REVIEW

Chorea and related disorders

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Chorea refers to irregular, flowing, non-stereotyped, random, involuntary movements that often possess a writhing quality referred to as choreoathetosis. When mild, chorea can be difficult to differentiate from restlessness. When chorea is proximal and of large amplitude, it is called ballism. Chorea is usually worsened by anxiety and stress and subsides during sleep. Most patients attempt to disguise chorea by incorporating it into a purposeful activity. Whereas ballism is most often encountered as hemiballism due to contralateral structural lesions of the subthalamic nucleus and/or its afferent or efferent projections, chorea may be the expression of a wide range of disorders, including metabolic, infectious, inflammatory, vascular, and neurodegenerative, as well as drug induced syndromes. In clinical practice, Sydenham's chorea is the most common form of childhood chorea, whereas Huntington's disease and drug induced chorea account for the majority of adult onset cases. The aim of this review is to provide an up to date discussion of this disorder, as well as a practical approach to its management.

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Chorea is a manifestation of a number of diseases, both acquired and inherited. Although not completely understood, current evidence suggests that chorea results from the imbalance in the direct and indirect pathways in the basal ganglia circuitry. The disruption of the indirect pathway causes a loss of inhibition on the pallidum, allowing hyperkinetic movements to occur. In addition, enhanced activity of dopaminergic receptors and excessive dopaminergic activity are proposed mechanisms for the development of chorea at the level of the striatum. Based on current knowledge, it is possible to understand chorea and ballism as manifestations of a common pathophysiological chain of events so that classification of choreic syndromes are increasingly based on aetiology, while phenomenologically based distinctions between chorea and ballism are becoming less important. Chorea is characterised as primary when idiopathic or genetic in origin or secondary when related to infectious, immunological, or other medical causes (table 1). When chorea is proximal and of large amplitude, it is termed ballism. Athetosis refers to irregular, forceful, slow, writhing movements generally of the extremities, commonly with finger movements. These movements frequently overlap and coexist in the same patient. Huntington's disease is a choreic prototypic disorder of inherited origin. Other inherited causes are also discussed in more detail later in this review. In secondary chorea, tardive syndromes are the most common causes, related to long term use of dopamine blocking agents. Choreiform movements can also result from structural brain lesions, mainly in the striatum, although most cases of secondary chorea do not demonstrate any specific structural lesions.

HEREDITARY CAUSES OF CHOREA

Huntington's disease

Huntington's disease, the most common cause of chorea, is an autosomal dominant disorder caused by an expansion of an unstable trinucleotide repeat near the telomere of chromosome 4.[1 2] Each offspring of an affected family member has a 50% chance of having inherited the fully penetrant mutation. According to the first description of the disease by George Huntington in 1872, there are three marked peculiarities in this disease: (1) its hereditary nature; (2) a tendency for insanity and suicide; (3) manifestation as a grave disease only in adult life.[3] However, Huntington failed to mention cognitive decline, which is now recognised as a cardinal feature of the disease.[4]

Epidemiology

Huntington's disease has a worldwide prevalence of 4–8 per 100 000 with no gender preponderance.[5] Huntington's disease has the highest prevalence rate in the region of Lake Maracaibo in Venezuela, with approximately 2% of the population affected, and the Moray Firth region of Scotland.[5] Huntington's disease is notably rare in Finland, Norway, and Japan but data for Eastern Asia and Africa are inadequate. It is believed that the mutation for Huntington's disease arose independently in multiple locations and does not represent a founder effect. New mutations are extraordinarily rare, accounting for a very small population of cases.

Genetics

Although the familial nature of Huntington's disease was recognised more than a century ago, the gene mutation and altered protein (huntingtin) was described only recently.[6] Huntington's disease is a member of the growing family of neurodegenerative disorders associated with trinucleotide repeat expansion. The cytosine-adenosine-guanidine (CAG) triplet expansion in exon 1 encodes an enlarged polyglutamine tract in the huntingtin protein. In unaffected

Abbreviations: DRPLA, dentatorubralpallodoluysian atrophy; KF rings, Kayser-Fleischer rings; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; SSRIs, selective serotonin reuptake inhibitors

Table 1 Classification of chorea (only common causes listed)

Primary chorea	Secondary chorea	Others
Huntington's disease	Sydenham's chorea	Metabolic disorders
Neuroacanthocytosis	Drug induced chorea	Vitamin deficiency: vitamin B1 and B12
Dentatorubralpallidoluysian atrophy	Immune mediated chorea	Exposure to toxins
Benign hereditary chorea	Infectious chorea	Paraneoplastic syndromes
Wilson's disease	Vascular chorea	Postpump choreoathetosis
Pantothenate kinase associated neurodegeneration (PKAN or formerly Hallervorden-Spatz syndrome)	Hormonal disorders	
Paroxysmal choreoathetosis		
Senile chorea		

individuals, the repeat length ranges between 9 and 34 with a median normal chromosome length of 19. Expansion of a CAG repeat beyond the critical threshold of 36 repeats results in disease, and forms the basis of the polymerase chain reaction based genetic test. This expanded repeat is somewhat unstable and tends to increase in subsequent offspring, termed ''anticipation''. Expansion size is inversely related to age at onset, but the range in age at onset for a given repeat size is so large (with a 95% confidence interval of $\pm$18 years for any given repeat length) that repeat size is not a useful predictor for individuals.[6 7] It is likely that other genetic or environmental factors have a significant role in determining age of onset. With the exception of juvenile onset cases, there has been poor correlation between phenotype and CAG repeat length. Because of meiotic instability with a tendency to increasing expansion size during spermatogenesis, juvenile onset cases with very large expansions usually have an affected father.[8] Predictive genetic testing of asymptomatic at-risk relatives of affected patients is available and governed by international guidelines.[9] However, the implications of Huntington's disease predictive testing are many and demand careful consideration.

Clinical features

Huntington's disease is a progressive disabling neurodegenerative disorder characterised by the triad of movement disorders, dementia, and behavioural disturbances. Illness may emerge at any time of life, with the highest occurrence between 35 and 40 years of age. Although the involuntary choreiform movements are the hallmark of Huntington's disease, it is the mental alterations that often represent the most debilitating aspect of the disease and place the greatest burden on families of Huntington's disease patients. There is also a large variability in the clinical presentation and some of this variability is predictable; for example, the juvenile onset form may present with parkinsonism (the so-called Westphal variant), while late onset form may present with chorea alone.[10]

Box 1: Clinical features of Huntington's disease (modified from Poewe *et al*[64])

- Autosomal dominant disorder with 100% penetrance (CAG trinucleotide expansion on chromosome 4).
- Prevalence of 4–8 per 100 000 people.
- Age of onset: 40 years (5% juvenile onset at $<$20 years of age, 30% late onset at $>$50 years of age).
- Choreic movements and hypotonia.
- Personality and mood changes, psychosis, and dementia are common.
- Oculomotor abnormalities: slowing of saccades and increased response latency.
- Rigidity, hypokinesia, and dystonia are common in juvenile onset cases.
- No curative treatment; symptomatic treatment with dopamine agonists.
- Relentlessly progressive with mean duration of 17 years.

Chorea is the prototypical motor abnormality characteristic of Huntington's disease, accounting for 90% of affected patients. Chorea usually starts with slight movements of the fingers and toes and progresses to involve facial grimacing, eyelid elevations, and writhing limb movements. Motor impersistence is another important associated feature, whereby individuals are unable to maintain tongue protrusion or eyelid closure. Other motor manifestations are also common in Huntington's disease including eye movement abnormalities (slowing of saccades and increased latency of response), parakinesias, rigidity, myoclonus, and ataxia.[11] Dystonia tends to occur when the disease is advanced or is associated with the use of dopaminergic medications. While dysarthria is common, aphasia is rare. Dysphagia tends to be the most prominent in the terminal stage and aspiration is a common cause of death.

Cognitive impairment seems to be inevitable in all patients with Huntington's disease whether to a greater or lesser degree.[12 13] Typically, the impairment begins as selective deficits involving psychomotor, executive, and visuospatial abilities and progresses to more global impairment, although higher cortical language tends to be spared.

Although Huntington focused on the tendency of insanity and suicide, a wide range of psychiatric and behavioural disturbances are recognised in Huntington's disease, with affective disorders among the most common, thought to be secondary to the disruption of the frontal-subcortical neural pathway.[13] Depression occurs up to 50% of patients. The suicide rate in Huntington's disease is fivefold that of the general population.[14] Psychosis is also common, usually with paranoid delusions. Hallucinations are rare. Apathy and aggressive behaviour are commonly reported by caregivers. Presently, it is unclear whether cognitive and psychiatric difficulties antedate other manifestations of Huntington's disease.[12 15]

Differential diagnosis

A variety of hereditary and acquired neurological disorders may mimic Huntington's disease. Benign hereditary chorea is a clinically distinct condition from Huntington's disease. Although inherited in an autosomal dominant fashion like Huntington's disease, the symptoms are non-progressive with no alterations in cognitive or behavioural functions.

The onset is much earlier than Huntington's disease, usually before the age of 5 years. Other dominant disorders that may mimic Huntington's disease include dentatorubralpallidoluysian atrophy (DRPLA), which is a triplet repeat polyglutamine disorder with profound clinical heterogeneity. It is rarely reported in North America and Europe, but is more common than Huntington's disease in Japan. Symptoms vary and may include chorea, myoclonus, ataxia, epilepsy, and dementia. Although its pathology is reminiscent of Huntington's disease, the involvement of the dentate nucleus of the cerebellum differentiates the disorder. Spinocerebellar ataxia type 17 may also present with chorea, associated with prominent cerebellar ataxia. Patients with Huntington's disease-like 2 usually have clinical and pathological features indistinguishable from Huntington's disease. It is due to CTG expansion in junctophilin-3 and it is almost exclusively in African ethnicity. In a group of recessive disorders, the presence of sensorimotor neuropathy may suggest alternative diagnosis of neuroacanthocytosis. This is a genetically heterogeneous disorder and may be clinically indistinguishable from Huntington's disease. The diagnosis is supported by the presence of acanthocytes on a peripheral smear in the context of appropriate clinical presentation. Wilson's disease should be considered in all patients with movement disorders who are less than 40 years of age, although patients with Wilson's disease rarely exhibit chorea. Pantothenate kinase associated neurodegeneration, formerly known as Hallervorden-Spatz syndrome, is characterised by early onset dystonia, spasticity and dementia, although chorea is a less frequent manifestation. Other forms of hereditary conditions, such as McLeod's syndrome (X-linked) or mitochondrial disorders may also present with chorea.

Neuropathology

Grossly, the Huntington's disease brain shows significant atrophy of the head of caudate and putamen, and to a lesser extent, the cortex, globus pallidus, substantia nigra, subthalamic nucleus, and locus coeruleus.[16] Microscopically, medium spiny neurons are the vulnerable population in Huntington's disease.[17] Indirect projections to the external globus pallidus are the first to degenerate. In addition, intraneuronal inclusions have been reported in the nuclei and neurophil of striatal and cortical neurons and represent aggregates of the mutant huntingtin protein and ubiquitin.[18]

Treatment

Unfortunately, there are currently no effective therapies to slow the progression or delay the onset of Huntington's disease. An excitotoxic pattern of cell death resulting from mitochondrial dysfunction has been suggested as a contributing factor in Huntington's disease; intrastriatal injections in animals as well as systemic administration of mitochondrial toxins in animals and people can produce the symptoms and neuropathological lesions of Huntington's disease. Therefore, both symptoms and lesions may be partially blocked or reduced by *N*-methyl-D-aspartate receptor blockade or deafferentation of cortical glutamatergic inputs. Different agents are currently under investigations including coenzyme Q10, racemide hydrochloride, and riluzole.[19]

Current treatments in Huntington's disease are largely symptomatic, aimed at reducing the motor and psychological dysfunction of the individual patient. In general, treatment of chorea is not recommended unless it is causing disabling functional or social impairment. Olanzapine or risperidone, atypical antipsychotics, have been found to reduce chorea with less risk of the extrapyramidal side effects, compared to the typical agents. Other agents including riluzole, tetrabenazine, and amantadine have been shown to improve chorea.[20 21] Traditional neuroleptics such as haloperidol can improve chorea but are associated with increased risk of tardive dyskinesia, dystonia, difficulty swallowing, and gait disturbances, and should not be considered first line agents.

The selective serotonin reuptake inhibitors (SSRIs) have become the first line agents in the treatment of depression in Huntington's disease. Although there are no controlled trials of SSRIs in depressed patients with Huntington's disease, these agents seem to be well tolerated and effective. In addition, SSRIs may suppress chorea and reduce aggression in Huntington's disease.[22] The dose should be started low and doubled every two weeks if necessary. A brief course of benzodiazepines may be useful for co-occurring anxiety. The new antipsychotic agents, such as clozapine, quetiapine, and olanzapine are often required to treat psychosis in Huntington's disease.[23] Valproic acid may be useful in the long term management of aggression and irritability.[24]

Human fetal striatal grafts may survive transplantation and induce clinical benefits in patients with Huntington's disease.[25] Functional neuroimaging studies have shown increased metabolic activity and small improvements in motor, cognitive, and behavioural measures in some patients.[26] This treatment approach is still experimental and information about long term outcome is not yet available.

Neuroacanthocytosis

Clinical features

Neuroacanthocytosis is a rare, multisystem, degenerative disorder of unknown aetiology that is characterised by the presence of deformed erythrocytes with spicules known as acanthocytes and abnormal involuntary movements. The disorder seems to be particularly common in Japan and can be transmitted by autosomal recessive, dominant, or X-linked inheritance.[27] The mean age of onset is around 30 years and tends to be progressive, with death occurring within 15 years of diagnosis. Involuntary choreic and dystonic movements of the orofacial region, as well as tongue and lip biting are virtually diagnostic, although a full spectrum of movement disorders may be seen.[28] Other clinical features include chorea of the limbs (predominantly the legs) that can mimic Huntington's disease, axonal neuropathy (50% of cases), areflexia, and raised plasma creatine kinase level. Seizures are also common and can be a presenting feature. Psychiatric symptoms are typical and include apathy, depression, anxiety, and obsessive-compulsive syndrome. However, in contrast to Huntington's disease, mental deterioration is minimal.[29]

Diagnosis and treatment

Diagnosis is usually made on the basis of family history, morphological analysis of erythrocytes, and a raised plasma

Box 2: Clinical features of neuroacanthocytosis

- A multisystem degenerative disorder of unknown aetiology.
- Variable mode of inheritance.
- Age of onset: approximately 30 years.
- Chorea as well as orofacial-lingual dystonia are prominent.
- Axonal neuropathy in 50% of cases.
- Presence of acanthocytes on peripheral blood smears.
- No curative treatment available; treatment is largely supportive.
- Relentlessly progressive (mean duration 15 years).

creatine kinase level. The pathogenesis of acanthocyte formation is still unclear.[28] Magnetic resonance imaging (MRI) has shown degeneration of the caudate and more generalised cerebral atrophy. Increased signal on T2-weighted MRI in the caudate and putamen is a common feature. These findings are non-specific. The most consistent neuropathological finding is extensive loss of predominantly small and medium sized neurons and gliosis in the caudate, putamen, pallidum, and substantia nigra with relative sparing of the subthalamic nucleus and cerebral cortex.[30] Treatment is largely supportive.

Dentatorubralpallidoluysian atrophy

DRPLA is a triplet repeat polyglutamine disorder with the gene defect localised to chromosome 12.[31] Development of clinical phenotypes is associated with CAG repeat lengths exceeding 53.[32] Atrophin-1 is a mutant protein and its function is not known. The condition is rarely reported in North America and Europe but it is more common in Japan.[33] It is inherited in an autosomal dominant fashion and clinical features include chorea, myoclonus, ataxia, epilepsy, and cognitive decline. Neuroimaging studies have revealed atrophy of the cerebellum, midbrain tegmentum, and cerebral hemispheres with ventricular dilatation. Pathologically, there is neuronal loss and gliosis in the dentate nucleus, red nucleus, globus pallidus, and subthalamic nucleus.[31]

Wilson's disease

Wilson's disease is an autosomal recessive disorder with a single disease locus residing on chromosome 13q14.3.[34] The gene appears to be fully penetrant, with all individuals homozygous for Wilson's disease developing some form of the disease and a 25% of their siblings developing the disease. Most aspects of clinical heterogeneity of hepatic versus neurological presentations do not seem to be determined by features of genetic heterogeneity. Although the exact pathophysiology in Wilson's disease remains unknown, the main defect is most likely to be a problem of protein complexing, resulting in impairment of copper excretion.[35]

Clinical features

The most puzzling aspect of Wilson's disease is the marked variety in clinical presentation. The manifestations usually begin monosymptomatically or simultaneously with other clinical features with a tendency for asymmetric or focal deficits. Almost half of all patients with Wilson's disease first experience neurological problems in the second or third decade of life. Tremor is usually the initial symptom, which can be at rest, during action, or postural while chorea tends not to occur alone, rather as a combination with dystonia, rigidity, and dysarthria. The most characteristic pattern of tremor in Wilson's disease involves a coarse, irregular, to-and-fro movement elicited by action when the arms are held forward and flexed horizontally with a ''wing beating'' quality. Cerebellar findings are also common, resembling a common pattern of multiple sclerosis. Seizures, sometimes undifferentiated from paroxysmal movement disorders, have been described, although they are more common in juvenile cases. It is important to recognise that excess copper load can be severe even in patients with mild symptoms.

One of the most striking ophthalmological presentations in Wilson's disease is the presence of Kayser-Fleischer rings (KF rings). KF rings have a brownish or greenish tint and are generally found in the upper pole of the peripheral cornea. KF rings can be missed by direct ophthalmoscopic examination and a definitive analysis requires a careful slit lamp examination by an experienced ophthalmologist. With appropriate clinical history, the diagnosis of Wilson's disease, especially the neurological form, can be made when a KF ring is present.

Recognition of subtle clinical features is the major challenge in clinical diagnosis of Wilson's disease. Variable physical signs and symptoms that can be intermittent pose another difficulty in early diagnosis. This diagnosis should always be considered in all patients with movement disorders of any type who are younger than 40 years old, as missing the opportunity for diagnosis when its signs and symptoms are mild is one of the greatest challenges in this treatable disorder.

Diagnosis and treatment

Although a diagnostic blood test of genetic abnormalities in Wilson's disease has recently become available, diagnosis still very much relies on appropriate clinical history and compatible clinical findings, along with blood tests involving copper metabolism for which the results can vary with disease stage. While serum ceruloplasmin is a simple and useful screening test, ceruloplasmin deficiency is not unique for Wilson's disease and can be found in other conditions such as nephrotic syndrome, protein-losing enteropathy, and sprue. Measurement of 24 hour urine copper excretion provides a more sensitive result, although the finding can be normal in asymptomatic patients or patients with hepatic Wilson's disease. Liver biopsy is the most sensitive and accurate test, yielding an increased hepatic copper content in almost all patients with Wilson's disease; however, this test is invasive and not widely available. MRI of the brain is usually abnormal in patients with neurological Wilson's disease, revealing increased signal intensity on T2-weighted images involving basal ganglia, midbrain, and pons. However, these abnormal findings can improve after successful treatment. Therefore, in typical newly diagnosed symptomatic patients, we should expect to see a reduced serum ceruloplasmin level ($<$300 mg/l), high 24 hour urinary copper excretion ($>$100 μg/day), a high hepatic copper content from biopsy (if performed), and the presence of KF ring in neurological cases.

As mentioned, Wilson's disease is treatable and there is a potentially curative treatment by liver transplantation. This disease, if diagnosed and treated early, can be associated with full recovery. On the other hand, if missed, the disease may result in irreversible neurological disabilities in affected individuals. Low copper or copper-free food, as in lactovegetarian diet, is seldom adequate without additional therapy. The role of zinc therapy in symptomatic Wilson's disease is unclear, although it is generally recommended in asymptomatic individuals. Penicillamine is probably the most potent copper chelating agent available and has been mostly used as the first line therapy for initial and long term management, although chronic treatment is associated with various side effects, mainly skin rash and discoloration. Penicillamine can trigger neurological deterioration after the start of therapy.

Benign hereditary chorea

Benign hereditary chorea or essential chorea is another disorder inherited in an autosomal dominant fashion and characterised by choreiform movements, but is distinct from Huntington's disease in several ways (table 2). In contrast to Huntington's disease, the onset of choreiform movements in benign hereditary chorea is in early childhood; severity of symptoms peaks in the second decade and the condition is non-progressive.[36 37] Life expectancy is normal and some reports have suggested that the disease improves with age. The condition is not associated with other neurological deficits, although some authors believe that it is a heterogeneous syndrome that may have a variety of causes.[38] In addition, some families with this initial diagnosis prove to have other disorders when more thoroughly investigated.

Table 2 Distinguished features between Huntington's disease, benign hereditary chorea (BHC), dentatorubralpallidoluysian atrophy (DRPLA), and neuroacanthocytosis

Features	Huntington's disease	BHC	DRPLA	Neuroacanthocytosis
Onset	4th decade	Early childhood	<20 years, or >40 years	3rd decade
Genetics	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive, dominant, or X-linked
Natural history	Progressive, mean disease duration 17 years	Non- progressive, normal life expectancy	Progressive	Progressive, mean disease duration 15 years
Seizures	May be present	None	Present in juvenile type	Common
Dystonia	Later in disease course	None	Present	Present, esp. in orofacial region
Myoclonus	Later in disease course	None	Common in juvenile type	Present
Ataxia	Later in disease course	None	Common (100%)	May be present
Cognitive deficits	Invariably	None	Invariably	Minimal
Psychiatric symptoms	Common and prominent	None	Present	Present
Others	Motor impersistence, dysarthria	None	Mental retardation (100%)	Sensorimotor neuropathy, acanthocytes, raised creatine kinase

Nevertheless, benign hereditary chorea is considered to be a distinct disease of early onset, non-progressive, uncomplicated chorea with a mutation in TITF-1 gene on chromosome 14q.[37 39]

Others

There are other inherited neurological disorders that can present with prominent chorea. These conditions are rare and the details are not included in this review. Examples include paroxysmal choreoathetosis, familial chorea-ataxia-myoclonus syndrome, pantothenate kinase associated neurodegeneration (PKAN or Hallervorden-Spatz syndrome), intracerebral calcification with neuropsychiatric features, multisystem degeneration, olivopontocerebellar atrophy, and spinocerebellar degeneration (Sanger Brown type).[40]

NON-HEREDITARY CAUSES OF CHOREA

Sydenham's chorea

Sydenham's chorea is a delayed complication of group Aβ haemolytic streptococcal infections and forms one of the major criteria of acute rheumatic fever.[41] It is characterised by chorea, muscular weakness, and a number of neuropsychiatric symptoms. It is considered to be an autoantibody mediated disorder with the evidence suggesting that patients with Sydenham's chorea produce antibodies that cross react with streptococcal, caudate, and subthalamic nuclei.[42] However, documented evidence of previous streptococcal infection is found in only 20%–30% of cases. The age of presentation is usually between 5 and 15 years with female preponderance. Chorea is usually generalised, consisting of finer and more rapid movements than those seen in Huntington's disease. It occurs at rest or with activity but remits during sleep. The condition is self limited within five to 16 weeks, but recurs in 20% of patients. It has a good prognosis for full recovery so treatment is not warranted in most cases. However, symptomatic treatment with neuroleptics, tetrabenazine,[43] or valproic acid can be considered in severe cases with generalised chorea. Previously affected females are at increased risk of developing chorea during pregnancy (chorea gravidarum) and during sex hormone therapy. Evidence of striatal dysfunction in Sydenham's chorea is supported by MRI revealing lesions in the caudate and putamen in some patients and reversible striatal hypermetabolism on brain single photon emission computed tomography during the acute illness.[44–46]

Box 3: Clinical features of Sydenham's chorea

- Preceding streptococcal group A infection.
- Age of onset: 5–15 years.
- Female predominant.
- Symmetrical chorea.
- Personality change can occur including obsessive-compulsive disorder and irritability.
- Self limiting course.
- Raised antistreptolysin titre.

Other immune mediated chorea

Although central nervous system involvement in systemic lupus erythematosus (SLE) is common, occurring in 50% to 70% of cases, chorea has been reported in less than 2% of these patients.[47] It usually appears early in the course of the disease and is characteristically generalised. It is often difficult to recognise chorea as a manifestation of a systemic autoimmune disease because it can simulate Sydenham's and Huntington's chorea and not infrequently appears in childhood long before other manifestations of SLE or antiphospholipid syndrome have emerged.[48] The use of oestrogen-containing oral contraceptives or pregnancy may precipitate the appearance of chorea. In addition, chorea can occur not only in patients with well defined SLE, but also in patients with ''probable'' or ''lupus-like'' SLE and in patients with primary antiphospholipid antibody without clinical features of SLE.[49] The mechanism of action of these antiphospholipid antibodies remains obscure, although the concept of primary endothelial cell damage and impairment of production of endothelial cell products or damage to platelets have been proposed. Treatment of chorea in autoimmune disease has not been well established, although some reports suggested that steroid therapy can lead to resolution.

Less commonly, chorea can be associated with other autoimmune diseases including polyarteritis nodosa,

Behçet's disease, and isolated angiitis of the central nervous system.[50]

Drug induced chorea

Drug induced chorea may be an acute phenomenon or the consequence of long term therapy. Multiple drugs including dopamine agonists, levodopa therapy, oral contraceptives, and anticonvulsants have been implicated in the acute chorea (box 4). Levodopa induces dyskinesias and, to a lesser extent, the dopamine agonists only induce chorea in patients with idiopathic Parkinson's disease or other parkinsonian disorders. Dopamine antagonists, on the other hand, seem to be capable of inducing dyskinesias in everyone exposed. However, the nature of the induced abnormal movements—chorea, dystonia, or others—as well as their incidence depends on additional factors including age, dose, potency, and duration of exposure (table 3). When drug induced chorea occurs, withdrawal of the offending agent is the treatment of choice. However, the movement disorder does not always remit with the discontinuation of the offending drug. When the onset of chorea is after exposure to dopamine antagonists, it is called tardive dyskinesia. Tardive dyskinesia is an involuntary, choreic movement disorder that typically affects the mouth and tongue causing random and stereotyped tongue protrusion and facial grimacing. Elderly females are the most susceptible, with an incidence of 20%–50% in patients being treated with neuroleptics. Other risk factors are duration of exposure, patients' age, and prior neurological deficits. In contrast, tardive dystonia develops more often in younger patients and presents with dystonic symptoms such as retrocollis and blepharospasm. The classic neuroleptics such as haloperidol, which possess high affinity for blocking D2 dopamine receptors, are most commonly implicated. Although the exact aetiology of delayed onset tardive dyskinesia is unclear, the most popular hypothesis is denervation hypersensitivity of blocked dopamine receptors. Tardive movements can also develop during the stable treatment or may be unmasked during attempts at dose reduction (withdrawal emergent). Once the offending medication has been withdrawn, the resolution of tardive movements can be a slow process (months to years) and is not assured. A dopamine depleting agent, such as reserpine or tetrabenazine can be considered in resistant cases. Vitamin E has been shown to hasten the resolution. When multiple medications are implicated, withdrawal of one medication at a time will allow the identification of the most offending agent. Discontinuation should begin with the most recent addition to the regimen. Although many medications have been tied to the induction of dyskinesia, very few medications other than neuroleptics produce permanent movement disorders.[29]

Infectious chorea

Multiple infectious agents that affect the central nervous system have been associated with chorea. Chorea can occur in the setting of acute manifestation of bacterial meningitis, encephalitis, tuberculous meningitis, or aseptic meningitis. Movement disorders are also encountered in 2% to 3% of all patients with AIDS. In the setting of AIDS, hemichorea and hemiballismus are relatively common due to toxoplasmosis abscess; however, direct HIV invasion and injury to the basal ganglia resulting in chorea can occur.[51] Less commonly, Lyme's disease has been reported to cause chorea.[52]

Vascular chorea

Chorea is the most common movement disorder after stroke.[53] The subthalamic nucleus is the most common reported location of ischaemic or haemorrhagic damage in patients with poststroke chorea, especially when the chorea is severe and proximal (called hemiballismus).[54] Chorea can also occur in polycythaemia vera, although it manifests in less than 1% of cases.[55] It remains unclear how polycythaemia can give rise to chorea. Several mechanisms have been proposed including transient ischaemia, reduced levels of catecholamines, or receptor upregulation.

Box 4: Drugs known to cause chorea (in addition to antipsychotic medications) (modified from Jain *et al*[63])

1. Anticonvulsant medications: common causative agents include:
   - Phenytoin.
   - Carbamazepine.
   - Valproate.
   - Gabapentin.
2. Central nervous system stimulants:
   - Amphetamines.
   - Cocaine.
   - Methylphenidate.
3. Benzodiazepines.
4. Oestrogens.
5. Lithium.
6. Levodopa.
7. Dopamine agonists.
8. COMT inhibitor in conjunction with levodopa.
9. Antihistamines: H1 and H2.
10. Others—for example, baclofen, cimetidine, aminophylline, etc.

Hormonal disorders

Hormonal disorders including hyperthyroidism, hypoparathyroidism with hypocalcaemia, pregnancy, and oral contraceptives have been implicated in the induction of dyskinesias. Two percent of patients with hyperthyroidism have chorea.[56] The movements are usually generalised and improve once treatment has been initiated. Hypocalcaemia with hypoparathyroidism can produce both generalised and focal dyskinesias.

Chorea gravidarum or chorea occurring during pregnancy is an increasingly rare disorder. Affected patients usually have the previous episodes of chorea associated with the use of oral contraceptives or history of rheumatic fever.[57] It is plausible that hormonal changes in pregnancy may require immunological cofactors from previous streptococcal infection to produce chorea. The movements usually remit after the delivery but may recur in the subsequent pregnancy.

Other causes of chorea

Metabolic alterations including hyperglycaemia and hypoglycaemia, hypernatraemia and hyponatraemia, hypomagnesaemia, hypocalcaemia, and hepatic or renal failure have been implicated in the development of various movement disorders including chorea. Correction of the metabolic abnormality leads to the resolution of the movement disorders. Postoperative encephalopathy with choreoathetosis or post-pump choreoathetosis is a recognised complication of childhood cardiac surgery.[58]

Exposure to various toxins including alcohol, amphetamines, heroin, glue sniffing, thallium, and mercury can cause choreiform movements. The movements can be transient or permanent. Intoxication with carbon monoxide, methanol,

Table 3 Drug induced chorea (Modified from Poewe *et al*[54])

Features	Neuroleptic induced chorea	Levodopa induced chorea in Parkinson's disease
Age of onset	Elderly > young	Young > elderly
Sex	Female > male	Female = male
Prevalence	10% after month/years of treatment	50% after 3–5 years of treatment
Treatment	Discontinuation of neuroleptics or replacement by clozapine, tetrabenazine	Reduction of levodopa combined with the use of dopamine agonists

cyanide, or manganese produces bilateral necrosis of the pallidum, causing unconsciousness or parkinsonism. Involuntary movements can be a delayed sequel to acute high level exposure and disappear after a few months.[59] Chorea can also occur in the setting of paraneoplastic syndrome associated with small cell lung carcinoma, renal cell carcinoma, and lymphoma.[60]

Diagnosis and management

Although there are extensive causes of chorea, careful history and a concomitant neurological and psychiatric review of systems will guide the individual workup. A detailed medical history is very important to rule out, in particular, prior streptococcal infections or rheumatic fever. As previously mentioned, a past history of rheumatic fever predisposes individuals to the development of a paroxysmal movement disorders under the influence of different agents. A family history of choreic or degenerative illness should be noted as well as a medication history of potential causative agents. Most of the time, the above history will narrow down the exhaustive differential list. Genetic testing, neuroimaging, and laboratory investigations will help us confirm the suspected diagnosis. Box 5 provides a list and when to consider individual tests. Despite the above careful workup in most patients, causes are unidentified in 6% of cases.[52]

For primary chorea, dopaminergic antagonists such as neuroleptic medications are effective in treating chorea; however, their use is limited due to the side effects of mainly parkinsonism and tardive syndromes. Dopamine-depleting agents such as tetrabenazine, which inhibits the presynaptic dopamine release and blocks postsynaptic dopamine receptors, show favourable results compared with other medications used to treat chorea, especially in Huntington's disease, and have been reported to have synergistic effects when used in combination with the dopamine antagonist pimozide.[20 61] For secondary chorea, the treatment objective should focus on the primary causative factor. If chorea is due to exogeneous agent, the offending agent should be withdrawn. Infectious process should be treated accordingly. The drug used to treat primary chorea can be used to symptomatically treat secondary chorea.

Box 5: Recommended investigations in patients with chorea (careful history and physical examination will guide individual workup)

Start with careful history, including psychiatric, drug, and family history and physical examination, focusing in the distribution of chorea, evidence of motor impersistence, and frontal lobe dysfunction.

1. Complete blood count.
2. Electrolytes, calcium.
3. Magnesium.
4. Renal function tests.
5. Hepatic function tests.
6. Venereal Disease Research Laboratory test.
7. HIV antibody.
8. Thyroid function tests.
9. Erythrocyte sedimentation rate and antinuclear antibody titre: in cases with suspected autoimmune aetiology.
10. Antistreptolysin O titre: in cases with suspected streptococcal infection.
11. Lyme disease: in cases with recent travel history to endemic areas.
12. Toxoplasmosis titres: in immunosuppressed patients.
13. A copper study with serum ceruloplasmin and 24 hour urine copper: in cases with movement disorders under the age of 40, especially with a family history of neuropsychiatric symptoms or medical history of liver disease
14. MRI: in rule to intracranial structural lesion, especially in the setting of acute choreiform movements in older patients or younger patients with focal neurological signs.
15. Electroencephalography: when need to differentiate between paroxysmal movement disorders and seizures.

SUMMARY

Chorea is a common finding in rare diseases as well as a rare manifestation of some common conditions. Although the exact pathophysiology of chorea is not well understood, most physiological and anatomical evidence suggests that disruption of the indirect pathway either structurally or neurochemically causes chorea.[62] With such evidence, the concept of therapy can be potentially approached. Although not currently curative, most current therapies may alter the disease course, especially in Huntington's disease, or decrease the mortality and morbidity. Neurosurgical interventions may have a significant role in cases with medication resistant or progressively debilitating chorea. Keeping in mind the various ethical issues, additional longitudinal research is needed to further our understanding of this condition, which will lead to the effective treatment in the future.

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