Seminar on choreas

Francisco Cardoso, Klaus Seppi, Katherina J Mair, Gregor K Wenning, Werner Poewe

Chorea is one of the major types of involuntary movement disorders originating from dysfunctional neuronal networks interconnecting the basal ganglia and frontal cortical motor areas. The syndrome is characterised by a continuous flow of random, brief, involuntary muscle contractions and can result from a wide variety of causes. Diagnostic work-up can be straightforward in patients with a positive family history of Huntington's disease or acute-onset hemichorea in patients with lacunar stroke, but it can be a challenging and complex task in rare autoimmune or genetic choreas. Principles of management focus on establishing an aetiological classification and, if possible, removal of the cause. Preventive strategies may be possible in Huntington's disease where genetic counselling plays a major part. In this review we summarise the current understanding of the neuroanatomy and pathophysiology of chorea, its major aetiological classes, and principles of diagnostic work-up and management.

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Neurology Service, The Federal University of Minas Gerais, Brazil (F Cardoso MD); **and Department of Neurology, Innsbruck Medical University, Austria** (K Seppi MD, K J Mair MD, G K Wenning MD, W Poewe MD)

Correspondence to:
Prof Werner Poewe, Department of Neurology, Innsbruck Medical University, Anichstrasse 35, A-6020 Innsbruck, Austria
werner.poewe@uibk.ac.at

Introduction

The term "chorea" entered medical writings through descriptions of religiously inspired outbreaks of mass hysteria in the middle ages—coincident with outbreaks of the plague in central Europe—when pilgrims engaged in ecstatic jumping or dancing movements for hours on end to the point of delirium and exhaustion.[1] These rituals were associated with various saints the worshippers called on, of whom Saint Vitus became the most widely known, and "Saint Vitus Dance" persisted as a synonymous term for chorea in 20th century textbooks of neurology. Paracelsus was probably the first to make a distinction between "chorea naturalis" (a true organic medical disorder) and non-organic forms, which he classified into "chorea imaginativa" and "chorea lasciva".[2] Thomas Sydenham further developed the concept of organic causes of chorea in the late 17th century with his description of childhood chorea.[3] The association between Sydenham's chorea, rheumatic fever, and endocarditis, however, was not appreciated before the 19th century, by which time there was also clear recognition of hereditary chorea through the concise report by George Huntington on affected families in the state of New York.[4] Today, chorea is recognised as one of the major categories of movement disorders caused by dysfunctional neuronal networks connecting the basal ganglia and motor cortical areas. Choreas can be associated with a plethora of different causes.

Definition and clinical phenotype

Chorea is defined as a syndrome characterised by abrupt involuntary movements resulting from a continuous flow of random muscle contractions. The pattern of movement can sometimes seem playful and convey a feeling of restlessness to the observer. When choreic movements are more severe, assuming a flinging, sometimes violent, character, they are called ballism. Regardless of its cause, chorea has the same features. The differential diagnosis of choreic syndromes relies not so much on differences in the phenomenology of the hyperkinesia but the presence of accompanying findings.

The unpredictable nature of chorea is a feature that distinguishes it from tremor and dystonia. Chorea is characterised by rhythmic and oscillatory movements of body parts, whereas the hallmark of dystonia is the presence of sustained muscular contractions resulting in abnormal postures or torsion movements. Stereotypies are also caused by repetitive contractions but, unlike chorea, the resulting movements mimic complex motor behaviours that are part of the normal human repertoire. Tics can be readily differentiated from chorea because they also reproduce normal human movements or vocalisations, are commonly preceded by a local unpleasant sensation (sensory tic or prodrome), and can be voluntarily suppressed. Myoclonic jerks are brief (<200 ms) shock-like muscular contractions that lack the continuous random flow of movement typical of chorea.

Neuroanatomy and neurophysiology of chorea

Chorea results from dysfunction within a complex neuronal network interconnecting motor cortical areas and a group of subcortical nuclei collectively termed the basal ganglia. The latter include the caudate nucleus, putamen, external and internal segments of the globus pallidus (GPe and GPi) as well as associated structures such as the subthalamic nucleus and the substantia nigra (figure 1).

Over the past 15 years, there has been substantial progress in understanding how these corticosubcortical motor circuits facilitate voluntary movements and stop unwanted movements through parallel pathways that modulate thalamocortical motor projections.

The model of motor loops between the basal ganglia, thalamus, and motor cortical areas summarised in figure 2 was developed from primate studies.[5,6] According to this model, GABAergic projections from GPi modulate activity of the motor nuclei of the thalamus, which facilitate movement through excitatory glutamatergic projections to cortical motor areas (including the premotor cortex and supplementary motor area). Activity in the GPi itself is modulated by a dual set of striatopallidal GABAergic projections, which have been termed the "direct" and "indirect" pathways because one is a single neuron direct projection to the GPi and the other runs through synaptic stations in the GPe and subthalamic nucleus. Activation of the direct striatopallidal pathway

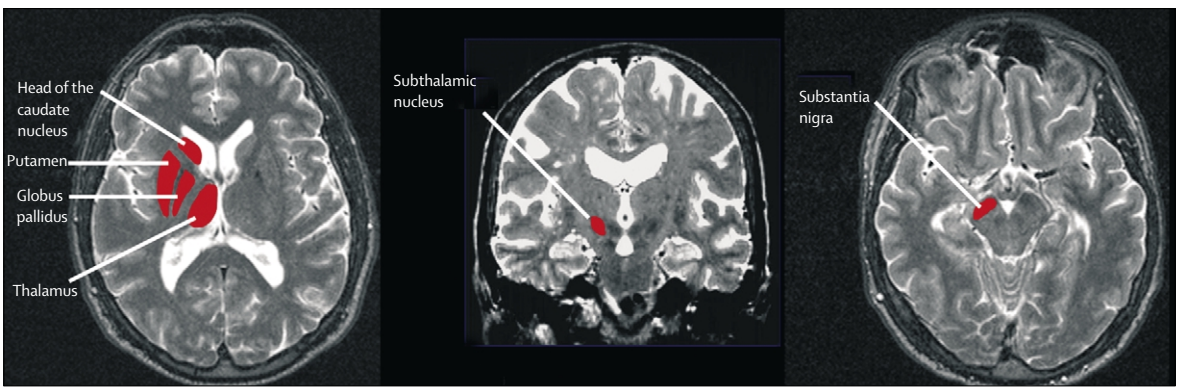

Figure 1: **MRI of basal ganglia**
MRI localisation of anatomic structures constituting the basal ganglia (left). The globus pallidus is reciprocally connected with the subthalamic nucleus of the diencephalon (middle) and putaminal activity is modulated by dopaminergic projections from the substantia nigra (right).

leads to GPi inhibition and thus thalamocortical motor facilitation, whereas increased activity in the indirect pathway results in GPi excitation and resultant thalamocortical motor inhibition. Therefore modulation of GABAergic inhibitory projections from the GPi to the motor thalamus via different states of activity in striato-pallidal projections can ease voluntary movements while suppressing unwanted motor activity, thereby focusing desired motor patterns (figure 2). Diverse types of chorea with different causes, such as Huntington's disease, levodopa-induced chorea in Parkinson's disease, or hemichorea after lesions of the subthalamic nucleus, could all be explained by deficient GPi inhibitory input to the motor thalamus resulting in excessive thalamocortical motor facilitation. However, there are inconsistencies between the model and clinical evidence, including the abolition of drug-induced chorea in Parkinson's disease through ablation of the GPi (pallidotomy), which, according to the model, should lead to increased excitatory thalamocortical drive and thus worsen chorea. Current views therefore maintain that more complex changes in the temporal and spatial firing pattern of the GPi underlie hyperkinetic movement disorders such as chorea.[7–9]

Aetiological classification of choreas

The neurophysiological imbalance causing chorea can result from many diverse causes including infections, autoimmune disease, genetic mutations, neurodegeneration, stroke, neoplasms, drug-exposure, and metabolic diseases (panel 1).

Huntingtons's disease

Huntington's disease is an autosomal-dominant progressive neurodegenerative disorder typically characterised by chorea, cognitive decline, and behavioural changes leading to relentlessly increasing disability and ultimately death. Neurodegeneration in Huntington's disease most prominently affects the striatum with loss of medium-sized spiny neurons and large neurons in layers III, IV, and V predominantly of the frontal cortex. The cytopathological hallmarks of Huntington's disease are intranuclear inclusions, consisting of amyloid-like fibrils that contain mutant huntingtin, ubiquitin, synuclein, and other proteins.[10–12]

The prevalence of Huntington's disease in European and North American studies is between three and seven people per 100 000, whereas annual incidence is between two and seven per 1 000 000 people.[13–18] Huntington's disease is caused by a trinucleotide (CAG) repeat expansion in the gene encoding huntingtin on chromosome 4p16.3; the exact function of normal huntingtin is still unknown, and it is widely expressed in the human brain.[19,20] The mutant protein forms nuclear aggregates but how this leads to neurodegeneration is unclear. Healthy individuals typically have fewer than 35 CAG repeats, and repeats of 40 or above cause Huntington's disease with complete penetrance. Individuals with 36–39 CAG repeats can also develop Huntington's disease but penetrance is incomplete.[21] A range of 27–35 CAG repeats is considered normal, but there is particular risk for expansion into the Huntington's disease range in the paternal germline.[22,23]

Carriers of the mutated Huntington's disease gene typically first develop symptoms during their mid thirties or forties, but age of onset for Huntington's disease varies from early childhood to seventies and eighties. Onset of Huntington's disease before age 20 years (Westphal variant) is strongly associated with very high CAG repeat lengths in the mutated Huntington's disease gene (>55), whereas the association between CAG repeat length and age of onset in the range 40–50 repeats is weak.[24,25]

Although chorea is the prototypical movement disorder in Huntington's disease and onset is typically present with middle age or elderly onset, the full spectrum of motor impairment in Huntington's disease includes eye-movement abnormalities, parkinsonian features and dystonia (particularly in juvenile Huntington's disease), myoclonus, tics, ataxia, dysarthria and dysphagia, spasticity with hyperreflexia as well as extensor plantar

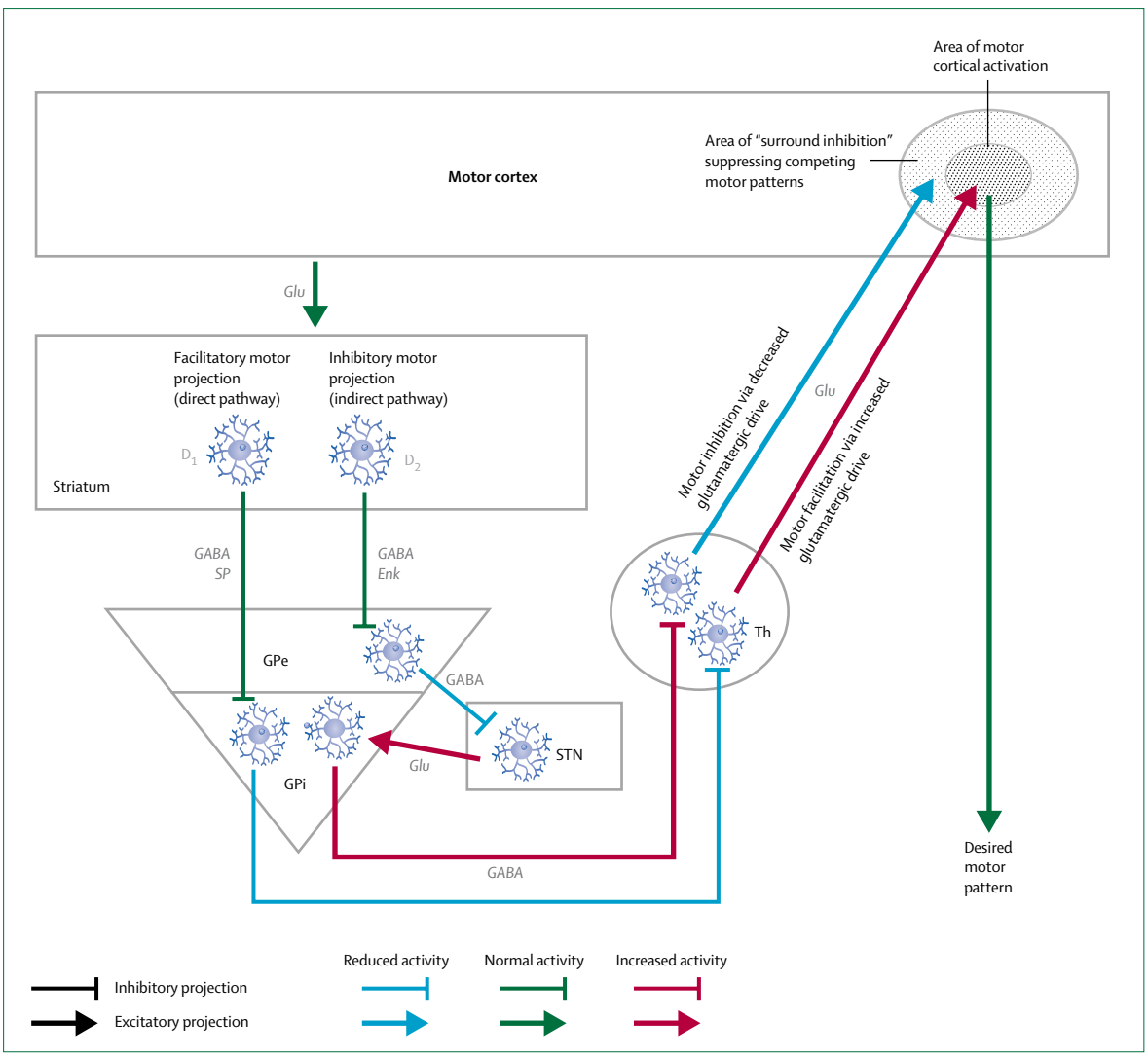

Figure 2: **Striatopallidothalamic output pathways facilitating (via direct pathway) or inhibiting (via indirect pathway) cortical motor activity**
Modulation is achieved by different activity levels of GABAergic inhibitory projections of the GPi to the motor nuclei of the thalamus. Different types of dysfunction in the striatopallidothalamic outflow system characterise aetiologically diverse types of chorea and result in net motor cortical disinhibition through a common final pathway. Degeneration of striatal indirect pathway neurons in Huntington's disease, overstimulation of the direct pathway striatal neurons in levodopa-induced dyskinesias of Parkinson's disease, or subthalamic nucleus lesions in vascular hemichorea ot hemiballism, all lead to increased thalamocortical motor drive with resultant increase of motor cortical activation producing chorea. Glu=glutamate; SP=substance p; Enk=enkephalin; STN=subthalamic nucleus; Th=thalamus.

responses.[26–30] With progressing illness, chorea is commonly superseded by dystonia or akinetorigid parkinsonian features.

Behavioural and cognitive impairment is universal in Huntington's disease and can occasionally precede motor symptoms. Depression is common and leads to high suicide rates in Huntington's disease; symptoms typically include anxiety or panic attacks. The spectrum of behavioural abnormalities in Huntington's disease is broad and includes obsessive compulsive symptoms, manic features, psychosis, irritability and aggressive behaviour, sexual disinhibition, and apathy.[31–37] Patients with Huntington's disease typically have cognitive decline, mental slowing, impaired problem-solving abilities, other signs of a frontal dysexecutive syndrome, and eventually develop dementia.[38–40]

Huntington's disease is relentlessly progressive with death 15–20 years after symptom onset, with particularly rapid progression in the juvenile Westphal variant. End-stage patients with Huntington's disease are typically rigid and akinetic, have dementia, and are mute. Immobility and dysphagia commonly lead to aspiration pneumonia, the most common cause of death in this illness.[41–43]

To date, there is no effective treatment to modify the relentlessly progressive course of Huntington's disease. Symptomatic treatment of chorea is needed when it causes functional disability or social embarrassment.[41]

Panel 1: **Aetiological classification of choreic syndromes**

Genetic choreas
Huntington's disease
Huntington's disease-like 2 and other HD-like syndromes
Dentatorubropallidoluysian atrophy
Neuroacanthocytosis
Ataxia teleangiectasia
Benign hereditary chorea
Spinocerebellar ataxia (types 2, 3, or 17)
Paroxysmal kinesigenic choreoathetosis

Structural basal-ganglia lesions
Vascular chorea in stroke
Mass lesions (eg, CNS lymphoma, metastatic brain tumours)
Multiple sclerosis plaques
Extrapontine myelinolysis

Parainfectious and autoimmune disorders
Sydenham's chorea
Systemic lupus erythematosus
Chorea gravidarum
Antiphospholipid antibody syndrome
Postinfectious or postvaccinal encephalitis
Paraneoplastic choreas

Infectious chorea
HIV encephalopathy
Toxoplasmosis
Cysticercosis
Diphtheria
Bacterial endocarditis
Neurosyphilis
Scarlet fever
Viral encephalitis (mumps, measles, varicella)

Metabolic or toxic encephalopathies
Acute intermittent porphyria
Hypo/hypernatraemia
Hypocalcaemia
Hyperthyroidism
Hypoparathyroidism
Hepatic/renal failure
Carbon monoxide poisoning
Manganese poisoning
Mercury poisoning
Organophosphate poisoning

Drug-induced chorea (see panel 2)

Atypical antipsychotics such as olanzapine, quetiapine, or risperidone may sufficiently and, at least transiently, reduce choreic movements but are generally less potent than typical neuroleptics. The benefit of these drugs has to be weighed against potential induction of parkinsonism or worsening of rigidity, postural instability, or dysphagia.[20,41,44] Mild to moderate chorea in Huntington's disease can also respond to tetrabenazine, a presynaptic dopamine depletor with weak D2-receptor blocking action, or glutamate antagonists such as amantadine or riluzole.[45–48] Atypical neuroleptics can also be useful in the management of emotional irritability, aggressiveness, and other forms of erratic behaviour.[35,37] Depression may respond to classical antidepressants like selective serotonin reuptake inhibitors or antimuscarinic drugs or to newer antidepressants such as mirtazapine, reboxetine, or venlafaxine, but there are no formal trial data to assess the relative efficacy and safety of these drugs in Huntington's disease.[37] Occasional reports have claimed mild beneficial effects of cholinesterase-inhibitor treatment to reduce cognitive dysfunction in Huntington's disease but there are no adequate studies to support their use.[49,50]

Other genetic choreas

Up to 7% of patients with otherwise typical features of Huntington's disease do not have the huntington gene mutation.[51,52] Such Huntington's disease-like disorders are genetically heterogeneous and include some autosomal dominant heredoataxias, Huntington's disease-like 2 (HDL2), benign hereditary chorea, the neuroacanthocytosis syndromes chorea-acanthocytosis, and McLeod syndrome (table).[12,52–65] HDL2, caused by mutations in the gene encoding junctophilin-3, bears striking resemblance to Huntington's disease. Although generally rare, the prevalence of HDL2 seems to be higher among individuals of African ancestry (table).[56,66]

The clinical variety of inherited prion diseases also includes a Huntington's disease-like phenotype (HDL1) where a 192-nucleotide is inserted in the region of *PRNP* encoding an octapeptide repeat in the prion protein.[67,68] Other mutations cause very rare disorders including HDL3, HDL4, or ferritin-associated basal ganglia disease.[69]

Some types of spinocerebellar ataxia (types 2, 3, or 17), which can rarely present with prominent choreic movement disorders, in particular types 3 and 17, may produce notable clinical similarities to Huntington's disease.[20,70,71] The same is true for dentatorubro-pallidoluysian atrophy, another CAG repeat disease with mutations of the gene encoding the atrophin-1 protein located on chromosome 12p.[71,72]

Other rare causes for genetic chorea such as autosomal recessive cerebellar ataxias with oculomotor apraxia including ataxia telangiectasia, ataxia-telangiectasia-like disorders, and ataxia with oculomotor apraxia types 1 and 2, Wilson's disease, paroxysmal kinesigenic choreoathetosis, infantile convulsions and paroxysmal choreoathetosis, or pantothenate-kinase-associated neurodegeneration are briefly summarised in the table .[55,61,64,73]

Sydenham's chorea

Sydenham's chorea, the neurological manifestation of rheumatic fever, is the prototype of chorea resulting from

	Mode of inheritance	Gene, location	Protein product	Usual age at onset (years)	Clinical signs
HDL2[56]	AD*	JPH3,16q	Junctophilin-3	20–40	Huntington's disease phenotype, sometimes acanthocytosis; almost exclusively African ethnicity
SCA17[53]	AD*	TBP,6q	TBP	10–30	Cerebellar ataxia, chorea, dystonia, hyper-reflexia, cognitive decline
DRPLA[57]	AD*	DRPLA,12p	Atrophin-1	About 20	Variable phenotypic picture including chorea, ataxia, seizures, psychiatric disturbances, dementia; more common in Japan than in Europe or USA
SCA3/MJD[58]	AD*	MJD,14q	Ataxin-3	35–40	Wide phenotypic variability with cerebellar ataxia, protruded eyes, chorea, dystonia, parkinsonian features, neuropathy, pyramidal tract features
SCA2[58]	AD*	Ataxin-2,12q	Ataxin-2	30–35	Cerebellar ataxia, chorea, markedly reduced velocity of saccadic eye movements, hyporeflexia
Chorea-acanthocytosis[59]	AR	VPS13A (formerly CHAC),9q	Chorein	20–50	Orofacial self-mutilation, dystonia, neuropathy, myopathy, seizures, acanthocytosis
McLeod syndrome[59]	X-linked, recessive	XK,Xp	XK-protein	40–70	Dystonia, neuropathy, myopathy, cardiomyopathy, seizures, acanthocytosis, raised creatine kinase, weak expression of Kell antigen
Neuroferritinopathy[60]	AD	FTL,19q	FTL	20–55	Chorea, dystonia, parkinsonian features; usually reduced serum ferritin; MR abnormalities with cyst formation and increased T2 signal in globus pallidus and putamen
AT and ATLD[61]	AR	ATM,11q (AT) MRE11,11q (ATLD)	ATM (AT) MRE 11 (ATLD)	Childhood	Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea, dystonia, and myoclonus. In AT: oculocutaneous telangiectasias; predisposition to malignancies, IgA and IgG deficiency, high alpha fetoprotein in serum and high concentrations of carcinoembryogenic antigen
AOA 1 and 2[61]	AR	APTX,9p (AOA 1) SETX,9q (AOA 2)	Aprataxin (AOA 1) Senataxin (AOA 2)	Childhood or adolescence (later onset in AOA 2)	Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea and dystonia; ataxia with oculomotorapraxia type 1: hypoalbuminaemia and hypercholesterolaemia; ataxia with oculomotorapraxia type 2: raised alpha fetoprotein in serum
Pantothenate kinase associated neurodegeneration (formerly Hallervorden-Spatz syndrome)[59]	AR	PANK2,20p	Pantothenate kinase 2	Childhood, but also adult-onset subtype	Chorea, dystonia, parkinsonian features, pyramidal tract features; MR abnormalities with decreased T2 signal in the globus pallidus and substantia nigra, "eye of the tiger" sign (hyperintense area within the hypointense area); sometimes acanthocytosis, abnormal cytosomes in lymphocytes
Lesch-Nyhan disease[62]	X-linked, recessive	HPRT,Xq	Hypoxanthine-guanine phosphoribosyl-transferase	Childhood	Chorea, dystonia, hypotonia, self-injurious behaviour with biting of fingers and lips, mental retardation; short stature, renal calculi, hyperuricaemia
Wilson's disease[63]	AR	ATP7B,13q	Copper transporting P-type ATPase	<40	Parkinsonian features, dystonia, tremor, rarely chorea, behavioural and cognitive change, corneal Kayser-Fleischer rings, liver disease
PKC syndrome and ICCA syndrome[64]	AD	Unknown,16p	Unknown	<1–40	Paroxysmal movement disorders presenting with recurrent brief episodes of abnormal involuntary movements with dramatic response to low dose carbamazepine (PKC); recurrent brief episodes of abnormal involuntary movements in association with infantile convulsions (ICCA)
Benign hereditary chorea[65]	AD	TITF-1,14q; other	Thyroid transcription factor 1	Childhood	Chorea, mild ataxia; genetically heterogeneous

HDL1, HDL3, and HDL4 are very rare conditions (only one family known) and therefore not included in the table. *Disorders based on expanded CAG repeats (HDL2 based on CAG/CTG repeats; SCA 17 based on CAG/CAA repeats); age of symptom onset inversely related to repeat size. SCA=spinocerebellar ataxia (types 2, 3, or 17); DRPLA=dentatorubropallidoluysian atrophy; MJD=Machado-Joseph disease; AT=ataxia telangiectasia; ATLD=ataxia telangiectasia like disorder; AOA=ataxia with oculomotor apraxia (types 1 or 2); PKC=paroxysmal kinesigenic choreoathetosis; ICCA=infantile convulsions and paroxysmal choreoathetosis syndrome; AD=autosomal dominant; AR=autosomal recessive

Table: **Genetic choreas**

immune mechanisms. Chorea occurs in 26% of patients with rheumatic fever.[74] Although now largely confined to areas outside North America and western Europe, Sydenham's chorea is still the most common cause of acute chorea in children worldwide and recent outbreaks of rheumatic fever with chorea have been reported in the USA and Australia.[75,76]

The typical age at onset of Sydenham's chorea is 8–9 years, although there are reports of patients developing chorea in their third decade. In most studies there is a female preponderance.[74] One important clinical finding is that Sydenham's chorea is very rarely seen below age 5 years.[77] Typically, patients develop this disease 4–8 weeks after an episode of group-A β-haemolytic streptococcal (GABHS) pharyngitis. Sydenham's chorea rapidly becomes generalised, but 20% of patients remain with hemichorea.[74,78] Muscular tone is typically decreased; and in less than 2% of cases this may cause patients to become bedridden (chorea paralytica). Patients with Sydenham's chorea commonly display other motor findings including motor impersistence and rarely tics, which can, however, be difficult to distinguish from chorea. Behavioural abnormalities are common in Sydenham's chorea and a

Panel 2: Drugs that can induce chorea

Dopamine receptor blocking agents
Phenothiazines
Butyrophenones
Benzamides

Antiparkinsonian drugs
L-dopa
Dopamine agonists
Anticholinergics

Antiepileptic drugs
Phenytoin
Carbamazepine
Valproic acid

Psychostimulants
Amphetamines
Pemoline
Cocaine

Calcium-channel blockers
Cinnarizine
Flunarizine
Verapamil

Others
Lithium
Baclofen
Digoxin
Tricyclic antidepressants
Ciclosporine
Steroids/oral contraceptives
Theophylline

recent study found obsessive-compulsive behaviour, obsessive-compulsive disorder, and attention-deficit and hyperactivity disorder in 20–30% of patients.[79]

Most patients with Sydenham's chorea have other symptoms of rheumatic fever: 60–80% of patients have cardiac involvement, particularly mitral-valve dysfunction, whereas arthritis is present in 30% of patients; however, in about 20% of patients, chorea is the only finding.[74]

The pathogenesis of Sydenham's chorea may be related to molecular mimicry between streptococcal and CNS antigens. GABHS infection leads to the formation of cross-reactive anti-basal-ganglia antibodies in genetically predisposed patients. Several studies have shown the presence of such circulating antibodies in 50–90% of patients with Sydenham's chorea.[80,81] However, the biological significance of these antibodies remains to be determined but two recent studies suggest that they may interfere with neuronal function.[82,83]

Sydenham's chorea is commonly a self-limited disorder, with spontaneous remission after a course of 8–9 months. However, prospective studies have shown that up to 50% of patients may have persistent chorea after a follow-up of 2 years and recurrences of Sydenham's chorea are also reported in up to 50% of patients.[84]

The most important consideration in the treatment of patients with Sydenham's chorea is secondary prophylaxis with penicillin or sulfa drugs for those who have a penicillin allergy, up to age 21 years. There are no controlled studies of symptomatic treatment of Sydenham's chorea. For most specialists, however, the first treatment choice for chorea is valproic acid although other anticonvulsants, such as carbamazepine, are also effective and well tolerated.[85,86] Dopamine-receptor blocking drugs, usually pimozide, are left for patients who do not respond to valproic acid or those rare cases with chorea paralytica; since dopamine-receptor blocking drugs can induce parkinsonism, dystonia, or both.[87]

Steroids are reserved for patients with persistent disabling chorea refractory to antichoreic drugs.[88] There are few reports describing the usefulness of plasma exchange or intravenous immunoglobulin in Sydenham's chorea.[89] Because of the efficacy of other drugs, potential complications, and high cost, these options are usually not recommended.

Other autoimmune choreas

Other immunological causes of chorea are systemic lupus erythematosus, primary antiphospholipid antibody syndrome, vasculitis, and paraneoplastic syndromes (panel 1). Systemic lupus erythematosus or primary antiphospholipid antibody syndromes are classically described as the prototypes of autoimmune choreas.[90] However, several reports show that chorea is reported in no more than 1–2% of large groups of patients with these disorders.[91,92] Autoimmune chorea has rarely been reported in the context of paraneoplastic syndromes associated with anti-Hu and anti-CRMP5 antibodies in patients with small-cell lung carcinoma.[93,94]

Infectious choreas

Sydenham's chorea could be regarded as a form of infectious chorea because it is induced by GABHS; however, in a strict sense the term is limited to instances where chorea results from injury to the brain directly produced by a microorganism (panel 1). HIV and its complications are the most commonly reported infectious cause of chorea. In one study of 42 consecutive patients with non-genetic chorea, AIDS was the cause in 12% of the patients.[95] In HIV positive patients, chorea is the result of either direct action of the virus, other mechanisms such as opportunistic infections (toxoplasmosis, syphilis, and others), or drugs.[96] Other infections associated with chorea are new variant Creutzfeldt-Jakob disease and tuberculosis.[97,98]

Drug-induced choreas

Chorea might result from the use of various drugs, and drug-induced chorea is probably the most commonly

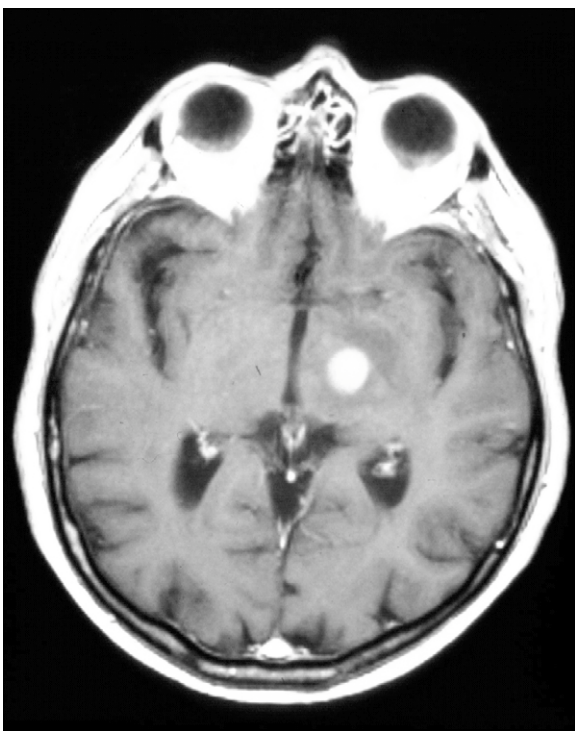

Figure 3: **MRI showing primary CNS lymphoma involving the basal ganglia**
This patient initially presented with contralateral hemichorea.

encountered type of chorea in neurological practice and in the community (panel 2).[99] Certain drugs seem to require pre-existing basal ganglia dysfunction, whereas others seem to be more universally choreogenic. Examples of the former are oral contraceptives,[100] which are particularly likely to induce chorea in patients with previous choreic episodes—such as Sydenham's chorea, chorea with systemic lupus erythematosus, or chorea gravidarum—[101]and levodopa,[102] which only induces chorea in patients with Parkinson's disease or other parkinsonian disorders. Dopamine antagonists, on the other hand, induce dyskinesias without a pre-existing basal ganglia abnormality.

The buccolinguomasticatory syndrome characterised by repetitive movements of tongue twisting and protusion, lip smacking and chewing, is the most common type of neuroleptic-induced tardive dyskinesia in elderly people. Patients with severe tardive dyskinesia and schizophrenia may have additional choreoathetoid movements of the trunk and extremities, which more closely resemble classic choreic syndromes like Huntington's disease.[103] Movements may improve after drug withdrawal but may also persist or worsen with time. The underlying pathophysiology of drug-induced choreas is unknown and may include postsynaptic dopamine hypersensitivity or striatal neuroplastic changes.[104–106]

Levodopa-induced chorea develops in more than 40% of patients with Parkinson's disease depending on age and duration and dose of levodopa treatment.[102,106] Pulsatile stimulation of postsynaptic dopamine receptors due to the short half-life of orally given levodopa is thought to induce changes in striatal connectivity generating chorea.[102] However, non-dopaminergic pathways such as the striatal opiate and adenosine projections are also involved.[107]

Furthermore, various other drugs have been associated with chorea in retrospective studies or anecdotal case reports (panel 2). These include tricyclic antidepressants and the selective serotonin reuptake inhibitors.[108–110] Phenytoin can also induce involuntary movements including orofacial chorea, particularly in association with the use of other antiepileptic drugs.[111] There are occasional reports of choreic dyskinesias induced by other antiepileptic drugs, such as carbamazepine[112] and more recently lamotrigine.[113] Chronic exposure to amphetamines and other stimulants may induce orofacial dyskinesias and choreic movements of the trunk and extremities.[114,115] The underlying pathophysiology of amphetamine-induced (or other stimulant-induced) dyskinesias is probably associated with hypersensitivity of postsynaptic dopamine receptors.[115]

Vascular choreas

A study in a tertiary referral centre showed that cerebrovascular disease was the most common cause of non-genetic chorea, accounting for 21 of 42 cases.[95] Conversely, chorea is a rare complication of acute vascular lesions, reported in less than 1% of patients with acute stroke. Vascular hemichorea or hemiballism is typically associated with ischaemic or haemorrhagic lesions of the basal ganglia and adjacent white matter in the territory of the middle or the posterior cerebral artery. By contrast with classical textbook concepts of hemiballism, most patients with vascular chorea have lesions outside the subthalamus.[116] Although spontaneous remission is the rule, treatment with antichoreic drugs such as neuroleptics or dopamine depletors may be necessary in the acute phase. A few patients with vascular chorea might have a persistent movement disorder; in these circumstances, patients can be effectively treated with stereotactic surgery such as thalamotomy or posteroventral pallidotomy.[117,118]

An uncommon cause of chorea is moyamoya disease, an intracranial vasculopathy that presents with an ischaemic lesion or, less commonly, haemorrhagic stroke of the basal ganglia.[119] Another rare form of vascular chorea is post-pump chorea, a complication of extracorporeal circulation. The pathogenesis of this movement disorder is thought to be associated with vascular insult of the basal ganglia during the surgical procedure. The natural history of post-pump chorea is benign with spontaneous remission in most cases.[120]

Chorea in neoplastic brain disease

Focal choreic limb movements or hemichorea can be a rare presenting symptom of primary or secondary brain

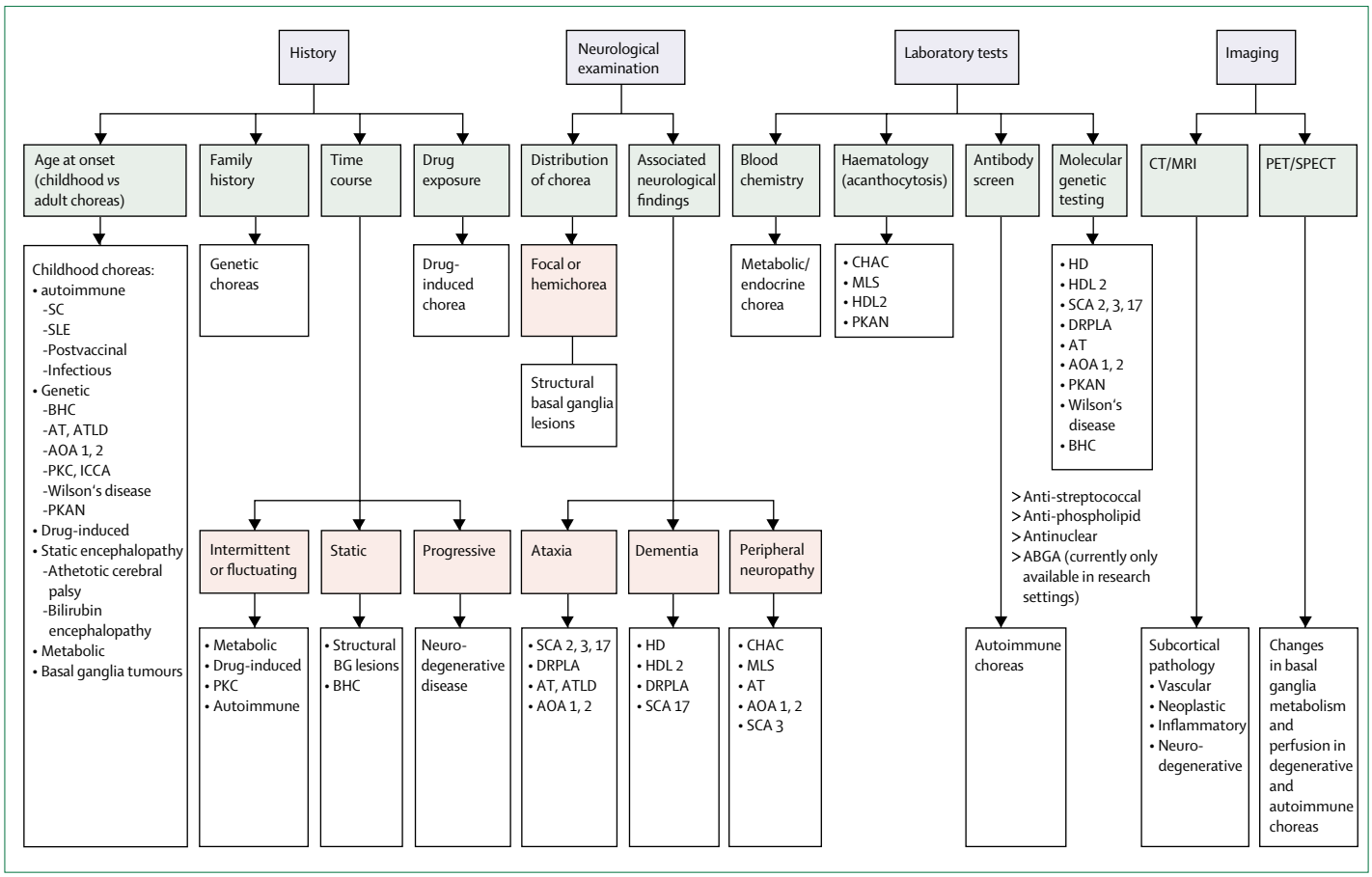

Figure 4: **Diagnostic work-up of chorea**
HD=Huntington's disease; SC=Sydenham's chorea; SLE=systemic lupus erythematosus; BHC=benign hereditary chorea; AT=ataxia teleangiectasia; ATLD=ataxia teleangiectasia like disorder; AOA=ataxia with oculomotor apraxia (types 1 or 2); PKC=paroxysmal kinesigenic choreoathetosis; ICCA=infantile convulsions and choreoathetosis; PKAN=pantothenate kinase-associated neurodegeneration; BHC=benign heriditary chorea; SCA=spinocerebellar ataxia (types 2, 3, or 17); DRPLA=dentatorubropallidoluysian atrophy; CHAC=chorea-acanthocytosis; MLS=McLeod syndrome; ABGA=anti-basal ganglia antibodies

neoplasms involving the basal ganglia, subthalamic nucleus, or adjacent areas. This type of presentation has been described most often for primary CNS lymphoma[121] (figure 3) but can occur with any type of subcortical tumour disrupting striatopallidothalamocortical motor circuitry. Therefore brain imaging is mandatory in any new-onset focal or hemichoreic syndrome.

Chorea in metabolic and toxic encephalopathy

Chronic acquired hepatolenticular degeneration was the first well-characterised metabolic cause of chorea. Originally described in the context of alcoholic hepatopathy, it can occur in any form of acquired liver disease. The clinical picture is heterogeneous, because patients may present with a variable combination of neurological and hepatic symptoms. Most patients have a combination of different movement disorders, but a few present with isolated chorea. MRI of the brain shows not only images compatible with cavitations in the basal ganglia (hyperintense signal on T2 and hypointense on T1) but also hyperintense T1 signal in the pallidum, putamen, and upper brainstem. The latter is thought to be caused by deposition of manganese.[122]

More recently, there is growing interest in the association of chorea and non-ketotic hyperglycaemia in type II diabetes mellitus; a disorder particularly common among patients of Asian or ethnic background. Unlike the usual neurological symptoms of non-ketotic hyperglycaemia, patients do not have change in the level of consciousness but develop unilateral or generalised chorea-ballism. The MRI findings are characteristic with hyperintense signal of the pallidum on T1 possibly indicating microhaemorrhages of the pallidum. Once glycaemic control is achieved, there is gradual remission of chorea.[123,124]

A few patients with hyperthyroidism develop generalised chorea or even ballism associated with this endocrine dysfunction. The lack of structural changes in the brain, appearance with onset of thyrotoxicosis, and remission with endocrine control suggest that the basal ganglia dysfunction is induced by hormones.[125] Other rare possible metabolic causes

of chorea include hypoglycaemia, renal failure, and a ketogenic diet.[97]

Diagnostic work-up

Clinical differential diagnosis is guided by age at onset, family and drug histories, associated non-choreic symptoms, course of illness, and ancillary tests (figure 4).

History

Age at onset

Chorea with onset in childhood has a somewhat different diagnostic spectrum from adult-onset cases. Further work-up in children and adolescents should consider autoimmune choreas like Sydenham's chorea and systemic lupus erythematosus,[74] infectious chorea associated with viral or postvaccination encephalitis, metabolic disorders (panel 1), drug exposure (panel 2), static encephalopathies such as athetotic cerebral palsy or bilirubin encephalopathy, or rarely tumours involving the basal ganglia.[126,127] Some rarer genetic forms of chorea typically present in childhood or adolescence including benign hereditary chorea, paroxysmal kinesigenic choreoathetosis, infantile convulsions and paroxysmal choreoathetosis, ataxia with oculomotor apraxia, ataxia telangiectasia, Wilson's disease, or pantothenate-kinase-associated neurodegeneration, whereas juvenile Huntington's disease is typically non-choreic[126,128] (table and figure 4).

Family history

Patients with a family history should be tested for genetic choreas with routinely available molecular genetic tests for Huntington's disease, HDL2, dentatorubropallidoluysian atrophy, spinocerebellar ataxia (types 2, 3, and 17), ataxia telangiectasia, ataxia with oculomotor apraxia (types 1 and 2), pantothenate-kinase-associated neurodegeneration, Wilson's disease, and benign hereditary chorea. Other molecular tests for other genetic choreas are only available for research and these include chorea-acanthocytosis, McLeod syndrome, neuroferritinopathy, inherited prion diseases, paroxysmal kinesigenic choreoathetosis, infantile convulsion and paroxysmal choreoathetosis, and ataxia telangiectasia-like disorders.

A typical clinical picture and a family history consistent with autosomal dominant transmission suggest Huntington's disease. Up to a quarter of newly diagnosed patients with Huntington's disease, however, have a negative or uninformative family history due to non-paternity, ancestral death before disease manifestation, de-novo CAG expansions of unstable intermediate alleles, or incomplete penetrance in cases of mutations of CAG repeats in the lower affected range, such that genetic testing for Huntington's disease also has to be considered in patients with progressive chorea and a negative family history.[15,16,129] Presymptomatic testing for unaffected at-risk individuals and prenatal testing can be offered to determine the Huntington's disease carrier status of individuals at risk. Importantly, as a result of the absence of preventive measures or treatment, intensive pre-test and post-test counselling and psychological support is necessary.[130]

Drug history

Drug-induced chorea is among the commonest types of chorea encountered in clinical practice and a careful history of previous drug exposure is of paramount importance in the work-up of patients, especially when other causes are not apparent.[99] Potential candidate classes of chorea-inducing drugs[100,102,104,108–115] are listed in panel 2.

Time course

Chronic and progressive chorea is typical for neurodegenerative diseases like Huntington's disease, spinocerebellar ataxia (types 3 and 17), dentatorubropallidoluysian atrophy,[20,41] and other types of genetic chorea, whereas static chorea is more commonly indicative of structural or toxic insults to the basal ganglia,[95,116] but is also characteristic for benign hereditary chorea.[54] Intermittent presentations should lead to consideration of the paroxysmal choreas, but fluctuating intensity is reported in metabolic or autoimmune choreas (figure 4).

Neurological examination

The topical distribution of choreic movements and associated neurological abnormalities are the main signs when planning differential diagnostic work-ups. Focal chorea or hemichorea should always raise a suspicion of underlying structural basal ganglia lesions, including vascular lacunes or neoplasms and therefore usually requires MRI, but hemichorea is also common in autoimmune choreas like Sydenham's chorea. Associated non-choreic movement disorders like ataxia, dystonia, parkinsonism, coexistent dementia, or peripheral neuropathy all open up their own differential diagnostic possibilities (figure 4).

Laboratory tests

Results of routine blood chemistry and haematology tests are usually normal in patients with chorea but can be informative in metabolic choreas of hepatopathy, hyperglycaemia, hypoglycaemia, uraemia, or may reveal acanthocytes specifically ordered to exclude neuroacanthocytosis syndromes. The use of isotonically diluted blood samples combined with unfixed wet blood preparation with a normal range of <6·3% of total erythrocytes is recommended to search for a significant acanthocytosis in movement disorders.[131] Also patients with HDL2 and pantothenate-kinase-associated neurodegeneration may have acanthocytosis. In addition, Kell blood-group typing should be done in patients with

suspected neuroacanthocytosis with specific antibodies to confirm the weak expression of Kell antigens typical for the McLeod blood phenotype in McLeod syndrome.[55]

Antibody screens help to confirm a suspected diagnosis of autoimmune choreas. Tests for anti-basal ganglia antibodies are not available on a routine basis and the issue of their proper assessment and diagnostic value is unresolved. Chorea with acute or subacute onset associated with additional major or minor symptoms of rheumatic fever[74,84,132] and lack of clinical and laboratory evidence of alternative cause supports a diagnosis of Sydenham's chorea. There are several tests that are much less helpful in diagnosing Sydenham's chorea than in other forms of rheumatic fever, due to the usual long latency between the infection and the onset of the movement disorder: these include tests of acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, leucocytosis; other blood tests like rheumatoid factor, mucoproteins, protein electrophoresis; and supporting evidence of preceding streptococcal infection (increased antistreptolysin-O, antiDNAse-B, or other antistreptococcal antibodies; positive throat culture for group A streptococcus; recent scarlet fever).[133] High titres of antistreptolysin-O antibodies can be found in populations with a high prevalence of streptococcal infection. Furthermore, the antistreptolysin-O titre declines if the interval between infection and rheumatic fever is greater than 2 months.[74] Titres of anti-DNase-B, however, can be high up to 1 year after streptococcal pharyngitis. Heart assessment (ie, doppler echo-cardiography) is mandatory because of the common association of Syndenham's chorea with carditis. Serological studies for systemic lupus erythematosus and primary antiphospholipid antibody syndrome must be done to rule out these disorders. Results of spinal-fluid analysis are normal in most choreic syndromes and so it is not part of the routine clinic work-up.

Neuroimaging

Neuroimaging will help to rule out structural causes of chorea. Cranial CT is not as sensitive as MRI, which should be done in all cases of focal or hemichorea to exclude vascular, neoplastic, or inflammatory pathology in the basal ganglia or adjacent structures. In addition, MRI can reveal evidence of pathologies of the basal ganglia also in immunological or metabolic choreas like Sydenham's chorea[134] or chorea associated with hyperglycaemia.[135] MRI can also detect pathology in genetic choreas like frontal and caudate atrophy in Huntington's disease, cerebellar atrophy in spinocerebellar ataxia type 3, or striatal hyperintensities in choreacanthocytosis.

Functional imaging with PET or single-photon-emission CT has mainly been used in research settings and findings include basal-ganglia hyperperfusion in Sydenham's chorea,[136] hypometabolism of the striatum in Huntington's disease,[137–139] or basal ganglia hypometabolism using single-photon emission CT in systemic lupus erythematosus-associated chorea.[140] However, the differential diagnostic potential of these methods to distinguish between different causes is unclear.

Principles of management

Therapeutic management of chorea should aim to remove the cause and this can be successful in drug-induced chorea, metabolic or endocrine choreas, and to some extent even in autoimmune choreas like Sydenham's chorea with penicillin prophylaxis. Preventive strategies come into play in genetic choreas like Huntington's disease, where careful genetic counselling of affected patients and their relatives is needed. In most choreic syndromes seen in clinical practice, causal therapies are not available and symptomatic treatment is needed.

Antidopaminergic drugs are the mainstay of pharmacological treatment of choreas regardless of cause. As a rule, the more D2-receptor blocking action, the greater the antichoreic efficacy. Although there are no controlled studies, open-label reports and clinical experience indicate that atypical drugs such as olanzapine, quetiapine, and clozapine have limited roles in the treatment of chorea.[44] Although, typical neuroleptics are quite effective in reducing chorea, they are commonly associated with unacceptable side-effects such as sedation, acute dystonic reaction, tardive dyskinesia, and parkinsonism. The latter can be a problem in Huntington's disease, where with progression of the illness there is a tendency for development of rigidity and dystonia;[141] or in hemiballism–hemichorea where chorea suppression on one side of the body may be accompanied by simultaneous development of parkinsonism on the opposite side. Risperidone and olanzapine are atypical antipsychotics with definite antichoreic activity but lesser potential to induce parkinsonism than typical neuroleptics. Tetrabenazine, a presynaptic dopamine depletor with weak D2-blocking action is efficacious in treating chorea in open-label case reports[142,143] as well as in a recent placebo-controlled trial in Huntington's disease.[45]

Non-dopaminergic drugs can also be effective in the management of chorea. Amantadine acts primarily via an NMDA blocking mechanism. There are a few small controlled studies of this drug in Huntington's disease;[144,145] although the results are contradictory, the weight of evidence is in favour of a weak antichoreic action in this disorder. Valproic acid is widely used in the treatment of chorea in Sydenham's chorea. Although a few open-label studies and clinical experience strongly support the efficacy of the drug in this indication, no controlled studies have addressed this issue.[85,146] Carbamazepine is also rarely used to treat Sydenham's chorea.[85,86] Valproic acid has also been reported as efficacious to treat choreas of other causes such as kernicterus, post-traumatic chorea, postanoxic chorea

Search strategies and selection criteria

References for this Review were identified by searches of MEDLINE until April 2006 with the terms "chorea", "Huntington's disease", "Sydenham's chorea", "PANDAS", "hemiballism", and "drug-induced chorea". References were also selected from relevant articles and chapters of recent books on movement disorders. Only papers published in English were included

and vascular hemiballism–hemichorea;[147–150] however, whether the latter is really responsive to valproic acid is unclear.[151] Autoimmune choreas, including Sydenham's chorea, systemic lupus erythematosus, and primary antiphospholipid antibody syndrome, are also responsive to corticosteroids.[88,152–154]

Surgery is rarely needed to treat chorea. However, in a few patients with persistent vascular chorea (arbitrarily defined as duration longer than 1 year) stereotactic surgery such as thalamotomy or posteroventral pallidotomy were effective.[117,118] There are also a few reports of the effectiveness of surgery to treat chorea associated with cerebral palsy,[155] senile chorea,[156] dentato-rubralpallidoluysian atrophy.[157] Finally, pallidotomy, pallidal-stimulation, and fetal neural transplants have also been used in Huntington's disease.[9,158,159]

Conclusion

Although easily diagnosed as a syndrome based on a characteristic and distinctive pattern of involuntary movements, the differential diagnosis of chorea is complex, including genetic neurodegenerative diseases like Huntington's disease, autoimmune processes targeting the basal ganglia like Sydenham's chorea, structural basal ganglia lesions, or various drug-induced, toxic, or metabolic insults to basal ganglia–cortical networks. A carefully taken history will give clues to common causes like drug exposure or genetic choreas and a comprehensive neurological examination will reveal additional motor and non-motor deficits that accompany many of the choreic syndromes and characterise different aetiological subtypes. Genetic and laboratory testing and neuroimaging should be based on reasonable differential diagnostic possibilities and will then allow correct classifications in most cases. Treatment is palliative in progressive neurodegenerative choreas like Huntington's disease but can be highly effective in many of the other choreic disorders.

Contributors

FC and WP jointly designed and supervised this seminar. KS and GW contributed to the writing of this seminar. KJM searched for relevant references and made the figures. FC did the literature search, contributed to the writing of this seminar, and reviewed the figures. WP contributed to the writing of this seminar, wrote the final version of the article, and had overall supervision of writing this seminar.

Conflicts of interest

We have no conflicts of interest.

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