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Differential Diagnosis of Chorea

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Abstract Chorea is a common movement disorder that can be caused by a large variety of structural, neurochemical (including pharmacologic), or metabolic disturbances to basal ganglia function, indicating the vulnerability of this brain region. The diagnosis is rarely indicated by the simple phenotypic appearance of chorea, and can be challenging, with many patients remaining undiagnosed. Clues to diagnosis may be found in the patient's family or medical history, on neurologic examination, or upon laboratory testing and neuroimaging. Increasingly, advances in genetic medicine are identifying new disorders and expanding the phenotype of recognized conditions. Although most therapies at present are supportive, correct diagnosis is essential for appropriate genetic counseling, and ultimately, for future molecular therapies.

Keywords Chorea · Huntington's disease · Basal ganglia · Neuroacanthocytosis · Huntington disease-like

Introduction: An Approach to the Patient with Chorea

Chorea refers to involuntary movements of limbs, trunk, neck, or face that rapidly flit from region to region in an irregular, flowing, non-sterotyped pattern. This hyperkinetic movement disorder may be generated by a large number of causes, including genetic, pharmacologic, metabolic, and structural. Although the appearance of the movement disorder itself is typically not diagnostically helpful, there may be features of the patient's history and examination that can be informative (Table 1). The work-up of the patient with chorea can be extensive (Table 2), and yet some patients may remain undiagnosed. Here, I focus upon different elements of the patient's medical history and examination as a framework for generating the differential diagnosis. I have indicated some of the main diagnoses under the different headings below, although it will be evident that salient diagnostic features of different disorders could be included in various places.

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Family History: Genetic Causes of Chorea

Any positive family history should be carefully evaluated, even if it suggests an unrelated disorder. If present, the pattern of inheritance should provide a guide to possible diagnoses; however, the absence of a family history does not exclude a genetic cause. Possible reasons for this in the case of autosomal-dominant disorders include adoption, non-paternity, non-disclosure of illness, parental death before disease manifestation, mis- or non-diagnosis, and decreased penetrance in a parent. In the case of autosomal-recessive inheritance, a small sibship size may preclude the appearance of other affected siblings.

Autosomal-Dominant Choreas

Huntington's disease (HD) remains the most common inherited cause of chorea. A family history of HD should only be taken at face value if the diagnosis has been

Table 1 History and clinical features in the evaluation of the patient with chorea.

Key element	Possible diagnosis
Family history	AD, AR, X-linked, mitochondrial disease
Medical history	Metabolic effect (e.g. thyroid disease, diabetes); CNS involvement (e.g. autoimmune disease, metastatic disease, paraneoplastic syndrome)
Medication exposure	Direct medication side-effect or tardive syndrome
Onset: acute vs chronic; fluctuating	Stroke, metabolic disorder vs neurodegenerative disease; paroxysmal dyskinesia
Localizing neurologic features	Structural lesion; multifocal disease
Psychiatric features, cognitive impairment	Frontotemporal cortical involvement; subcortical dementia

AD autosomal dominant, *AR* autosomal recessive

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Table 2 Laboratory evaluation of the patient with chorea

Test	Possible diagnosis
Blood chemistry	Hyper/hypoglycemia; hyper/hyponatremia; hypomagnesemia hyper/hypocalcemia; Lesch-Nyhan syndrome
CBC with smear	Neuroacanthocytosis syndrome (ChAc, MLS, HDL2, PKAN)
Liver function tests	Wilson's disease; ChAc; MLS
Thyroid function tests	Hypo-/hyper-thyroidism
Parathyroid levels	Hypo-/hyper-parathyroidism, pseudohypoparathyroidism
Pregnancy test	Chorea gravidarum
Creatine phosphokinase	ChAc; MLS
Ceruloplasmin	Wilson's disease; aceruloplasminemia
Ferritin	Neuroferritinopathy
Sedimentation rate, antinuclear antibodies, anti-DNA, anti-SSA, anti-SSB, anti-Ro, anti-La, etc.	Autoimmune disease
Lupus anticoagulant	Systemic lupus erythematosus
Antiphospholipid antibodies	Antiphospholipid syndrome
ASO, anti-DNase B titres	Sydenham's chorea
HIV test	HIV/AIDS-related infection
Anti-gliadin antibodies	Coeliac disease
RPR, CSF FTA	Syphilis
B12	B12 deficiency
Serum lead	Lead toxicity
Antineuronal antibodies (anti-CRMP-5/CV2, anti-Hu, anti-Yo, anti-NMDA receptor)	Paraneoplastic syndromes
Plasma lactate/pyruvate	Mitochondrial and other energy metabolism disorders
Alpha-fetoprotein	Ataxia-telangiectasia, ataxia with oculomotor apraxia 1, 2
Cholesterol	Ataxia with oculomotor apraxia 1, 2
Erythrocyte Kx and Kell antigens	MLS
Genetic testing	As indicated
MRI/CT + contrast	Structural lesions; iron deposition, calcification
EEG	Seizure-related syndrome; Creutzfeldt-Jakob disease
Lumbar puncture	Creutzfeldt-Jakob disease; chronic infection; lactate/pyruvate for mitochondrial and other energy metabolism disorders
Urinary and serum organic and amino acids	Organic/amino acidopathies

ChAc chorea-acanthocytosis, *HDL2* Huntington's disease-like 2, *MLS* McLeod syndrome, *PKAN* pantothenate kinase-associated neurodegeneration

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genetically confirmed, as many patients were given this diagnosis presumptively prior to the availability of genetic testing.

Huntington's Disease

HD is caused by inheritance of an expanded trinucleotide repeat (> 39) within the *htt* gene on chromosome 4p16.3. This gene encodes for the protein huntingtin whose function is not yet known, but the expanded polyglutamine tract appears to potentially interfere with a number of cellular functions. The normal range of repeats is between 6 and 26; in the range of 27 to 35 repeats the expansion is unstable, and is liable to expand in subsequent generations, especially when passed on from the father. There are apparent cases of clinical HD in subjects with repeats within this range but most are unaffected carriers [1]. Subjects with expansions in the premutation range 35 to 39 may pass on a pathologically expanded allele to their offspring and may be clinically affected themselves, usually at much older ages.

The size of the expansion correlates with age of disease onset and rate of disease progression, although there can be considerable variation between individuals [2]. The age of onset is clearly determined by a variety of other genetic and environmental factors [3], possibly including the size of the non-mutant allele [4]. Neuropsychiatric symptoms including personality changes, irritability, social withdrawal, obsessive-compulsive disorder, psychosis, and depression may precede the development of the movement disorder. These symptoms should be aggressively treated because suicide is not uncommon.

In adults the movement disorder may manifest initially as fidgeting. Patients may attempt to disguise the involuntary movements as purposeful ones (parakinesias). With time chorea becomes more evident, and other hyperkinetic movements such as myoclonic jerks and dystonia may be present. Motor impersistence interferes with function and results in dropping things and falls. With more advanced disease, patients can become parkinsonian, also impairing balance. With larger repeat sizes, resulting in onset below the age of 20 years, the parkinsonian "Westphal variant," is typical. This may respond to l-dopa and other dopaminergic agents, but these should be used with caution because they may exacerbate psychosis.

Huntington's Disease-Like 2

Huntington's disease-like 2 (HDL2) has only been reported to date in families of African ancestry [5, 6]. Symptoms develop in young-mid adulthood, with an age of onset inversely related to size of the trinucleotide repeat expansion [7], and look very similar to those of HD. Dystonia and parkinsonism appear to be more prominent than in HD, regardless of repeat size [8]. As in HD, early signs may be personality change and psychiatric symptoms.

HDL2 is due to a CTG/CAG trinucleotide repeat expansion within junctophilin-3 (*JPH3*) on chromosome 16q24.3 [5]. Affected individuals have repeat expansions of 41 to 58 triplets. Acanthocytosis is reported in about 10% of cases, resulting in confusion with other neuroacanthocytosis syndromes [9].

Spinocerebellar Ataxias and Dentatorubropallidoluysian Atrophy

Movement disorders can be seen in several of the spinocerebellar ataxias (SCAs), due to trinucleotide repeat expansions or to conventional mutations of a variety of genes [10•]. The size of the expansions does not in general appear to correlate with the phenotype.

Cerebellar findings are typically present, including abnormalities of eye movement and gait ataxia, but may be less prominent in some cases than the movement disorder. SCA3 (Machado-Joseph disease), the most common SCA in most populations, can present with parkinsonism, dystonia, and chorea. Patients with SCA1 [11, 12] and SCA2 [13] may occasionally present with or develop chorea. Parkinsonism, dystonia, and chorea may be seen in SCA17 [6, 14], in addition to the typical phenotype of ataxia, dementia, and hyperreflexia.

Chorea and myoclonus can be seen in dentatorubropallidoluysian atrophy (DRPLA), usually in addition to ataxia and dementia. Although more common in Japanese populations, DRPLA has occasionally been reported in Caucasian [15, 16] and African-American [17] families.

Benign Hereditary Chorea

Benign hereditary chorea may develop in childhood, and is not associated with cognitive impairment or other significant neurologic abnormalities apart from mild ataxia. Mutations may be found in the gene for thyroid transcription factor 1 (*TITF-1;* also *NKX2.1*) [18], or other genes [19].

The chorea may respond to levodopa [20]. Mutations in *TITF-1* may also cause a severe multisystem disorder with congenital hypothyroidism, hypotonia, and pulmonary problems, in addition to chorea [21].

Neuroferritinopathy

Neuroferritinopathy is due to a mutation of the gene for the light chain of ferritin, and is the only autosomal-dominant neurodegeneration with brain iron accumulation (NBIA) disorder [22]. Onset is at age 40 to 55 years with a variety of movement disorders, including chorea, dystonia, and parkinsonism [23, 24], and occasional cognitive impairment.

GLUT1 Deficiency

This pediatric disorder has recently been recognized to account for an increasing spectrum of neurologic deficits including chorea, mental retardation, epilepsy, and dystonia (DYT18) [25, 26•]. The movement disorders may be present at rest or seen only following prolonged exertion. Mutations of *SLC2A1* affect the glucose transporter 1, which transports glucose into the brain; thus, the diagnosis is suggested by a decreased ratio of cerebrospinal fluid: serum glucose. Patients may show improvements with a ketogenic diet, and thus recognition is important.

Fahr's Disease

"Fahr's disease" (idiopathic basal ganglia calcification) refers to a heterogeneous group of disorders defined by the radiologic finding of calcium deposition in the basal ganglia and other regions, often including the deep cerebellar nuclei. Dystonia, parkinsonism, chorea, ataxia, cognitive impairment, and behavioral changes may be seen. It is likely that several different genes may be implicated [27–29], including those for mitochondrial functions [30].

Association with Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

Chorea may be seen in patients with mutations of TDP-43, normally associated with familial amyotrophic lateral sclerosis (ALS) [31], and with familial [32] or sporadic ALS [33]. Patients with behavioral-variant frontotemporal dementia (of unknown genotype and pathology) may also develop chorea [34].

Autosomal-Recessive Choreas

Wilson's Disease

Chorea may occasionally be seen in Wilson's disease [35] but is not common as a presenting symptom. However, it is essential to exclude this treatable disorder by ophthalmological slit-lamp examination, serum ceruloplasmin, and 24-hour copper excretion.

Autosomal-Recessive Ataxias

Friedreich's ataxia is the most common inherited autosomal-recessive ataxia, usually characterized by onset during childhood and areflexia. Although deep tendon reflexes are normally lost, in some cases, they are abnormally increased, and there is spasticity with dystonic posturing. Rarely chorea can be seen, which may even be a presenting symptom prior to the development of other features [36, 37].

Ataxia-telangiectasia and ataxia with oculomotor apraxia types 1 and 2 typically present with ataxia during infancy and childhood, and may present with or develop chorea. Ataxia-telangiectasia has been reported to present in adulthood [38•]. Serum levels of α-fetoprotein, albumin, and cholesterol may be abnormal and may help guide the diagnosis. The genes responsible for these disorders are involved in DNA repair, and patients are susceptible to the effects of ionizing radiation, with increased risk of malignancy, particularly leukemia and lymphoma, and infection.

Chorea-Acanthocytosis

Chorea-acanthocytosis (ChAc) presents in young-mid adulthood with tics, behavioral changes, psychiatric disease, or subtle cognitive dysfunction. Chorea, parkinsonism, and lingual-buccal-facial dystonia, with lip and tongue biting, develop subsequently [39]. A total of 40% of patients have seizures, which may predate the appearance of the movement disorder, and are often temporal lobe in origin. Peripheral (motor) neuropathy with areflexia and muscle atrophy is typical. Dystonic tongue protrusion on eating strongly suggests this diagnosis.

Elevated creatine kinase and liver enzymes are common. Detection of acanthocytosis may be enhanced by use of a standard protocol [40], but a negative result does not exclude the diagnosis. Neuroradiologically, ChAc resembles HD.

ChAc is due to mutations of *VPS13A* localized to chromosome 9q21, which codes for chorein [41]. Absence of chorein in erythrocytes on Western blot confirms the diagnosis [42], and is available on a research basis (http://www.nefo.med.uni-muenchen.de/~adanek/Chorein_Blot.pdf). The disorder, originally known as "Levine-Critchley syndrome," has recently been confirmed to be ChAc, at least in Critchley's original Kentucky family [43].

Neurodegeneration with Brain Iron Accumulation

Abnormal brain iron accumulation in the basal ganglia is seen in an increasing number of disorders, including neuroferritinopathy (above), pantothenate-kinase–associated neurodegeneration, infantile neuroaxonal dystrophy (INAD), FA2H-associated neurodegeneration, and aceruloplasminemia. The diagnostic MRI shows the "eye-of-the-tiger," although there are differences in the different disorders. Clinically, dystonia and parkinsonism are characteristic, but occasionally chorea is reported (e.g., in a disorder that transpired to be INAD) [44].

Chorea is seen in aceruloplasminemia, due to inheritance of mutations of the gene for ceruloplasmin [45]. Neurologic signs appear in middle age, usually ataxia, followed by orofacial dystonia, parkinsonism, and chorea. Retinal degeneration and

diabetes mellitus usually precede these symptoms by about 10 years. Cognitive impairment may be present initially [46]. Symptomatic heteroplasmic carriers have been reported [46].

Other Pediatric Inherited Metabolic Disorders

There are a number of metabolic disorders in which movement disorders may be seen, typically in combination with other neurologic features. The presentation may vary with age of onset, with dystonia being more prominent at younger ages. The associated neurologic and non-neurologic features help guide the evaluation, which may involve assaying blood and urine for amino acids, lymphocytic enzymes, and/or genetic testing.

Glutaric acidura tends to present with a crisis in early infancy with generalized dystonia and encephalopathy. Less catastrophic presentations may be seen in later childhood or even adulthood. Chorea is sometimes seen [47]. The typical MRI finding is of dilation of the sylvian fissures and lesions of the putamen.

Chorea can occasionally be seen in various amino acidopathies, including propionic acidemia, due to propionic–coenzyme A carboxylase deficiency [48], 3-methylglutaconic acidemia [49], and succinic semialdehyde dehydrogenase deficiency. Atypical, mild forms of non-ketotic hyperglycinemia can cause chorea and encephalopathy in childhood or adulthood, often precipitated by febrile illness [50] or medication [51].

Pyruvate dehydrogenase deficiency typical presents in the neonatal period with hypotonia, encephalopathy, and seizures, but may present at an older age with dystonia or chorea [52]. Patients may benefit from a ketogenic diet [53].

Other occasional causes of chorea, either during childhood or adulthood, include Niemann-Pick C [54], chronic GM2 [55], and late-onset GM1 gangliosidoses, neuronal intranuclear inclusion disease, and metachromatic leukodystrophy.

X-linked Choreas

McLeod Syndrome

McLeod neuroacanthocytosis syndrome (MLS) [56] is similar in presentation to autosomal-recessive ChAc, with the additional involvement of other organ systems. It is diagnosed by decreased expression of Kell and Kx antigens on erythrocytes, known as the "McLeod phenotype," caused by mutation of the *XK* gene. The diagnosis is made at regional blood banks, which have the requisite panel of anti-Kx and anti-Kell antibodies. (A report of "Kell negative" is not adequate.)

The neurologic symptoms of MLS develop in middle-aged males [56]. Patients may be identified earlier if they undergo blood typing. Patients present initially with neuropsychiatric disease or behavioral changes, and subsequently develop chorea, dystonia, tics, and parkinsonism. As in ChAc, peripheral sensorimotor neuropathy and seizures are typical.

More important for management is cardiac involvement, which is seen in two thirds of patients, and may be a significant source of morbidity and mortality [56]. As in ChAc, liver enzymes are often elevated, as is creatine kinase, and patients may have frank myopathy [56, 57]. Acanthocytosis is typical, but not invariable. Neuroimaging shows atrophy of the caudate nucleus and putamen. Patients should bank their own blood in case of need for transfusion, to avoid the production of anti-Kell antibodies, and subsequent transfusion reactions.

Lubag

This disorder is found solely among Filipinos from the province of Capiz. Although dystonia and parkinsonism are typical, a range of movement disorders has been reported, including chorea, tremor, and myoclonus [58]. Occasionally, affected carrier females have been reported [58]. Rare non-Filipino patients have been reported to have the pathology of Lubag, which is striatal mosaic pattern gliosis [59, 60].

Lesch-Nyhan Syndrome

This disorder is due to mutation of hypoxanthine phosphoribosyltransferase, resulting in the accumulation of uric acid. It presents at 3 to 6 months with psychomotor retardation and hypotonia, with subsequent development of spasticity, dystonia, and choreoathetosis. Self-mutilation with biting of the hands and lips is a classical feature. Affected boys typically have gout.

Mitochondrial Causes of Chorea

Leigh's syndrome may be seen with various mutations of mitochondrial DNA. Onset is in early childhood, but may occasionally be in adulthood [61]. Neurologic findings may include acute encephalopathy, psychomotor retardation, hypotonia, spasticity, myopathy, dysarthria, seizures, and dystonia. Neuroimaging demonstrates lesions in the thalamus or caudate/putamen. An overlap with mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) [62] and other mitochondrial disorders [63, 64] may occur.

Medical History

Metabolic Disorders

Hemichorea can be seen acutely in patients with non-ketotic hyperglycemia. MRI demonstrates hyperintensity of

the contralateral putamen [65]. It is not known why only one side might be affected but some patients can have bilateral changes. Correction of the metabolic abnormality is normally curative, but rarely chorea may persist for months after resolution of the hyperglycemia [66]. Occasionally, if there are permanent vascular changes in the striatum, the chorea may remain for longer periods.

Disturbances of electrolytes may occasionally result in chorea, including elevated or decreased sodium, calcium, and magnesium. Chorea has also been reported following correction of hyponatremia causing central pontine myelinolysis.

Screening for thyroid disease should be performed in evaluating any new movement disorder. Hyperthyroidism has been reported to cause chorea, although it is more typically associated with an action tremor. Hypo- and hyperparathyroidism and pseudohypoparathryoidism have been associated with chorea, in some cases paroxysmal, most likely due to disturbances of calcium.

A pregnancy test should be performed in women of child-bearing age, as chorea may occasionally appear during pregnancy, known as chorea gravidarum. This occurs more often in women with a history of Sydenham's chorea or another autoimmune disorder, and may be due to be a sensitization of dopamine receptors by estrogens.

Deficiency of vitamin B_{12} is reported to cause a reversible chorea [67, 68].

Infectious and Post-Infectious

A relatively common cause of chorea in childhood is Sydenham's chorea, which occurs after a streptococcal throat infection. It is due to cross-reaction of antistreptococcal antibodies with basal ganglia neurons [69]. Cases are usually self-limited but the movements can be quite violent and bizarre and require treatment with neuroleptics or valproic acid.

New variant Creutzfeldt-Jakob disease should be considered in an adult with a time course of subacute cognitive and motor deterioration over months [70, 71]. Chorea can be seen with HIV infection, either as the result of a secondary mass lesion, such as lymphoma or abscess (eg, toxoplasmosis), or as a direct effect of HIV encephalopathy [72, 73]. In the case of focal lesions, hemichorea or hemiballiam have been reported. Syphilis has rarely been reported to cause chorea [74]. In children, striatal necrosis may occur as a complication of encephalitis from various infectious agents, including measles, mycoplasma pneumoniae, parvovirus, and herpes simplex.

Autoimmune Disorders

The basal ganglia may be vulnerable in systemic autoimmune disorders, including systemic lupus erythematosus [75, 76], Sjögren's syndrome [77], and antiphospholipid antibody syndrome [78]. In polycythemia vera, chorea may be due either to autoantibodies, or, as currently appears more likely, to hyperviscosity [79]. Although controversial, celiac disease has been associated with various possible neurologic conditions, including chorea, which may respond to a gluten-free diet (Walker, Personal observations) [80].

Paraneoplastic Disorders

Recognition of paraneoplastic neurologic syndromes is expanding as new autoantibodies are being identified; thus, it is critical to exclude cancer in any patient with a subacute or acute presentation of chorea in whom other etiologies have been excluded. Renal, small cell lung, breast, Hodgkin's and non-Hodgkin's lymphomas have been reported as causative. Antibodies detected include anti-CRMP-5/CV2 [81], anti-Hu [82] or anti-Yo [83]. A syndrome of encephalopathy and bizarre stereotyped involuntary movements, particularly cranial in distribution, has recently been ascribed to anti–*N*-methly-D-aspartate (NMDA) receptor antibodies [84•, 85], usually related to ovarian teratomas. Thorough radiological studies should be performed if this diagnosis is suspected, and in some cases exploratory surgery may be indicated.

Hepatic Disease

If there are signs of liver disease, Wilson's disease should be considered. If work-up for this is negative, McLeod syndrome or ChAc should be considered. In patients with advanced liver disease, acquired hepatocerebral degeneration may result in chorea, especially affecting the lower face.

Cardiopulmonary Surgery

Post-pump chorea may occur in children who have undergone open heart surgery on cardiopulmonary bypass. It is postulated that this phenomenon is due to microemboli or a hyperviscosity syndrome. A similar condition has been recently reported in adults [86, 87].

Medication History

The chorea most commonly seen in neurologic practice is that caused by levodopa in patients with Parkinson's disease. The term "levodopa-induced dyskinesia" refers to movements that are technically choreiform in nature, and occasionally dystonic or mixed. Although the diagnosis is not in question in these patients, this complication of dopaminergic therapy is worth mentioning because it has provided insights into mechanisms and treatment of chorea

in other conditions. Several patterns are seen, most commonly at peak dose followed by diphasic (as medication is kicking on or wearing off) or square wave (when dyskinesia is present the entire "on" time).

Tardive dyskinesia (TD) classically involves the lower face and tongue and appears following chronic use of dopamine-blocking medications. Some patients develop generalized chorea as well and 50% or more are irreversible. Often these movements are relatively well tolerated apart from cosmetic effects. Typical neuroleptics such as haloperidol, chlorpromazine, and fluphenazine are well recognized as causes. Anti-nausea medications with a dopamine-blocking mechanism, such as prochlorperazine and metoclopramide, may also be responsible. Although probably less common, TD occurs with the second-generation "atypical" antipsychotics as well. TD-like movements and generalized chorea have been reported to occur with medications with other mechanisms of action, including selective serotonin reuptake inhibitors, lithium, and anticonvulsant medications, but unlike classical TD these are always reversible with stopping the inciting agent within days to weeks. For several reasons, including the belief that atypical agents do not cause this movement disorder, TD is frequently under-recognized.

Estrogen may cause chorea, when administered either in the contraceptive pill or as hormone replacement therapy [88], presumably by the same mechanism as in chorea gravidarum. Suppression of estrogen with luteinizing hormone–releasing hormone may also result in chorea [89], however, making the explanation less clear.

Methotrexate can cause acute, reversible chorea, especially with intrathecal administration [90, 91].

Underlying structural deficits, such as in cerebral palsy and stroke, predispose patients to chorea as a medication side effect. This can be seen with medications from a variety of classes, including anticonvulsants such as gabapentin, lamotrigine, and valproic acid; antihistamines; lithium; and baclofen, especially intrathecal (eg, when used for complex regional pain syndrome) [92].

Stimulants may cause chorea, whether used therapeutically [93], or recreationally, such as amphetamine, cocaine, and specifically crack ("crack dancing") where it occurs after bingeing. Release of catecholamines is probably the mechanism of action.

Time Course

As in other neurologic diseases, the time course of symptoms can be informative, suggesting the sudden onset of a vascular lesion, a subacute onset with an expanding mass lesion or metabolic derangement, a chronic progressive course in neurodegenerative disease, or a stable course due to a medication effect or benign hereditary chorea.

A fluctuating course of chorea suggests a paroxysmal dyskinesia. Movements may be dystonic, choreiform, or a combination of both. Precipitating factors, time course, and associated neurologic features may be helpful in making the diagnosis. Most disorders are autosomal-dominantly inherited or sporadic.

Paroxysmal kinesigenic dyskinesia (PKD, paroxysmal kinesigenic dystonia, episodic kinesigenic dyskinesia 1 [EKD1], DYT10; and EKD2, DYT19) usually starts in childhood, and may be familial or sporadic. Very frequent, usually brief, episodes of limb dystonia are precipitated by exercise or other precipitants such as sudden movement, yawning, talking, or hyperventilation. Episodes often resolve with age, and a number of anticonvulsants have been reported to help. Different loci on chromosome 16 have been identified. One syndrome termed "benign infantile convulsions and paroxysmal choreoathetosis" (ICCA) is associated with seizures, suggestive of a channelopathy [94].

Paroxysmal non-kinesigenic dyskinesia (paroxysmal dystonic choreoathetosis; DYT8) also tends to start in infancy and resolve with age. Episodes of dystonic/choreic movements occur at rest, precipitated by stress, heat or cold, fatigue, fasting, caffeine, or alcohol and improved with sleep. A few episodes occur in a month, but last for several hours and are debilitating. There is often unilateral limb involvement and speech is affected. Benzodiazepines or acetazolamide may be beneficial whereas anticonvulsants are not. In some cases there is mutation of the myofibrillogenesis regulator gene 2q33 [95], an enzyme in the stress response pathway potentially involved in detoxifying alcohol and caffeine, which may explain the precipitants. However, in other families other genes appear to be causative.

Chorea may be seen during exacerbations in patients with episodic ataxia 1 [96], due to point mutations of a potassium channel gene *KCNA1* on 12p13 [97]. Acetazolamide may be helpful in these cases as well.

Paroxysmal choreoathetosis with spasticity (DYT9) results in episodes of dystonia, choreoathetosis, dysarthria, spasticity, and imbalance, following exercise, stress, alcohol consumption, or sleep deprivation.

Psychogenic chorea is uncommon relative to other movement disorders, but may be cautiously considered in a patient with episodic abnormal movements that suddenly start and stop.

Localizing Neurologic Features

The neurologic examination may be informative. This is most apparent when there is clear asymmetry of chorea and associated findings suggestive of a unilateral structural lesion. Many different types of lesions have been reported to cause chorea, including stroke, vasculitides, moyamoya

disease, cavernous angioma, arteriovenous malformation, multiple sclerosis, tumor, or abscess. I have also observed hemichorea in the setting of contralateral frontal lobe hypoperfusion, as demonstrated on single positron emission computed tomography (SPECT), in a patient with chronic occlusion of the internal carotid artery, presumably due to subsequent gradual occlusion of collateral circulation.

Although most lesions involve the basal ganglia, particularly the putamen, or the subthalamic nucleus, it is not clear why some cause chorea and others do not. Even more difficult to explain are cases associated with herniated cervical discs that responded to the appropriate surgery.

Other features of the neurologic examination may indicate a specific diagnosis. The presence of abnormal eye movements and ataxia may indicate cerebellar involvement. Peripheral neuropathy may be seen in some of inherited ataxias, and also in ChAc or McLeod syndrome.

Treatment

If possible, therapy should be directed at the underlying cause, but in general, treatment of chorea is symptomatic. Goals should be to improve function, which may or may not involve reducing the involuntary movements. For example, most Parkinson's disease patients would rather be dyskinetic than akinetic. It may be of greater importance to the patient and caregivers to address other symptoms, particularly psychiatric and behavioral in the neurodegenerative conditions. Ideally, a multidisciplinary team approach should be used, to address psychological, nutritional, communicative, motor, and psychiatric issues in a cohesive, goal-oriented, manner.

A variety of pharmacologic approaches has been used with positive outcomes, indicating the potential pathophysiologic complexity of chorea. Decreasing dopamine neurotransmission is a major therapeutic mechanism, and may be achieved through postsynaptic blockade, ideally with atypical neuroleptics, or with presynaptic depletion, using tetrabenazine or reserpine. With these agents care should be taken to monitor for the side effects of depression, parkinsonism, and akathisia. Glutamate NMDA receptor antagonists, such as amantadine, may be helpful in HD, presumably through a similar mechanism of action to that in levodopa-induced dyskinesias in Parkinson's disease. Anticonvulsants may be tried, particularly levetiracetam, valproic acid, and carbamazepine. The mechanism of action of these agents in chorea is unclear.

A small number of reported cases, mainly HD and TD, have undergone surgical therapies, specifically deep brain stimulation or ablative procedures, with mixed outcomes [98, 99]. The customary target is the internal segment of the globus pallidus; however, the subthalamic nucleus and the motor thalamic nuclei have also been targeted. Risks and benefits of these procedures in disorders with progressive neurodegeneration should be carefully weighed; however, this may be an appropriate option for nonprogressive disorders [100]. Neural cell transplantation for HD has shown some limited benefits, and may still be promising, but has not been as dramatically therapeutic as was initially hoped [101, 102].

Conclusions

The family, medical, and medication history, and the neurologic examination may suggest the underlying cause in the patient with chorea. Basic laboratory and neuroimaging evaluation can identify some causes, and should exclude potentially treatable or reversible etiologies. Despite extensive testing, a significant proportion of patients remain undiagnosed. The best treatment at this time remains dopamine depleters and receptor blockers.

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