

Dystonia and chorea in acquired systemic disorders

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Dystonia and chorea are uncommon abnormal movements which can be seen in a wide array of disorders. One quarter of dystonias and essentially all choreas are symptomatic or secondary, the underlying cause being an identifiable neurodegenerative disorder, hereditary metabolic defect, or acquired systemic medical disorder. Dystonia and chorea associated with neurodegenerative or heritable metabolic disorders have been reviewed frequently.¹ Here we review the underlying pathogenesis of chorea and dystonia in acquired general medical disorders (table 1), and discuss diagnostic and therapeutic approaches. The most common aetiologies are hypoxia-ischaemia and medications.²⁻⁴ Infections and autoimmune and metabolic disorders are less frequent causes. Not uncommonly, a given systemic disorder may induce more than one type of dyskinesia by more than one mechanism.

The areas of the brain associated with particular movement disorders have been determined by cerebral imaging and necropsies of patients, and by animal lesioning studies.⁵⁻⁷ Based on such data, chorea seems to result from hypofunction of the indirect pathway from the putamen to the internal globus pallidus, and dystonia correlates more strongly with hyperfunction of the direct relative to the indirect pathway between the putamen and internal globus pallidus, both resulting in inappropriate disinhibition of thalamic projections to the premotor and motor cortex (figure). Chorea has been most consistently associated with lesions in the caudate nucleus or putamen, resulting in disinhibition of the external globus pallidus. Lesions of the subthalamo-internal pallidal pathway also result in chorea.

Associated neurotransmitter abnormalities include deficient striatal GABA-ergic function and striatal cholinergic interneuron activity, and dopaminergic hyperactivity in the nigro-striatal pathway. Dystonia has been correlated with lesions of the contralateral putamen, external globus pallidus, posterior and posterior lateral thalamus, red nucleus, or subthalamic nucleus, or a combination of these structures. The result is decreased activity in the pathways from the medial pallidus to the ventral anterior and ventrolateral thalamus, and from the substantia nigra reticulata to the brainstem, culminating in cortical disinhibition. Altered sensory input from the periphery may also produce cortical motor overactivity and dystonia in some cases.⁸ To date, the changes found in striatal neurotransmitter concentrations in dystonia include an increase in noradrenaline and a decrease in dopamine concentrations.

Hypoxic-ischaemic causes

MECHANISMS

Chorea and dystonia may result from hypoxia-ischaemia due to global cerebral hypoperfusion or cellular hypoxia, such as in toxic mitochondrial dysfunction. Two hypotheses have been put forward to explain hypoxic-ischaemic injury to the basal ganglia: selective hypoperfusion of certain vascular territories and an intrinsic metabolic susceptibility of the striatum to hypoxia-ischaemia due to its high oxidative metabolism.⁷ The internal segment and the medial outer segment of the globus pallidus are supplied by the anterior choroidal artery, and the caudate head and putamen are fed by the lenticulostriate artery. Changes in perfusion may randomly affect either or both vessels, or one vessel preferentially if other vascular lesions are also present.

There is often a delay in onset of the movement disorder after hypoxic injury, which may reflect the time required for remyelination, inflammatory changes, ephaptic transmission, oxidation reactions, maturational or aberrant synaptic reorganisation, trans-synaptic neuronal degeneration, or denervation supersensitivity to occur.⁴

As discussed earlier, dystonia and chorea most commonly result from striatal dysfunction, and hypoxia-ischaemia has been shown to alter several neurotransmitter systems in the striatum. Glutamate is the main neurotransmitter in cortical neurons projecting to the

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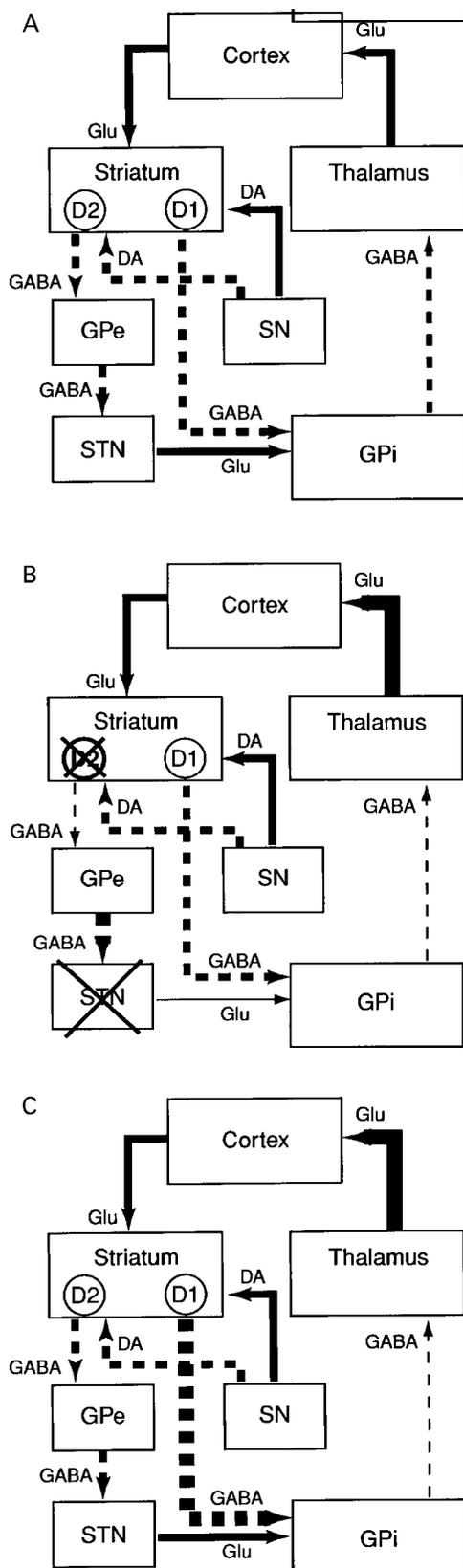
Table 1 Aetiologies of secondary chorea and dystonia*

Primary cause	Mechanism
Hypoxia-ischaemia	Global hypoperfusion
Toxins	Cellular (mitochondrial) injury
Neurotransmitter imbalance	Receptor antagonism
	Receptor stimulation
	Neurotransmitter reuptake inhibition
	Neurotransmitter depletion
Infection	Altered neurotransmitter turnover
	Vasculopathy due to antibodies or organism
	Antibodies to basal ganglia epitopes
	Direct basal ganglia invasion by the organism
	Neuronal injury by an elaborated cytotoxin
Antibody mediated	Vasculopathy
Metabolic disorders	Cross reaction with basal ganglia epitopes
	Endocrine dysfunction
	Electrolyte abnormalities

*More than one mechanism may be involved in the generation of specific dyskinesias.

striatum and may contribute excitotoxic injury. Hypoxia-ischaemia has been shown to increase striatal extracellular glutamate, and decrease glutamate transporter concentrations. Direct lesioning of the globus pallidus with excitatory amino acids in monkeys

produces cocontraction of opposing muscle groups on reaching, as in dystonia.⁹ Extracellular dopamine concentrations rise and concentrations of dopamine metabolites fall after hypoxia-ischaemia.⁷⁻¹⁰ Dopamine may also potentiate the excitotoxic properties of glutamate, and depleting the striatum of dopamine before hypoxia-ischaemia decreases the degree of striatal injury. In the neonatal rat model of cerebral hypoxia-ischaemia, striatal D1 and D2 dopamine receptor numbers fluctuate until 9 to 11 weeks after injury, at which time the D1 receptor number has returned to normal but the reduction in D2 receptors persists.¹¹ Hypoxia-ischaemia also results in areas of complete loss of preproenkephalin mRNA in the dorsal striatum of the rat brain.¹² Enkephalin, together with GABA, is an inhibitory neurotransmitter in the projections from the putamen to the external pallidum. Hypoxic-ischaemic necrosis of medium sized spiny striatal neurons may be responsible for decreased concentrations of the inhibitory neurotransmitter, GABA. By contrast, the striatal cholinergic system remains relatively preserved or even upregulated after hypoxia-ischaemia, as evidenced by an increase in cholinergic fibres and cell bodies, and an increase in acetylcholine release.¹³ This is interesting in that anticholinergic medications often ameliorate dystonic movements.



CLINICAL FEATURES

Global cerebral hypoxia-ischaemia is most often a cause of dystonia and chorea when it occurs perinatally. However, regardless of aetiology or timing, it may also cause movement disorders in children and adults. Despite the global insult, patients often have focal or unilateral findings clinically and on imaging studies. Uncommonly, brain CT or MRI is normal or discloses mild diffuse atrophy.

PERINATAL HYPOXIC ISCHAEMIA

Perinatal hypoxic-ischaemic injury may result in any pattern of dystonia, often after an impressive interval of time. Summarising data from three studies of 37 patients, the latency of onset ranged from 6 to 58 years, and usually began as a focal, and rarely, segmental dystonia. In most patients, the dystonia became more extensive over a range of 6 months to 28 years such that it progressed to segmental dystonia in 41%, developed into hemidystonia in 27%, and became generalised in 24%.⁴⁻¹⁴⁻¹⁵ However, the longer the interval between the

Thalamocortico-basal ganglionic circuitry. (A) Normal. The striatum receives inputs from the cortex and SN and projects to the GPi through direct and indirect pathways. The direct pathway mediates GABA-ergic inhibition of the GPi. The indirect pathway projects to the GPi by way of the GPe and STN. The GPi maintains inhibitory tone on thalamocortical projections. (B) In chorea, there is underactivity of the indirect pathway due to dysfunction (X) either of the striatum or STN, with resultant disinhibition of the thalamus. (C) In dystonia, overactivity of the direct pathway is postulated, resulting in disinhibition of thalamic projections to the cortex. GPe/i=globus pallidus externa/interna; SN=substantia nigra; STN=subthalamic nucleus; GABA= γ -aminobutyric acid; Glu=glutamate; DA=dopamine; \rightarrow =excitatory; $- - \rightarrow$ =inhibitory.

hypoxic insult and the development of dystonia, the less certain is an aetiological relation, emphasising the importance of a complete evaluation for other causes. These studies did not correlate the aetiology or duration of the perinatal hypoxic-ischaemic injury with the latency, pattern, or severity of dystonia. Pathologically, the lesion most often found is status marmoratus of the striatum (marble-like appearance due to altered myelination).¹⁶

POST-PUMP CHOREA

“Post-pump chorea” is a childhood syndrome of chorea or ballismus, episodic eye deviations, and hypotonia beginning within 12 days of cardiac surgery, typically after an initial asymptomatic period.¹⁷ It is seen in 1% to 2% of patients, from older infants to those in mid-childhood, and can be severe and irreversible, with a significant death rate. Infants less than 6 weeks of age are less vulnerable; in affected children up to 12 months of age, the chorea is often mild and reversible. All affected patients have undergone hypothermia and cardiopulmonary bypass during surgery, and many required total circulatory arrest. There is a trend towards lower temperatures and longer bypass times in patients developing chorea. Although occurrence of the syndrome cannot be consistently predicted, these risk factors suggest that hypoxic-ischaemic injury contributes to the development of the syndrome, perhaps compounded by underlying developmental brain abnormalities, chronic central hypoxia due to the cardiac condition, reperfusion injury, disordered cerebral autoregulation, and the higher cerebral metabolic rate in 3 to 9 year old children compared with infants and adults. Pathologically, neuronal loss and gliosis are most conspicuous in the external globus pallidus.

HYPoxic INJURY IN CHILDREN OR ADULTS

Hypoxic injury in previously normal children and adults may also cause dystonia. Bhatt *et al*¹⁸ recently found that 6 to 21 year old patients with acute hypoxia related to asthma, anaesthesia, or drowning sometimes developed pure dystonia after 1 week to 3 years. The dystonia became generalised over 4 to 96 months, and imaging showed a disproportionate number of lesions in the putamen. By contrast, older patients developed a non-progressive akinetic-rigid syndrome between 1 week and 12 months after cardiac arrest, hypotension or anaesthesia. Rarely, dystonia became superimposed within 3 years of the initial event. Lesions in the globus pallidus predominated on imaging. These findings are supported in a review of 88 other cases.¹⁸

POLYCYTHAEMIA

Polycythaemic chorea is difficult to categorise by aetiology because the exact mechanisms are not known. It is discussed here because the fundamental abnormality is an excess of erythrocytes, the primary function of which is oxygenation. Chorea is hypothesised to result from sluggish cerebral blood flow, particularly in the basal ganglia; reduced turnover and content of

cerebral catecholamines and serotonin in older people, resulting in receptor upregulation; the oestrogen deficit in postmenopausal women, resulting in dopamine receptor hypersensitivity; and, possibly, an excess of dopamine due to platelet congestion in cerebral vessels.^{19, 20} Polycythaemia occurs more often in men (3:2), but polycythaemic chorea is seen predominantly in women (5:2), usually after the age of 50, with an overall prevalence of 1% to 2.5%.^{19, 20} As many as two thirds of the patients present with chorea, and on examination are found to have facial erythrosis and splenomegaly consistent with polycythaemia. The chorea may begin insidiously or acutely, is sometimes episodic, and may initially be asymmetric, although it typically becomes generalised, with predominantly facial, lingual, and brachial involvement. The limbs are hypotonic, with pendular patellar tendon reflexes. The chorea may last from a few weeks to several years. There may be spontaneous remissions and recurrences, with more consistent improvement after treatment of the polycythaemia, but the relation between red blood cell counts and chorea is often weak. The usual treatment involves ³²P or venesection. Pathologically, the dural and parenchymal veins in patients with polycythaemic chorea are congested and thrombosed, with perivenous demyelination.

OUTCOME

Thus, regardless of the type of hypoxic-ischaemic injury, outcomes differ in infants, children, and adults.¹⁴ In infants and children, compared with adults, there is typically a longer delay before the movement disorder develops, and a greater likelihood that the abnormal movements will generalise.¹⁸ In adults, there may first be a motor deficit caused by the injury, and chorea or dystonia appears as the strength improves, and usually remains localised. Only in post-pump chorea in young children and after thalamotomy in adults does the dyskinesia commonly begin within a week of the injury. These differences may relate to age dependent changes in neuroplasticity or variability in the metabolic response of the brain to injury.^{21, 22}

Toxins

The neurological manifestations of poisoning by certain gases and heavy metals have been attributed to cellular hypoxia due to mitochondrial dysfunction or to the generation of free radicals (table 2). Heavy metal poisoning is a rare cause of encephalopathy, parkinsonism, and dystonia after exposure for months to years. Manganese toxicity follows occupational exposure and presents with apathy, restlessness, and slowed movements, progressing to rigidity, hyperreflexia, extensor plantar responses, gait instability, and postural tremor. Dystonia is seen particularly when extrapyramidal symptoms are severe. The syndrome may resolve if further exposure is prevented at an early stage, but it usually follows a progressive course. New studies in manganese intoxicated monkeys confirm previous necropsy findings in humans of damage to the globus

Table 2 Toxins causing dystonia or chorea

Dystonia:
Manganese
Cyanide
Carbon monoxide
Methanol
Copper (Wilson's disease)
Mercury (organic and inorganic)
Alcohol/disulfiram
Chorea:
Copper (Wilson's disease)
Organic mercury

pallidus and substantia nigra pars reticulata—pathways downstream from the nigrostriatal dopaminergic pathway—and are consistent with the lack of response to levodopa.^{23–24} Manganese has been shown to increase free radical formation and inhibit antioxidant function. It may be a mitochondrial toxin that reduces energy production and possibly increases neurotoxic glutamate effects. Other possible mechanisms of manganese neurotoxicity include replacement of dopamine by manganese, decreased dopamine synthesis due to insufficient cofactor, and direct neuronal membrane toxicity by manganese.

Cyanide intoxication may also result in delayed parkinsonian symptoms and dystonia.^{25–26} With time the movement abnormalities stabilise, followed by gradual but incomplete recovery. Imaging studies show diffuse cerebral atrophy, particularly of the cerebellum, and hypodensity on CT, or T2 hyperintensity on MRI in the pallida and putamina bilaterally. The few existing pathological investigations confirm the global atrophy.²⁷ Cyanide poisons the mitochondria by reacting with cytochrome C oxidase, causing cellular hypoxia, to which particularly the basal ganglia and brainstem respiratory centre are sensitive.

Survivors of carbon monoxide poisoning initially improve, even from coma, but often undergo a delayed deterioration up to 6 weeks later, developing parkinsonism, sometimes with dystonia; about 75% will recover within a year.^{25–26–28} Imaging discloses generalised atrophy with focal injury particularly to the pallida, but also in the striatum, hippocampus, cerebellum, and substantia nigra. Pathologically, the pallida are necrotic and there is diffuse gliosis. Carbon monoxide binds to haemoglobin and cytochromes, thereby inhibiting the electron transport chain and resulting in cellular hypoxia.

Methanol intoxication can result in parkinsonism, bradykinetic dystonia, and blindness.²⁹ The clinical abnormalities stabilise and may

Table 3 Medications causing acute dystonic reactions

Anticonvulsant drugs (phenytoin, phenobarbitone, ethosuximide, carbamazepine, valproate)
Dopamine agonists
Neuroleptic drugs (metaclopramide, prochlorperazine)
Tricyclic antidepressants
Calcium channel blockers
Diazepam
Inderal
Chloroxazone
Cimetidine ³¹
Bromazepam ³²
Sulpiride ³³
Domperidone ³⁴

slowly improve over time. Methanol is converted to formaldehyde in the liver, and the liver and erythrocytes synthesise formic acid that inhibits cytochrome oxidase and, thereby, mitochondrial electron transport and ATP production in the tissues. A severe metabolic acidosis develops, with injury to the retina and optic nerves, and necrosis in the putamina as well as the subcortical white matter, cerebellum, brainstem, and spinal cord.

Dystonia secondary to hepatic copper accumulation occurs in Wilson's disease or severe cholestatic liver disease, and can result in dystonia, choreoathetosis, encephalopathy, and muscle weakness. In excess, copper preferentially damages mitochondrial enzymes, but can also impair cytosolic enzymes, particularly those with sulphhydryl groups. Pathologically, neurons and astrocytes degenerate in the basal ganglia, cortical grey matter, and subthalamic and medullary nuclei. If hepatic damage is not severe, significant improvement follows chelator therapy with penicillamine or tetrathiomolybdate in almost all patients. In non-responders and those with severe liver dysfunction, however, liver transplantation is the only treatment option. For symptomatic treatment of the movement disorder, trihexphenidyl is sometimes more successful than levodopa, bromocriptine, or amantadine.

Organic mercury poisoning causes neuronal loss and gliosis, resulting in visual loss, ataxia, paraesthesias, and cognitive dysfunction. Choreoathetosis, parkinsonism, and tremor are prominent, with dystonic posturing occasionally seen. Inorganic mercury poisoning produces a psychotic encephalopathy and tremor, but pathological localisation is not available.

Disulfiram and alcohol overdose rarely may also cause akinesia and dystonia.³⁰ Psychomotor slowing and parkinsonism developed within days of awakening from coma in one such case and dystonia of one leg, dystonic speech, and blepharospasm developed over 10 years. Brain MRI disclosed lesions bilaterally in the pallida and inferior portions of the putamina.

Drug induced dystonia

Neuroleptic drugs, dopamine agonists, anti-convulsant drugs, and certain other medications can cause idiopathic, reversible, acute dystonic reactions that are distinct from tardive dystonia and occur with an incidence of 2% to 10% (table 3). Torticollis, opisthotonus, chorea, dyskinesia, or oculogyric crisis may develop within hours of taking the offending medication, and may occur with the first dose or after days to weeks of use; these remit with anticholinergic treatment or discontinuation of the causal agent. Patients with AIDS dementia complex are particularly susceptible to neuroleptic related acute dystonic reactions,³⁵ and this has been attributed to dopaminergic dysfunction and dopamine receptor hypersensitivity.³⁶ Pathologically, patients with AIDS dementia complex may have gliosis in the caudate nucleus and putamen, and some have shown relative hypermetabolism in the basal ganglia on PET.

The treatment of acute dystonic reactions requires discontinuation of the responsible medication and the intravenous administration of 50 to 100 mg diphenhydramine, 1 to 2 mg benztropine mesylate, or 10 to 50 mg chlorpheniramine. Anticholinergic drugs may need to be continued for several days, particularly if the offending medication had been given regularly or in depot form.

A common cause of secondary dystonia is medications, typically neuroleptic drugs, of which haloperidol remains the most frequent offender. It is widely considered that neuroleptic agents cause dystonia by inhibiting dopamine receptors in the basal ganglia. However, this is unlikely to be the sole explanation, and another mechanism is suggested by the finding that haloperidol mimics the dystonia producing effect of agonists at sigma opiate receptors when injected into the red nucleus or substantia nigra of rats.³⁷

In a comprehensive study in 1993 of 100 patients with tardive dyskinesias, the most common (78%) variety involved repetitive orolingual facial movements or repetitive movements of the head, trunk, and limbs.³⁸ Dystonias were found in 75%, akathisia in 31%, tremor in 5%, chorea in 3%, and myoclonus in 2%. The type of movement disorder did not correlate with the type or the number of neuroleptic agents or the duration of their use.

Patients with tardive dystonia tend to be younger (mean 45 years) than those with facial dyskinesias (mean 71 years), and the male to female ratio was 7:2 in one study.³⁸ Additionally, Burke *et al*³⁹ found a significantly lower mean age of onset in men (29 years) than in women (41.5 years), but onset in individual cases has ranged from 5 to 89 years. The onset is insidious and occurs after taking a neuroleptic medication for a mean of 6 years.³⁹ Dystonia predominantly affects the head and neck region, resulting in torticollis, blepharospasm, or oromandibular dystonia.^{38, 39} By contrast with idiopathic torsion dystonia, only 7% to 14% of patients with tardive dystonia have truncal, lower limb, or generalised involvement, and the face or neck is then also involved. Burke *et al*³⁹ also found that patients with generalised dystonia were younger (mean 22.5 years) than those with segmental (34 years) or focal dystonia (41.4 years). Typically, tardive dystonia progresses over months to years before stabilising. Discontinuing the neuroleptic drug occasionally produces remission, particularly in young patients, although often there is initial worsening, followed by gradual improvement.³⁹ Recovery in adults is often incomplete. Some patients improve with an increase in the neuroleptic drug or despite its continuation, but we do not recommend these options because of their potential to worsen the long term outlook. About 40% to 50% of patients benefit from dopamine depleting or blocking agents and anticholinergic treatment.³⁹ Reserpine is started at 0.1 mg/day and increased by 0.1 mg weekly to a maximum of 2 mg/day. Adverse effects may include parkinsonism, depression, and orthostatic hypotension. The addition of baclofen or benzo-

diazepines may provide further benefit. Tetrabenazine is useful in doses ranging from 12–250 mg/day, and usually requiring more than 100 mg/day for benefit.

Dose related dystonia or chorea is most commonly seen with carbidopa/levodopa⁴⁰ and anticonvulsant drugs, particularly in polytherapy (phenytoin,^{41–43} phenobarbitone,⁴⁴ ethosuximide,⁴⁵ carbamazepine,⁴⁶ valproate⁴⁷). Supratherapeutic doses of phenytoin decrease in vitro neuronal calcium influx and neurotransmitter release, inhibit calcium-calmodulin protein phosphorylation, increase the GABA concentration, and inhibit dopamine reuptake and breakdown.⁴² Oral contraceptives have been reported to cause chorea, although many affected patients have had striatal abnormalities on imaging studies, previous Sydenham's chorea, chorea gravidarum, or chorea with Henoch-Schönlein purpura, suggesting that pre-existing injury to the basal ganglia is required.⁴⁸ Rarely, children treated with theophylline for an asthma exacerbation have developed transient orobuccal-lingual dyskinesias or generalised chorea, although the precipitating factor is unclear because they were also taking other medication.^{49, 50}

Cocaine and amphetamines have been associated with dyskinesias. Cocaine initially blocks reuptake and promotes release of noradrenaline and dopamine, but eventually results in their depletion.⁵¹ Cocaine also decreases serotonin turnover and degradation.

Choreoathetoid movements of the limbs, less often the head or trunk, or buccolingual dyskinesias may develop within 24 hours of cocaine use and may recur with its subsequent use.^{52–54} The severity and duration of the involuntary movements vary with the quantity of cocaine used, and resolve without treatment in 2 to 6 days. Brain CT is unrevealing. Cocaine may exacerbate pre-existing idiopathic or tardive dystonia⁵⁵ and for unknown reasons, cocaine users seem predisposed to developing acute dystonic reactions to neuroleptic drugs, perhaps reflecting more chronic changes in dopaminergic systems as have been found in patients with the AIDS dementia complex.^{56, 57}

Amphetamines are thought to cause chorea or dystonia by exerting central dopaminergic effects. Choreoathetosis and psychosis have been described in amphetamine users and are usually transient, but may persist for years in chronic users.^{58–61}

As well as altering brain neurotransmitter systems, cocaine and amphetamines can cause a cerebral vasculitis or vasospasm. Therefore, in assessing these patients in the emergency department, CT of the head must be obtained to evaluate the possibility of cerebral haemorrhage or infarction. In the absence of cerebral haemorrhage, MRI of the brain will be more sensitive for cerebral ischaemia.

Infections

Meningitis and encephalitis caused by viral, bacterial, and fungal infections of the brain have been associated with dystonia, choreoathetosis, and ballismus. Movement abnormalities usually develop during the acute phase

Table 4 Infectious aetiologies of dystonia and chorea

Bacterial	Viral and fungal
Group A <i>Streptococcus</i>	Viral:
<i>Mycoplasma pneumoniae</i>	Varicella
<i>Legionella pneumophila</i>	Herpes simplex
<i>Borrelia burgdorferi</i> ⁷⁷	ECHO ⁸⁸
<i>Treponema pallidum</i> ⁷⁸	Encephalitis lethargica ⁸⁹
<i>Streptococcus viridans</i> ⁷⁹	Human immunodeficiency virus
<i>Haemophilus influenzae</i> ⁸⁰	Fungal:
<i>Streptococcus pneumoniae</i> ⁸⁰	<i>Toxoplasma gondii</i>
<i>Neisseria meningitidis</i> ⁸⁰	<i>Cryptococcus neoformans</i>
<i>Mycoplasma tuberculosis</i> ⁸¹	

of the illness and are transient. The main mechanism, verified pathologically, is vasculitic ischaemia of the basal ganglia. Other proposed mechanisms include direct neuronal injury by the organism or a toxin, and autoimmune cross reactivity with basal ganglia epitopes, as in Sydenham's chorea.

BACTERIAL INFECTIONS

Sydenham's chorea is the classic infection related movement disorder. It is a transient chorea associated with rheumatic fever and preceding infection with group A *streptococcus*, usually occurring in childhood. Antibodies against type 6 streptococcal M-protein seem to react with brain epitopes.⁶² In a recent study, 13 of 50 children with rheumatic fever developed chorea; in nine it was a presenting symptom.⁶³ Sydenham's chorea occurs between the ages of 3 and 17 years,^{63 64} and after the age of 10 there is a 2:1 female predominance. The chorea is generalised in about 80% of patients,⁶⁴ with speech impairment in almost 40%, and encephalopathy in 10%. Neuroleptic drugs, valproic acid, and chlorpromazine improve symptoms, and spontaneous remission occurs by 6 months in 75% of instances,⁶⁵ although it can be delayed for up to 2 years. Twenty per cent may have recurrences, usually 1 to 2 years after the initial episode. The results of cerebral imaging studies are normal, or show reversible contralateral or bilateral striatal hypodensities on CT, or increased T2 signal on MRI, sometimes with enlargement of the caudate, putamen, and globus pallidus⁶⁶⁻⁶⁸ and PET shows reversible striatal hypermetabolism.^{69 70}

Mycoplasma pneumoniae, in addition to pulmonary involvement, affects the CNS in 2% to 7% of cases requiring hospital admission.⁷¹ Generalised choreoathetosis has been noted in three reports,⁷¹⁻⁷³ with dystonia in one. Cerebral imaging was normal in two, and showed bilateral caudate, putamen, and globus pallidus lesions in the third. The CSF is normal or exhibits a mild lymphocytosis with a raised protein concentration. The diagnosis is made by respiratory cultures and the presence of serum and CSF complement fixing and cold agglutinin antibodies.

Legionella pneumophila causes pneumonia with high fevers, rarely accompanied by chorea.⁷⁴⁻⁷⁶ The CSF and brain CT are normal, and the diagnosis is made by serial serologies. The neurological abnormalities may improve with treatment but do not always normalise, and chorea may persist for up to 2 years.

Other bacterial infections associated with dystonia or chorea are listed in table 4.

VIRAL INFECTIONS

Movement disorders in viral encephalitides are seen, particularly in children. Varicella is associated with transient bilateral facial, jaw, and arm chorea and dystonia and, less often, with hemichorea or generalised chorea.^{82 83} Herpes simplex tends to affect infants more often than older children, and although chorea can be present early in the course of the encephalitis, it more often signals a relapse after treatment.⁸⁴⁻⁸⁷ Most patients also have seizures, and anticonvulsant medication may contribute to the development of dyskinesias. Anecdotally haloperidol, procyclidine, and anticonvulsant drugs have been found to decrease the dyskinesias. Other viral infections associated with dystonia or chorea are listed in table 4.

FUNGAL INFECTIONS

Cerebral fungal infections are common in immunocompromised patients, and may lead to movement disorders. There are changes in cerebral dopamine function in patients with AIDS dementia complex³⁵ and HIV infection has presented with chorea in two cases,⁹⁰ none the less, in this setting cerebral toxoplasmosis is most commonly responsible. Toxoplasma abscesses in the subthalamic nucleus, thalamus, caudate nucleus, or globus pallidus have been associated with contralateral limb ballism, choreoathetosis, and dystonia.⁹¹⁻⁹⁶ About 15% of these patients present with the dyskinesia, usually together with confusion, headache, or paresis. The toxoplasmosis responds well to treatment, but the dyskinesias improve only in 25% of instances, suggesting permanent basal ganglia injury.⁹³ Improvement of abnormal movements in individual cases has been seen with pimozide, tetrabenazine, isoniazid, and haloperidol, although worsening has also been seen with haloperidol.⁹³ Hemichorea and hemiballismus have each been reported only once in HIV seronegative patients with cryptococcal meningitis, one of whom was taking steroids.^{97 98} The dyskinesia has been attributed to spasm or thrombosis of the penetrating vessels to the basal ganglia due to basilar meningitis.

Causes mediated by antibodies

Dystonia and chorea occasionally occur in autoimmune and collagen vascular diseases in which there is commonly a generalised increase in circulating autoantibodies (table 5). Three possible mechanisms exist.^{99 100} Firstly, the antibodies may generate an inflammatory vasculopathy in cerebral vessels, resulting in transient or permanent ischaemic injury to the basal ganglia. Secondly, neuronal dysfunction may result from antibody binding to the cell surface, immune complex deposition with inflammation, and the effects of cytokines. Thirdly, immune and non-immune effects of infection, toxins, and metabolic disturbances may also be responsible.

Up to 4% of patients with systemic lupus erythematosus experience choreoathetosis.⁹⁹⁻¹⁰² Chorea is noted after the diagnosis of systemic lupus erythematosus in about 50% of patients, is present before the diagnosis in about a quar-

Table 5 Causes of dystonia and chorea mediated by antibodies

Systemic lupus erythematosus
Primary antiphospholipid antibody syndrome
Polyarteritis nodosa
Behçet's disease
Isolated angiitis of the CNS
Churg-Strauss syndrome
Hashimoto's thyroiditis
Paraneoplastic syndrome

ter, and is noted at the time of diagnosis in another quarter.⁹⁹ Chorea occurs at any age (but most patients are under 30 years of age¹⁰¹) and tends to manifest during a lupus flare, but may develop at any time. Generalised chorea and hemichorea are most common and are usually transient, lasting from 3 days to 3 years; recurrence is seen in up to 25% of cases; rarely the chorea is permanent. It may respond to steroid treatment or haloperidol. In patients undergoing cerebral imaging, brain MRI is more often abnormal than CT.¹⁰¹ The location of the lesions, however, does not always explain the chorea, and some subjects with chorea have normal imaging, and many patients with systemic lupus erythematosus without chorea have abnormal MRI.

Some patients with systemic lupus erythematosus and chorea, many of whom developed subsequent cerebral infarction, have been found to possess antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibody) that predispose to venous or arterial thrombosis.¹⁰¹⁻¹⁰⁵ About 30% of patients with systemic lupus erythematosus with these antibodies have thrombotic events. The whole blood clotting time is prolonged, and the prothrombin time and the Russell's viper venom time may be abnormal. The antibodies seem to inhibit protein C activation and prostacyclin and antithrombin III activity, and may affect platelet membranes. Thus chorea in systemic lupus erythematosus may be due to autoimmune vasculitic cerebral microthrombosis or to cytotoxic antibody effects on the basal ganglia,¹⁰¹ but the correlation with systemic lupus erythematosus disease activity, treatment, and detectable basal ganglia lesions remains inconsistent.

In patients without systemic lupus erythematosus, the primary antiphospholipid syndrome is described by antiphospholipid antibodies and thrombocytopenia resulting in a hypercoagulable state.^{101 105 106} In addition to lupus anticoagulant and an IgG anticardiolipin antibody, almost half of the patients with primary antiphospholipid syndrome have a low titre ANA antibody, 30% may have a false positive venereal disease research laboratory test, and many have antithyroid antibodies. Primary antiphospholipid syndrome can present at any age, with a female to male ratio of 2:1.^{101 103 107} The onset of dyskinesia has ranged from 6 to 77 years, with the vast majority less than 30 years old, and a female to male ratio of 14:1.^{101 103} Most patients with the disease present with the acute onset of generalised chorea, hemichorea, hemidystonia, or hemibalismus, occasionally during pregnancy or after starting oral contraceptives.¹⁰¹ As in systemic

lupus erythematosus, brain MRI shows lesions more often than CT, but the lesions do not always explain the chorea, and some patients with primary antiphospholipid syndrome and chorea have normal imaging studies.^{101 104 107} The lack or transience of imaging abnormalities in some cases has prompted speculation about a direct effect of the antibodies on the basal ganglia. Cervera *et al* suggest that cases previously reported as chorea gravidarum and oestrogen containing oral contraceptive related chorea may actually be women with antiphospholipid antibodies, with or without systemic lupus erythematosus.¹⁰¹

A recent trial in patients with antiphospholipid antibodies, with or without a diagnosis of systemic lupus erythematosus, showed that anticoagulation with warfarin to an international normalised ratio (INR) of at least 3, resulted in a 90% 5 year probability of no new thrombotic events.¹⁰⁵ Among untreated patients, those treated with aspirin alone, or with warfarin to an INR of less than 3, only 30% to 50% were free of recurrence at 5 years.

Chorea is a rare complication of polyarteritis nodosa, Behçet's disease, and isolated angiitis of the CNS.¹⁰⁸⁻¹¹¹ Patients with chorea and Behçet's disease have had raised CSF protein and lymphocytosis, and respond to pimozide or corticosteroid/ACTH treatment.^{108 110} A child presenting with generalised chorea and bilateral globus pallidus hyperintensities on MRI was diagnosed with Churg-Strauss syndrome and responded to cyclophosphamide, tiapride, and corticosteroids.¹¹²

In Hashimoto's thyroiditis, five major thyroid-related autoantibodies can disrupt thyroid function and cause an encephalopathy which is sometimes associated with choreoathetosis or myoclonus.^{113 114} The CSF has a raised protein concentration in 75% of cases, and a mononuclear pleocytosis and oligoclonal bands each occur in 25% of cases; the EEG can be normal, show slowing, or epileptiform activity, and there may be transient or permanent areas of increased T2 signal on brain MRI, particularly in the frontal and temporal lobes. These findings may be present despite a euthyroid state, and therefore are postulated to be due to a direct effect of the autoantibodies on the brain. Patients respond in a day to 6 weeks to oral prednisone treatment, which can be tapered slowly once improvement is stable. Complete remissions on prednisone are the rule, but there may be residual deficits, and relapses sometimes occur. Spontaneous remissions also occur.

Chorea and dystonia have been reported in one patient with small cell carcinoma, cerebellar ataxia, multiple cranial neuropathies, and a pure sensory neuropathy.¹¹⁵ At necropsy there was neuronal loss in the cerebellum and brainstem, demyelination of the posterior columns, and diffuse oedema, consistent with a paraneoplastic process.

Metabolic causes

Hormonally mediated changes in the basal metabolic rate or catecholaminergic tone, as well as significant glucose or electrolyte shifts

Table 6 Metabolic aetiologies of dystonia and chorea

Hyperthyroidism
Hypocalcaemia (hypoparathyroidism)
Hypoglycaemia
Hyperglycaemia
Hypernatraemia
Hyponatraemia
Hypomagnesaemia
Osmotic demyelination syndrome (central pontine myelinolysis)
Splenorenal shunt

might be expected to affect those cerebral regions with high metabolic rates, such as the basal ganglia (table 6). In the absence of structural injury, the changes are reversible.

The association between thyrotoxicosis and choreoathetosis or dystonic posturing was first noted by Gowers in 1893 and usually occurs in young women (14 to 23 years), although middle aged persons of either sex are sometimes affected.¹¹⁶⁻¹¹⁸ The movement disorder usually presents and remits in conjunction with signs of hyperthyroidism. Choreoathetoid movements most commonly affect the limbs, unilaterally or bilaterally, and distally more than proximally; the neck and tongue may also be involved. The abnormal movements are usually continuous, but paroxysmal choreoathetosis has been reported¹¹⁹ and paroxysmal and kinesigenic choreoathetosis has been associated with exogenous hyperthyroidism.¹²⁰ No cerebral lesions have been noted at necropsy or on MRI. The response of the chorea to dopamine receptor blockers before the resolution of hyperthyroidism, and the presence of decreased concentrations of the dopamine metabolite, homovanillic acid, in the CSF of hyperthyroid patients, suggest that altered dopamine turnover or increased dopamine receptor sensitivity may be responsible.¹²¹ Adrenergic blockade with propranolol can also provide symptomatic relief until the hyperthyroidism is definitively treated.

Hypocalcaemia is a rare cause of dystonia or choreoathetosis. Usually the aetiology is idiopathic hypoparathyroidism.¹²²⁻¹²⁴ Patients may present with the abnormal movements, which may be asymmetric, are usually paroxysmal and, rarely, kinesigenic.^{122 125 126} Affected patients are young, with calcium concentrations of 4-6 mg/dl, low serum magnesium, and raised serum phosphorus concentrations. The dyskinesia subsides with treatment and is therefore unlikely to be due to the irreversible basal ganglia calcifications that are often seen on cerebral imaging. One hypothesis is that hypocalcaemia increases neuronal and muscle membrane permeability, resulting in hyperexcitability.¹²⁴

Extremes in serum glucose concentrations are often accompanied by a depressed level of consciousness and altered cognition. Focal seizures, involuntary movements, and abnormal posturing occur less commonly and may be difficult to differentiate. Generalised chorea or hemiballism-hemichorea is more commonly related to non-ketotic hyperosmolar hyperglycaemia and resolves with treatment of the hyperglycaemia.¹²⁷⁻¹²⁹ Serum glucose concentrations are 300 to 1000 mg/dl, and serum osmolality ranges from 300 to 390 mOsm/l. Brain CT is unrevealing. Dyskinesias in this

setting seem to be more common in postmenopausal women than in other patients, perhaps because of striatal dopamine receptor supersensitivity.¹²⁷ Other pathophysiological mechanisms that may be involved include a hyperglycaemia induced shift towards anaerobic metabolism resulting in GABA metabolism as an alternative energy source in the absence of ketosis, and small deep lacunar basal ganglia infarctions not visible on brain CT.¹²⁷ In one study,¹³⁰ nine out of 10 patients in ketotic hyperglycaemia with chorea had CT and T1 MRI within a week of the onset; this showed high density or high signal in the caudate and/or putamen unilaterally or bilaterally, correlating with the initial side of involvement. The same regions showed hypoperfusion on SPECT, and residual hypointensity on T2 MRI months later, whereas the chorea resolved within 2 days of treatment. This pattern of imaging changes in the striatum may represent petechial haemorrhage or demyelination.¹³⁰

Severe hypoglycemia may be accompanied by tonic posturing of all four limbs¹³¹ or bilateral choreoathetotic movements,¹³² which usually resolve with the reestablishment of normoglycaemia. Repeated episodes of hypoglycaemic coma have resulted in permanent bilateral chorea.¹³³

Other metabolic disturbances in which dystonia or chorea have rarely been noted are hypernatraemic dehydration, hyponatraemia, and hypomagnesaemia, although the recent literature is lacking in cases.¹³⁴⁻¹³⁶ In a few instances of osmotic demyelination syndrome, tetraparesis has been followed in 1 to 4 months by transient or permanent bilateral dystonia or choreoathetosis of the arms, face, or tongue.^{137 138}

An encephalopathy associated with choreoathetosis was reported in one patient with a splenorenal shunt without cirrhosis.¹³⁹ Both aspects improved on treatment with a low protein diet and lactulose.

Summary

Dystonia and chorea are uncommon accompaniments, but sometimes the presenting features of certain acquired systemic disorders that presumably alter basal ganglia function. Hypoxia-ischaemia may injure the basal ganglia through hypoperfusion of subcortical vascular watershed regions and by altering striatal neurotransmitter systems. Toxins interfere with striatal mitochondrial function, resulting in cellular hypoxia. Infections may affect the basal ganglia by causing vasculitic ischaemia, through the development of antibodies to basal ganglia epitopes, by direct invasion of the basal ganglia by the organism, or through cytotoxins causing neuronal injury. Autoimmune disorders alter striatal function by causing a vasculopathy, by direct reaction of antibodies with basal ganglia epitopes, or by stimulating the generation of a cytotoxic or inflammatory reaction. Endocrine and electrolyte abnormalities influence neurotransmitter balance or affect ion channel function and signalling in the basal ganglia. In general, the production of chorea involves dysfunction of the indirect pathway from the caudate and putamen to the internal

globus pallidus, whereas dystonia is generated by dysfunction of the direct pathway. The time of the onset of the movement disorder relative to the primary disease process, and course vary with the age of the patient and the underlying pathology. Treatment of dystonia or chorea associated with a systemic medical disorder must initially consider the systemic disorder.

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