann A, Walker RH. Diagnosis and treatment of chorea syndromes. *Curr Neurol Neurosci Rep* 2015;15:514. Springer ©2015, with permission.

Mutations of *C9ORF72* cause an autosomal dominantly inherited progressive neurodegeneration that can present with a variable phenotype, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), and occasionally chorea.

Chorea is a typical part of the presentation of the adult-onset neurodegeneration with brain iron accumulation (NBIA) disorders aceruloplasminemia and neuroferritinopathy. These are easily screened for, and may respond to iron chelation therapy.

A number of novel autoantibodies have recently been reported to be associated with chorea both associated with neoplasms and in non-paraneoplastic conditions. These often respond to immunomodulatory interventions.

Surgical interventions for movement disorders (in addition to other neurologic and psychiatric diseases) have been expanding as the technology has improved. Reports of individual cases and small case series of patients who underwent deep brain stimulation (DBS) indicate that this therapy may be useful when oral medications have failed.

ADCY5-related dyskinesia

It has long been recognized that the clinical entity best known as benign hereditary chorea is genetically heterogeneous and can be caused by mutations in genes other than *TITF1/NKX2.1*. In 2001, a family (initially described as having familial essential [benign] chorea) was reported with an autosomal dominantly inherited condition termed dyskinesia with facial myokymia. The causative mutation was subsequently found in *ADCY5* in this family.² Subsequently, several other affected families and sporadic cases with various mutations of the same gene, and some variation in the phenotype, have been identified recently.^{3–5} Inheritance is autosomal dominant, but new cases can appear due to de novo mutations³ or mosaicism.⁵

This syndrome is characterized as chorea of childhood onset, often with episodic worsening, particularly at night. Dystonia is typically present and can be the predominant movement disorder. Myoclonus can also be seen. In some patients, the frequency of the episodes increases with age, although in others there is an improvement. Hypotonia is often seen at baseline, but can episodically worsen to the extent that patients are unable to walk. Despite the hypotonia, hyperreflexia is typical.^{3,4} Cognitive function can be mild to moderately impaired or normal, but does not appear to deteriorate with time. The abnormal involuntary movements may worsen over the initial few years, but then are typically stable. Of the various medications reported to have been tried, the most consistent positive response appears to be to benzodiazepines.

The facial movements in the initial family were initially believed to be myokymia; however, this was not supported by EMG, and the movements appear to be either dystonic or choreic in nature, but with predominantly lower facial involvement, unlike in HD. In some families they are not very prominent.³

ADCY5 is found in high levels in the striatum and also in cardiac muscle. Interestingly, the original family had a high incidence of cardiomyopathy and congestive heart failure.³

C9ORF72 mutations as a cause of an HD-like phenotype

Mutations of the open reading frame 72 on chromosome 9 have been identified recently as the commonest cause of both autosomal dominantly inherited and sporadic ALS and FTD. In addition to these clinical presentations, an HD-like phenotype has been reported in a small percentage of patients. In some populations, especially those of European ancestry,^{6–8} this appears to be the commonest identified cause of non-HD chorea. It should be noted that the numbers in these studies are small, thus these data require further validation. (In populations of African ancestry, including in the United States, Brazil, and other South American countries, and black South Africans, HD-like 2 is likely responsible for this phenotype after exclusion of HD.) The phenotype, whether FTD, ALS, or HD-like, can vary within a family, for reasons that are not yet clear.

The mutation is an expansion of the hexanucleotide repeat GGGGCC. In unaffected people, there are typically 2–20 repeats, although the upper limit of the nonpathogenic range

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remains to be clearly defined. Expansions of between 20 and a few hundred repeats may be termed intermediate, while hundreds to thousands of repeats are found in those affected. There is no clear correlation of size with phenotype, and there is no evidence of anticipation with inheritance.

These patients appear to be characterized by prominent frontal lobe signs in combination with movement disorders. Age at onset may be in childhood, or more commonly in midlife.⁶ While the patients screened in these studies were classified as being HD-like, i.e., there were sufficient clinical features to merit testing for HD, positive family history was not always present. The movement disorders reported included parkinsonism, tremor, dystonia, myoclonus, and ataxia, in addition to chorea, and can be present in various combinations. Chorea may be marked in the lower face⁸ or more severe in the limbs, as is typical of HD.⁷ Temporal lobe atrophy on neuroimaging may be a useful diagnostic clue.⁸ Upper motor neuron signs are helpful findings, although not invariable.

Neuropathologically, brains of patients with *C9ORF72* mutations are characterized by widely distributed neuronal cytoplasmic inclusions containing TDP-43, similar to FTD or ALS of other etiologies. It is not yet known if the basal ganglia are specifically more affected in those with a movement disorder presentation.

Chorea in NBIA disorders

Patients with NBIA disorders are typically identified after MRI scanning revealing iron deposition in the basal ganglia, sometimes in addition to other sites, such as the cerebellum. The list of genetic causes of NBIA continues to grow. Most of these disorders are autosomal recessive childhood-onset disorders characterized by parkinsonism and dystonia, specifically pantothenate kinase–associated neurodegeneration and membrane protein–associated neurodegeneration. Beta-propeller-associated neurodegeneration is, unusually, an X-linked dominant disorder.

Phospholipase-associated neurodegeneration was initially identified as a childhood-onset disorder with dystonia-parkinsonism, and is now known to be allelic with infantile neuroaxonal dystrophy. The phenotype of disorders due to mutations of the causative gene (*PLA2G6*) is expanding, and adult-onset forms are recognized. Iron deposition in the basal ganglia is not an invariable finding. Childhood-onset chorea had been reported in a single family, but this observation has not yet been repeated.

In contrast to the pediatric NBIA cases, it is more typical of the adult-onset NBIA disorders to present with chorea. These disorders can be readily detected by abnormal serum ceruloplasmin and ferritin levels, in addition to iron deposition in the brain on MRI.

Aceruloplasminemia is an autosomal recessive disorder, due to mutations of the gene for ceruloplasmin, and is characterized by absent serum ceruloplasmin and elevated ferritin levels. Ceruloplasmin is a ferroxidase, thus deficiency results in the deposition of ferrous iron, which is not able to be transported by transferrin. Symptoms develop in adulthood, likely due to the gradual accumulation of iron in the brain, with cognitive impairment, psychiatric symptoms, behavioral problems, ataxia, dystonia, and chorea.⁹ Hyperkinetic movements of the lower face are typical. Iron accumulates in the cerebellum and basal ganglia, in addition to the pancreas, which results in diabetes. Iron chelation with desferrioxamine, along with fresh frozen plasma, is suggested to remove iron from brain and liver, and may improve symptoms. Due to the rarity of this disorder, it is unlikely that placebo-controlled, double-blind studies of this intervention will ever be performed. However, an intriguing recent publication described 2

siblings with this condition, one of whom was providentially treated with deferoxamine for another disease, and subsequently deferiprone, with a remarkably benign disease course.¹⁰ The untreated sibling progressed and died of the disease.

The only autosomal dominant NBIA disorder is neuroferritinopathy, due to mutation of the gene for ferritin light chain located on 9q13.3. A variety of movement disorders can be seen including chorea, dystonia, and parkinsonism.^{11,12} Some cases may present initially with dystonia.¹² Cognitive impairment is not typical, but can occasionally be a feature. The diagnosis is suggested by the presence of iron in the basal ganglia and reduced serum ferritin. Specific radiologic features may be informative,¹³ including a low-intensity cortical ribbon, described as “pencil lining.”^{12,13} As the disease progresses, iron deposition is seen in structures outside the basal ganglia, including the red nucleus and the dentate nucleus.¹² There is no evidence as yet that chelation therapies are helpful in neuroferritinopathy.

The expanding list of autoantibodies as a cause of chorea: Both neoplastic and non-neoplastic

Autoimmune causes of chorea have been recognized since the identification of anti-basal ganglia antibodies in Sydenham disease. While the precise substrate remains to be identified, immunomodulatory therapies, including corticosteroids, plasmapheresis, and IV immunoglobulin, can be useful in patients with severe or nonremitting symptoms.

New autoantibodies continue to be recognized, in both paraneoplastic and non-paraneoplastic syndromes, although their pathogenic role is not always clear, and their presence may be an epiphenomenon related to another, as yet unknown, etiologic process. The best evidence supporting a causative role of these antibodies is when clinical symptoms follow the levels of serum titers, and respond to immunomodulatory interventions. It is obviously critical to identify and treat a causative neoplasm, if a paraneoplastic syndrome is identified, while the administration of aggressive and sustained immunotherapy can markedly improve outcomes in nonparaneoplastic syndromes.

An autoimmune etiology should be suspected in patients with an otherwise unexplained neurologic syndrome presenting subacutely over days to weeks. The presentation of the autoimmune syndromes may be quite variable, and may include various neurologic symptoms in addition to chorea, including cerebellar signs, encephalitis, seizures, sleep disorders, and stiff-person syndrome.

Antibodies against leucine-rich glioma-inactivated 1 (LGI1), NMDA, IgLON5, contactin-associated protein 2 (CASPR), GAD65, and CRMP-5/CV2 have been associated with chorea in the absence of detectable tumor. Antibodies against Hu, Yo, LGI1, NMDA, IgLON5, CASPR, GAD65, and CRMP-5/CV2 and striational muscle have been reported in the presence of tumor. In general, these antibodies are present in both serum and CSF.

It is unclear why the presentations of these autoimmune syndromes can be so variable. For example, antibodies against LGI1 and CASPR are part of the group of autoantibodies against the Kv1 voltage-gated potassium channel complex of proteins. Anti-LGI1 antibodies are also associated with limbic encephalitis with tonic seizures, in addition to very characteristic faciobrachial dystonia seizures. Ion channel dysfunction is a reasonable explanation for these syndromes; however, it is not so clear why this mechanism should underlie chorea. Even more intriguing is why, in some cases, chorea should be asymmetric. Unilateral or asymmetric chorea has been reported in chorea of other autoimmune and metabolic etiologies (such as in nonketotic diabetic hyperglycemia). It is possible that this is related to a congenital asymmetry of brain structures such as the substantia nigra pars compacta and its dopaminergic innervation of the caudate-putamen.

IgLON5 autoantibodies recently have been reported in a disorder characterized by both REM and non-REM parasomnias, in which there is sleep-disordered breathing and, in some cases, chorea.^{14–16} A neoplastic etiology was not identified; however, in some cases, patients deteriorated rapidly and died of the disorder. The role of these antibodies in this disorder remains controversial, especially as several of the patients did not respond to immunotherapy.

Also, of note, IgLON5 belongs to an antibody family (immunoglobulin G4) generally thought to be anti-inflammatory,¹⁵ and additionally, neuropathologic examination in 2 cases demonstrated widespread tau pathology.¹⁴

As paraneoplastic syndromes are often associated with occult malignancies, full-body imaging with CT and PET should be performed. Treatment is directed at removal of the tumor.

In the absence of detectable tumor, aggressive immunomodulatory therapies should be considered on an empiric basis, including IV immunoglobulin, corticosteroids, and plasmapheresis. In some cases, prolonged treatment may be necessary, and patients should be monitored for relapses. The underlying etiology of these conditions is not yet clear but they may be triggered by infection.

Another rare but potentially reversible cause of chorea that should not be forgotten is celiac disease.¹⁷

DBS of the globus pallidus pars interna as treatment for chorea

In the past few decades, DBS has become the standard of care for patients with Parkinson disease (PD) whose symptoms are no longer satisfactorily controlled by medications and for patients with primary and some secondary dystonias. The predominant target, both in HD and other choreas, is the globus pallidus pars interna (GPi)¹⁸—the nucleus that has been the main site used for treatment of L-dopa-induced dyskinesia in PD. In HD, DBS was investigated in a small open-label, prospective trial. A significant benefit to chorea was reported, although this was limited by disease progression.¹⁹ As the therapeutic principles for the treatment of chorea are often extrapolated from HD to other disorders, DBS is increasingly being considered in patients with medication-resistant chorea of other etiologies.

A small case series collected and summarized all the available information on 15 patients with chorea-acanthocytosis from different centers who underwent GPi DBS.²⁰ In addition to a reduction in chorea, positive effects were also seen on self-mutilation and tongue-biting, symptoms that are typically very challenging to treat. In 2 cases, additional stimulation of the thalamic Vo region was required.

It is important to perform blinded evaluations of the efficacy of DBS in patients with progressive neurodegenerative disease, which in some cases may progress to a more hypokinetic form. Periodic clinical evaluations should be performed with the stimulators turned off and the patients and evaluators blinded as to the status.

Patients with static chorea are likely to be better candidates for DBS than those with progressive disease.¹⁸ Beneficial results have been reported with persistent chorea due to thalamic hemorrhage, cerebral palsy, and nonketotic diabetic hyperglycemia. In addition to DBS, pallidotomy has also been used in patients with chorea following nonketotic diabetic hyperglycemia.

In the progressive choreas, further study is evidently needed, focusing upon long-term quality of life and cognitive issues; however, DBS may be a reasonable option when severe involuntary movements are debilitating. Although the tendency of chorea due to structural/metabolic lesions, such as stroke or nonketotic diabetic hyperglycemia, is to improve with time, DBS is an appropriate intervention in nonresolving situations that are resistant to oral pharmacotherapy.

The non-HD choreas: Five new things

- The identification of mutations of the gene encoding for adenylate cyclase 5 as a cause of a nondegenerative, but potentially disabling, hyperkinetic disorder. The phenotype can include paroxysmal chorea, dystonia, myoclonus, and hypotonia.
- Hexanucleotide repeat expansions of C9ORF72 cause an autosomal dominant disease with a variable presentation that can include chorea, in addition to ALS and FTD.
- There is an increasing spectrum of neurologic phenotypes being reported in the NBIA disorders. In adults with movement disorders, serum ceruloplasmin and ferritin should always be performed.
- There is an expanding list of autoantibodies as a cause for chorea, in both neoplastic and non-neoplastic situations. If tumor is not found, patients may respond to immunomodulatory therapies.
- DBS of the GPi can be a useful treatment for chorea, especially for patients with non-neurodegenerative etiologies.

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