Post-stroke dyskinesias

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Abstract: Strokes, whether ischemic or hemorrhagic, are among the most common causes of secondary movement disorders in elderly patients. Stroke-related (vascular) movement disorders, however, are uncommon complications of this relatively common disease. The spectrum of post-stroke movement disorders is broad and includes both hypo- and hyperkinetic syndromes. Post-stroke dyskinesias are involuntary hyperkinetic movements arising from cerebrovascular insults and often present with mixed phenotypes of hyperkinesia which can sometimes be difficult to classify. Nevertheless, identification of the most relevant motor phenotype, whenever possible, allows for a more specific phenomenological categorization of the dyskinesia and thus helps guide its treatment. Fortunately, post-stroke dyskinesias are usually self-limiting and resolve within 6 to 12 months of onset, but a short-term pharmacotherapy might sometimes be required for symptom control. Functional neurosurgical interventions targeting the motor thalamus or globus pallidus interna might be considered for patients with severe, disabling, and persistent dyskinesias (arbitrarily defined as duration longer than 12 months).

Keywords: vascular dyskinesia, stroke, movement disorders

Introduction

Strokes and movement disorders are quite common diseases and come to the attention of all physicians, but most often neurologists, emergency physicians, and primary care providers. Stroke-related (vascular) movement disorders, however, are relatively uncommon and represent a recognized complication of either ischemic or hemorrhagic strokes. Although the prevalence of post-stroke movement disorders is unclear because of the lack of prospective studies, data from retrospective studies have estimated the overall prevalence to range from 1% to 4% of all strokes with both sexes affected equally.1–3

The spectrum of post-stroke movement disorders is broad and includes both hypo- and hyperkinetic syndromes. The latter often present as variable combinations of hyperkinetic movements (dyskinesias) and can be broadly classified into three main phenotypes: choreiform dyskinesias (ballism, chorea, and athetosis), dystonia, and non-choreo-dystonic dyskinesias (eg, tremor, asterixis, and myoclonus) (Figure 1). The prevalence of vascular dyskinesias remains uncertain. In the Lausanne Stroke Registry from Switzerland, 29 (1%) of 2,500 patients admitted to the registry over 14 years developed hyperkinetic movement disorders with an estimated incidence of 0.08% per year. However, the large loss to follow-up has likely underestimated the prevalence, particularly for delayed movement disorders.1 In another stroke registry from Ecuador, 56 (3.7%) of 1,500 patients admitted to the registry over 9 years developed post-stroke movement disorders within the first year after stroke: 50 patients (3.3%) had hyperkinetic movements and 6 patients (0.4%) parkinsonism.2 Although data from these two studies suggest that vascular hyperkinetic movement disorders are likely to regress spontaneously, it remains unknown whether that decreases their
Movement disorders are a group of basal ganglia and/or cerebellar circuit disorders characterized by impaired ability to control or coordinate movements. They are usually classified first based on an accurate description of the abnormal movement (phenomenology), and then subdivided according to the underlying cause (etiology). The “phenomenological classification” divides movement disorders into the following types: 1) Hypokinetic (parkinsonian) disorders, dominated by poverty (hypokinesia) or slowness (bradykinesia) of movement, 2) Hyperkinetic (dyskinetic) disorders, characterized by excessive, abnormal involuntary movements, and 3) Other movement disorder syndromes, cannot easily be grouped under the previous two categories, such as ataxia and akathisia. Furthermore, hyperkinesias (dyskinesias) are classified as “focal” if only one body region is involved, “segmental” if ≥2 adjacent body regions are affected, “multifocal” if ≥2 noncontiguous body regions are affected, “hemibody” if the ipsilateral arm and leg are involved, and “generalized” if the trunk and ≥2 other body regions are involved. The “etiological classification” of movement disorders, on the other hand, subdivides them into the following types: 1) Primary (genetic or idiopathic) disorders, without an identifiable secondary cause; 2) Secondary (symptomatic) disorders, due to a known acquired etiology such as vascular, toxic, or metabolic abnormalities; and 3) Psychogenic (functional) disorders, commonly due to conversion, somatic symptom, or factitious disorders.

Although “dyskinesia” is a broad term that can indicate any hyperkinesia, it is often employed in clinical practice to indicate mixed, unusual, or complex hyperkinetic movements, especially when these movements are challenging to describe; nevertheless, a more specific phenomenological categorization should be used whenever possible. For example, variable mixtures of ballism, chorea, and athetosis are often seen simultaneously in the same patient and are commonly referred to as “choreiform dyskinesias”. Not infrequently, dystonia coexists with choreiform movements and the term “choreo-dystonic dyskinesia” is often used in this clinical setting. Interestingly, the choreiform dyskinesias are considered variants within the same phenotypic spectrum, with ballism and athetosis representing its fastest and slowest motor phenotypes, respectively (Table 1).

Finally, the term “dyskinesia” is also used more specifically to indicate certain movement disorders such as levodopa-induced dyskinesia (due to chronic exposure to levodopa in Parkinson’s disease patients) and tardive dyskinesia (due to prolonged exposure to dopamine-blocking agents).

Pathophysiology
Motor control is a complex process that is governed by a sophisticated motor circuitry involving both pyramidal (cortical) and extrapyramidal (basal ganglionic and cerebellar) circuits. Motor commands are generated in the motor cortex, but basal ganglia and cerebellum closely refine these signals by acting as feedback loops to allow for smooth, accurate, coordinated movements. While the cortico-basal loop (basal ganglia circuitry) provides a tonic inhibitory output to the thalamus and thus the motor cortex, the output of the cortico-cerebellar loop (cerebellar circuitry) is tonically excitatory. Glutamate is the
alleviation. Inhibition is a key feature of the basal ganglia motor system, where acetylcholine is the main excitatory neurotransmitter and GABA is the major inhibitory neurotransmitter. Glutamate is also essential in the basal ganglia circuitry, acting as a neurotransmitter in the striatal output pathways and providing feedback to the brainstem and thalamus.

**Figures:***

- **Figure 2:** A simplified diagram of the motor control circuitry. The motor cortex projects to the cerebellum and basal ganglia and receives feedback signals from them. Although cerebellar output is tonically excitatory and basal ganglia output is tonically inhibitory, the balance between these two systems is of pivotal importance for motor control and coordination. GLU and GABA are the major excitatory and inhibitory neurotransmitters in this network, respectively.

- **Figure 3:** A simplified diagram of the basal ganglia motor circuitry, including its direct and indirect pathways. DA plays a central role in this circuit and acts as a neuromodulator that regulates the striatal function. Dopamine is the transmitter of the nigrostriatal pathway, whereas acetylcholine is a major transmitter of striatal interneurons. The striatum is the largest component of the basal ganglia motor circuit, and the vast majority of its neurons are GABAergic medium-sized spiny neurons whose axons comprise the striatal output pathways. These neurons are divided into two subsets of approximately equal numbers and provide two projection systems that have opposite effects on movement, the direct and indirect pathways. The direct pathway (GO pathway) originates from dopamine D1 receptor-expressing neurons and projects directly to the GPe.

**Abbreviations:** GLU, glutamate; GABA, gamma-aminobutyric acid; DA, dopamine; GPe, external globus pallidus; GPi, internal globus pallidus.
to disinhibit the thalamus and thus the motor cortex. The indirect pathway (NO-GO pathway) originates from D2 receptor-expressing neurons and projects to the GPe and subthalamic nucleus before terminating in the GPi. It is an inhibitory pathway because its net effect is to inhibit the thalamus and thus the motor cortex. Dopamine has differential effects on these two pathways: it activates D1 receptors and facilitates the direct pathway, but it inhibits D2 receptors and suppresses the indirect pathway. Therefore, the net effect of dopamine is to facilitate voluntary movements by promoting transient interruptions of the tonic inhibitory output of the basal ganglia via the simultaneous activation and suppression of the direct and indirect pathways, respectively.16–20

The cerebellum consists of a cortex, white matter, and deep cerebellar nuclei. It acts as a sensorimotor information processor by receiving information from all parts of the nervous system and comparing the motor commands of the cortex with the proprioceptive information coming from joints and muscles. This enables the cerebellum to detect errors in muscle contractions during active movements and thus to contribute to motor accuracy and coordination.15 Two cerebellar feedback loops are critical for this task, the dentato-rubro-olivary loop and the cortico-cerebellar loop. The dentato-rubro-olivary circuit (Guillain-Mollaret triangle) connects the dentate nucleus in the cerebellum with the contralateral red nucleus and inferior olivary nucleus in the brainstem via the superior cerebellar peduncle, the central tegmental tract, and the inferior cerebellar peduncle, respectively.21 This subcortical circuit is itself part of the larger cerebellar motor network, the cortico-cerebellar circuitry, in which the cerebral and cerebellar cortices are connected together indirectly. The motor cortex projects to the cerebellar cortex (via pontine nuclei) which, in turn, projects primarily to the VL nuclei of thalamus and then back to the cerebral cortex (Figure 4).14,15,23 As the inferior olivary nucleus receives collateral inputs from all afferent pathways projecting to the cerebellar cortex via mossy fibers, it compares intended with executed movements and conveys error signals to the cerebellar cortex via climbing fibers.14,15,24

The pathogenesis of stroke-related dyskinesias is still incompletely understood but suggested mechanisms include post-synaptic denervation hypersensitivity, trans-synaptic neuronal degeneration, as well as aberrant axonal and dendritic plasticity (remodeling) after the cerebrovascular injury.3 Post-stroke dyskinesias are relatively rare even with marked lesions, but they can arise after any stroke subtype at any level within the motor circuitry and after any interval period. Furthermore, no specific anatomical locations in the motor circuitry are reliably predictive of a particular dyskinesia, whereas the same dyskinesia can be caused by lesions in different locations in this circuitry. Due to this overlap, stroke-related movement disorders cannot be predicted from the location, size, or number of vascular insults.1,2,19 Interestingly, though the pathogenesis of vascular and primary movement disorders is different, they share similar underlying pathophysiology.

If symptomatic, vascular lesions involving the basal ganglia circuitry usually present with contralateral abnormal involuntary movements, but there have been rare case reports of ipsilateral dyskinesias.25 The most commonly involved areas in this regard are the striatum followed by the thalamus, but other reported locations include the fronto-parietal cortex, caudate, subthalamic nucleus, corona radiata, internal capsule, and pons.1,2,19 These vascular dyskinesias are believed to arise from underactivity of the indirect pathway (and/or overactivity of the direct pathway) leading to a decreased pallidal inhibitory output to the thalamus. The resultant thalamic disinhibition releases the motor cortex and allows movements that are normally suppressed.2,19,26,27 Vascular parkinsonism, on the other hand, is usually caused by diffuse or multiple insults in the basal ganglia loops and presents with non-tremulous, lower-body parkinsonism.

![Figure 4 A simplified diagram of the cerebellar motor circuitry. The dentato-rubro-olivary circuit (Guillain-Mollaret triangle) is part of the cortico-cerebellar loop. The dentate nucleus projects to red nucleus via the SCP, which in turn connects to inferior olivary nucleus via the CTT. The latter nucleus projects back to the dentate nucleus via ICP.](image)

**Abbreviations:** SCP, superior cerebellar peduncle; CTT, central tegmental tract; ICP, inferior cerebellar peduncle.
Non-structural causes, especially hypo-glycemia and nonketotic hyperglycemia, can occasionally present with dyskinesia. Interestingly, hemichorea-hemiballism is the most commonly reported dyskinesia arising secondary to either structural (eg, vascular) or non-structural (eg, dysglycemic) etiologies.

Differential Diagnosis

Acute focal, segmental, or hemibody dyskinesia should always raise a suspicion of structural lesions involving the motor circuitry. Although stroke is the most common cause after the age of 50 years, other structural pathologies have also been reported, including tumors, arteriovenous malformation, cerebral abscess, encephalitis, and multiple sclerosis. Non-structural causes, especially hypoglycemia and nonketotic hyperglycemia, can occasionally present with dyskinesia. Interestingly, hemichorea-hemiballism is the most commonly reported dyskinesia arising secondary to either structural (eg, vascular) or non-structural (eg, dysglycemic) etiologies.

Diagnosis

A careful history (including medical, drug, and family history) and identifying the dominant phenomenology remain the first step in the clinical assessment, as that steers the differential diagnosis and the subsequent diagnostic trajectory. Neuroimaging studies, such as computed tomography (CT) or magnetic resonance imaging (MRI), are important to confirm the diagnosis of stroke or to evaluate for structural stroke mimics.

Post-stroke dyskinesias often present as variable combinations of hyperkinetic movements and can sometimes be challenging to classify. Nevertheless, identification of the dominant abnormal movement, whenever possible, allows for a more specific phenomenological categorization. Furthermore, the relative predominance of one type of phenomenology might be state dependent (eg, a resting athetosis might evolve into ballism with voluntary movements or when the patient is stimulated or excited). Hemichorea-hemiballism is the most common vascular dyskinesia, but other reported mixed movements include chorea-ballism-dystonia, chorea-athetosis-dystonia, and dystonia-athetosis with or without action tremor or myoclonic jerks. Tremor, asterixis, and myoclonus are generally far less common than choreo-dystonic dyskinesias.

Post-stroke chorea usually presents as a hemichoreiform dyskinesia (hemichorea, hemiballism, and/or hemiathetosis) on the contralateral side of the vascular insult. Focal or segmental presentations are uncommon, and generalized forms are rare. The concomitant hemiparesis might initially prevent the expression of hemichorea, but improvement of the weakness unmasks this dyskinesia. Hemichorea can occasionally be the presenting sign of acute stroke, though careful examination often reveals an underlying mild hemiparesis with or without other subtle deficits.

Post-stroke dystonia usually affects the contralateral limb, and it is often associated with hypertonia due to underlying spasticity (spastic dystonia). Interestingly, dystonia in combination with spasticity is usually intensified by muscle activation in the affected limb or elsewhere (overflow phenomenon). Cervical dystonia (eg, torticollis) and cranial dystonias (eg, blepharospasm or oromandibular dystonia) are rarely observed in association with cerebrovascular insults.

Post-stroke tremor is a heterogeneous group of movement disorders characterized by various tremor phenomenologies, but isolated tremor unaccompanied by other abnormal movements is rare. Action tremor is by far the most common form, but rest tremor can occasionally be seen (eg, in vascular parkinsonism). Cerebellar tremor, the prototype vascular tremor, is primarily a slow intention tremor (<5 Hz) with frequent postural component. Holmes tremor is usually a low-frequency tremor (<5 Hz) with rest, postural, and intention components in the affected upper extremity. Palatal tremor is a slow tremor of the soft palate (<5 Hz) in which patients may complain of a disturbing clicking sound generated by palatal muscle contractions causing opening and closing of the eustachian tube. Dystonic tremor is usually a focal postural and/or kinetic tremor that occurs in association with dystonia, which might be subtle or overshadowed by the tremor. Despite being arrhythmic with variable frequencies, dystonic oscillations are traditionally referred to as “tremor.”

Post-stroke myoclonus and asterixis are usually focal or segmental with corresponding lesions reported in numerous, mostly contralateral, brain regions. Myoclonus is not an uncommon component of mixed vascular movement disorders, but isolated myoclonus is rare. Dystonic myoclonus
(myoclonic dystonia) has been described in patients with vascular dystonia secondary to thalamic infarcts.\(^2\,^3\,^19\)

**Prognosis**

The natural history of post-stroke dyskinesias is variable. Their onset can be either “early/acute”, occurring shortly after stroke, or “delayed/chronic”, emerging months to years later. On the other hand, their course can be transient, recurrent, persistent, or progressive.\(^1\,^4\,^3\,^44\) Although the latency interval seems to depend partially on the dyskinesia type, it still varies widely within each vascular hyperkinetic movement disorder.\(^2\,^3\) While dystonia is frequently delayed in onset, hemichorea-hemiballism usually occurs shortly after stroke and occasionally represents the initial manifestation of acute cerebral ischemia or intracerebral hemorrhage.\(^2\,^3\,^3\,^45\,^51\) Post-stroke dyskinesias are usually self-limited and resolve within 6 to 12 months of onset, but the overall long-term prognosis of the affected patients is similar to that of other stroke patients.\(^1\,^2\,^46\,^52\)

**Management**

Although post-stroke dyskinesias tend to resolve spontaneously, a short-term treatment might sometimes be required for symptom control.\(^1\,^2\) As in all cases of secondary movement disorders, treatment of the underlying etiology is of paramount importance. Control of vascular risk factors is crucial in reducing the incidence of vascular dyskinesias. The discussion of stroke prevention and management, however, is beyond the scope of this article. Symptomatic pharmacotherapy might be necessary for severe dyskinesias, but periodic trials of therapeutic withdrawal (ie, for patients with controlled symptoms) are required due to the high likelihood of spontaneous regression. Medications should be started at low doses and gradually titrated up until an effective and tolerable dosage is reached. Although there are no established treatment guidelines, most of the treatment options are similar to those for primary movement disorders based on similar underlying pathophysiology.

The symptomatic pharmacotherapy for post-stroke choreiform dyskinesias consists mainly of anti-dopaminergic therapy with typical or atypical antipsychotics (neuroleptics). Blockade of striatal dopamine D2 receptors is believed to be responsible for their anti-dyskinetic activity, as D2 receptor antagonists disinhibit the indirect pathway and, therefore, suppress abnormal involuntary movements. Unfortunately, dopaminergic blockade carries the risk of acute dystonic reactions, tardive dyskinesia, and drug-induced parkinsonism. Atypical antipsychotics (eg, risperidone), however, are less likely to cause these side effects compared to typical antipsychotics (eg, haloperidol) and, therefore, are generally preferred for this use.\(^53\,^54\) Tetrabenazine, a presynaptic dopamine depletor with weak postsynaptic D2 receptor blocking activity, is a reasonable alternative for patients who are intolerant or unresponsive to dopamine receptor antagonists.\(^55\) Tetrabenazine acts primarily as a reversible inhibitor of the vesicular monoamine transporter 2 (VMAT2) in the presynaptic nerve terminals, thus exposing dopamine and other monoamines to monoamine oxidase and leading to their depletion.\(^56\) Unlike dopamine receptor blockers, tetrabenazine rarely causes tardive dyskinesia because of its dominant presynaptic anti-dopaminergic properties.\(^3\,^37\) Non-dopaminergic drugs have been tried in the management of vascular choreiform dyskinesias with varying success. Case reports and small case series have suggested a potential beneficial effect of antiepileptic drugs including levetiracetam, topiramate, gabapentin, clonazepam, and valproate.\(^58\,^62\)

Chemonerveneration with botulinum toxin (BTX) injections is the cornerstone of the symptomatic treatment of focal or segmental post-stroke dystonia.\(^3\) BTX is a neurotoxic protein with several serotypes that cleaves the synaptic proteins (SNARE) in the presynaptic nerve terminals, thereby blocking the release of acetylcholine at the neuromuscular junction. SNARE proteins are required for the fusion of presynaptic storage vesicles containing acetylcholine with the presynaptic membrane.\(^52\) BTX injections are given intramuscularly, often under electromyography (EMG) guidance, and need to be repeated every 3 to 6 months.\(^64\) Vascular dystonia usually has a poor response to oral pharmacotherapy, including dopamine blocking and depleting agents, anticholinergic drugs, baclofen, and benzodiazepines. Oral medications, however, are widely used in generalized dystonia, dystonia mixed with other movement disorders, or as an adjuvant therapy in focal or segmental dystonia when there is an unsatisfactory response to BTX.\(^64\,^67\)

Post-stroke tremor is particularly refractory to pharmacotherapy. Trials of medications with GABA-agonistic activity (eg, clonazepam, valproate, topiramate, or primidone), alone or in combination, may be effective in individual cases. Because of the dopaminergic (nigrostriatal) system involvement in Holmes tremor, treatment with levodopa or dopamine agonists seems to be useful.\(^31\) Propranolol, one of the first-line treatments in essential tremor, is usually of limited benefit in vascular tremor. Dystonic and parkinsonian tremors are treated as vascular dystonia and parkinsonism, respectively.\(^3\,^19\)

Post-stroke myoclonus and asterixis usually improve spontaneously and do not require pharmacotherapy. When interfering with the patient’s functional abilities, like eating or writing, myoclonus is most frequently treated with
GABAergic medications (eg, clonazepam and valproate), but levetiracetam or piracetam can be very useful. Monotherapy should be attempted first, although eventually several drug combinations might be required.\textsuperscript{3,19,53} Dystonic myoclonus is treated as vascular dystonia.

Finally, stereotactic functional neurosurgery, whether ablative or deep brain stimulation (DBS), should be considered for patients with severe and persistent dyskinesias (arbitrarily defined as duration longer than 1 year).\textsuperscript{3,19,53} While lesioning procedures (eg, pallidotomy or thalamotomy) are carried out using radiofrequency ablation or gamma knife radiosurgery, DBS (eg, pallidal or thalamic DBS) uses high-frequency electrical stimulation of the targeted nuclei. Although the therapeutic mechanisms of action are not completely understood, ablative surgeries are believed to destroy abnormally hyperactive circuits in deep brain nuclei, while DBS suppresses abnormally excessive activity in the motor circuitry without significant destruction of the brain tissue.\textsuperscript{58,60} Neurostimulation, therefore, has largely replaced neuroablative treatment to refractory dyskinesias because it is less invasive, adjustable for maximal symptomatic benefit, and reversible in case of adverse effects. Stereotactic functional neurosurgery depends on the accurate identification of anatomically and functionally distinct deep brain structures to maximize therapeutic benefits and to minimize adverse neurological events of any surgical intervention. The contralateral motor thalamus or internal pallidum are the usual neurosurgical targets, but it is yet to be determined which target is more effective for specific dyskinesias.\textsuperscript{53,70} The ventrolateral “VL” nuclei, including ventralis intermedius and ventralis oralis posterior, are the most common nuclei targeted within the motor thalamus.\textsuperscript{71} Potential candidates with vascular dystonia should undergo surgery prior to the development of contractures and fixed deformities that may limit functional improvement as the dystonia improves.\textsuperscript{66}

**Conclusion**

Stroke is the leading cause of focal or segmental limb dyskinesia as well as hemidyskinesia in elderly patients, but other structural and non-structural brain abnormalities should also be considered in the differential diagnosis. Post-stroke dyskinesias, which can arise from either ischemic or hemorrhagic cerebrovascular insults, are often mixed and variable with several components of hyperkinetic movements. A comprehensive clinical and neuroimaging assessment are essential to establish the correct diagnosis. Fortunately, post-stroke dyskinesias tend to resolve spontaneously within 6 to 12 months. A short-term symptomatic pharmacotherapy may be required in some patients, whereas surgical treatment is reserved for persistent, disabling, and medically intractable cases.

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The authors report no conflicts of interest in this work.

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