

Apomorphine and Levodopa Challenge in Patients With a Focal Midbrain Lesion

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Summary: Three patients who presented with parkinsonian signs resulting from a focal midbrain lesion are reported. In all patients parkinsonian features occurred acutely and improved following acute challenge with apomorphine but not with levodopa. Remission of parkinsonian signs occurred spontaneously to a different degree. Inconsistent clinical response following administration of levodopa has been well documented in patients with focal midbrain lesions associated with parkinsonian

signs; however, the efficacy of apomorphine has not been tested before. Anatomic or etiologic features do not allow us to predict in which cases parkinsonian signs secondary to a midbrain lesion would respond to levodopa or to dopamine agonists. A trial with apomorphine is warranted in all such cases. **Key Words:** Apomorphine—Levodopa—Mesencephalon—Movement disorders—Parkinson's disease—Secondary parkinsonism.

It is known that discrete lesions of the midbrain may produce resting, postural, and action tremor^{1–3} or a secondary parkinsonian syndrome.^{1,4} Midbrain tremor is sometimes called “rubral,” although the involvement of the red nucleus is likely not to be necessary for tremor onset.⁵ A midbrain lesion can interrupt the cerebellothalamic tract, the rubro-olivo-cerebello-rubral loop (superior cerebellar peduncle, descending rubral projections, and dentate nucleus), or the nigrostriatal pathway.^{6,7} There is no published description of the combined response to levodopa and to apomorphine in parkinsonian syndromes secondary to a midbrain lesion.

We describe three patients with different types of midbrain lesions who had a significant improvement of parkinsonian signs after subcutaneous injection of apomorphine but not after oral levodopa.

PATIENTS AND METHODS

Drug Challenge

Acute challenge with antiparkinsonian drugs was always performed according to the following scheme. To

prevent side effects, all patients received 20 mg of the peripheral dopamine antagonist domperidone three times a day starting at least 24 hours before the assessment. All anti-parkinsonian medication was withheld for at least 12 hours according to published guidelines.⁸ Patients were tested early in the morning in a fasting state; they received a single standard oral dose of 250/25 mg levodopa/carbidopa on the first day and apomorphine on the following days. Apomorphine was given subcutaneously at a dosage of 1.5, 3.0, 4.5, or 6.0 mg with a delay of at least 90 minutes between two subsequent doses or on separate days. Dosage was increased until either side effects occurred or the maximum dose was reached. Levodopa was administered on a separate day. The Unified Parkinson's Disease Rating Scale (UPDRS) motor score or just the meaningful items (as in the case of patient 2) was administered before each acute challenge and 1 hour after levodopa or 30 minutes after apomorphine injection.

Patient 1

A 26-year-old woman first had a drug-resistant headache in July 1993. Her medical history had been uneventful until that time. A series of neurologic signs then gradually added up. In August she presented sensory loss on the left side of her face, left ageusia, and generalized weakness. A brain computed tomography (CT) scan re-

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vealed a triventricular hydrocephalus that was treated with a ventriculo-peritoneal shunt in September. By November the hydrocephalus was significantly reduced. The patient had no neurologic signs, no headache, and a normal papilla. Magnetic resonance imaging (MRI) scan showed a small tumor (8 mm in diameter) located in the midbrain tegmentum, just on the right of the midline, within and around the Sylvian aqueduct that was almost completely obstructed. Afterward, the clinical conditions gradually worsened. In December, the patient presented a bilateral parkinsonian syndrome with left prevalence: resting, postural, and action tremor of the upper limbs (more severe on the left) and chin, cogwheeling rigidity, and akinesia. In January 1994 levodopa/benserazide was prescribed at increasing doses (up to 600/150 mg daily), but no clinical improvement was observed.

In February 1994 we first saw the patient; she was in an intensive-care unit where a complete UPDRS could not be administered. An acute challenge with levodopa provided no benefit, while apomorphine (1.5 and 3 mg) produced a marked and short-lasting relief of resting tremor in the limbs and chin. Postural tremor did not change but rigidity and bradykinesia improved. These effects were maximal 25 minutes after the subcutaneous injection and lasted for approximately 45 minutes. As shown by MRI, the tumor abutted the nigrostriatal and cerebellothalamic tracts bilaterally, mainly affecting the right half. During the next 6 months, the patient recovered spontaneously. MRI scans were periodically repeated; they confirmed the persistence of a localized lesion in the midbrain periaqueductal gray (Fig. 1). A radiologic diagnosis of ependymal cyst was retained. The patient is still regularly followed up by neurosurgeons.

Patient 2

A 63-year-old woman with an aorto-mitral valve prosthesis had a stroke of the left midbrain tegmentum 2

years before coming to our attention. When her condition stabilized, she remained with a right hemiparesis and left third cranial nerve palsy (extrinsic and intrinsic). Approximately 8 months later, resting, postural, and action tremor and a moderate rigidity on the right side added up to the clinical picture. We saw the patient a few months afterward. MRI scan revealed a brain stem lesion located in the left midbrain peduncle and involving the periaqueductal gray area (Fig. 2). The clinical picture was that of an incomplete Benedikt's syndrome. Levodopa provided minimal benefit on resting tremor of the upper limb, whereas apomorphine markedly improved resting tremor in the upper and in the lower limb and rigidity in a dose-dependent fashion (see the videotape). The patient gradually recovered with time as resting tremor progressively improved.

Patient 3

A 64-year-old outpatient who had Parkinson's disease since 1985 had excellent response both to levodopa and dopamine agonists either after acute challenge or chronic administration (400 mg levodopa per day, 1.5 mg pergolide per day). His brain MRI scan was unremarkable until 1995 when he had a rapid worsening of his parkinsonian picture and was admitted to the Gemelli Hospital. Acute challenge showed a loss of improvement following levodopa; response to apomorphine was instead maintained (Table 1). A suspicion of Parkinson plus syndrome was posed. A new MRI scan revealed a small hemorrhage restricted to the midbrain tegmentum that directly affected the right substantia nigra (Fig. 3). Chronic therapy with subcutaneous infusion of apomorphine (up to 90 mg daily) effectively improved his motor condition until January 1997. He then developed dyskinesia which became increasingly more intense. A gradual reduction of apomorphine infusion relieved dyskinesia without worsening parkinsonian signs. Serial

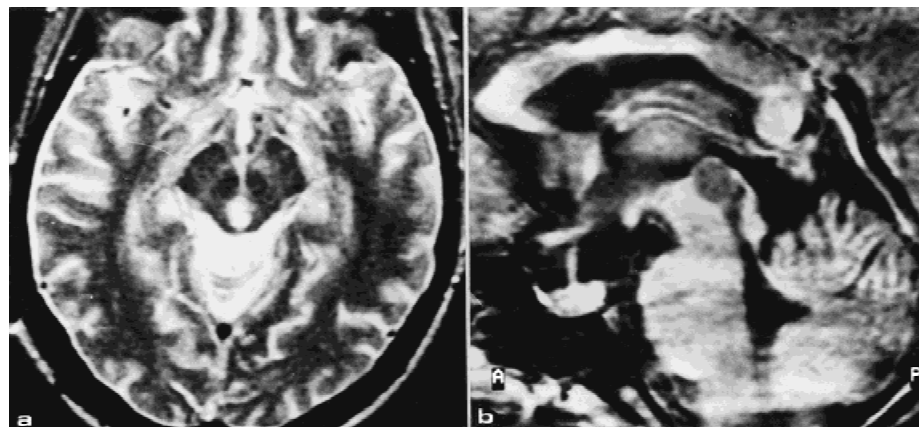


FIG. 1. MRI observation (0.5 T) of patient one 7 months after the occurrence of parkinsonian signs shows a small T2-hyperintense lesion (A) located in the midline, which prevalently extends in the right half of the midbrain and almost occludes the Sylvian aqueduct (B).

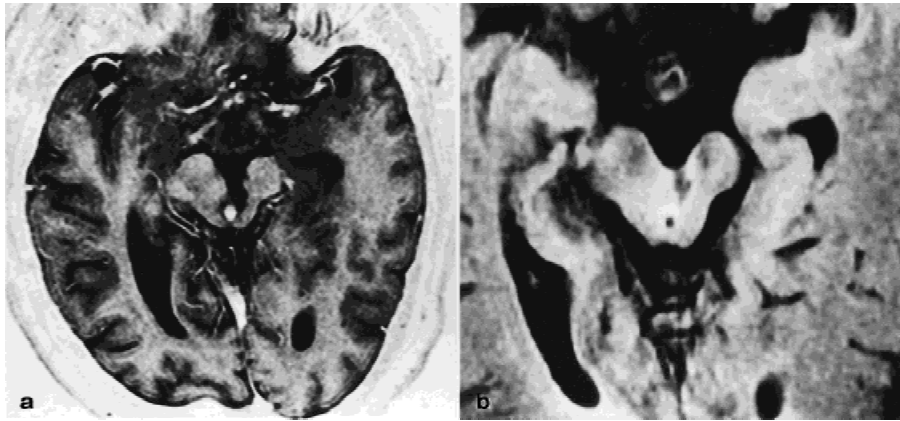


FIG. 2. MRI observation (1.5 T) of patient two 8 months after the stroke reveals a remarkable atrophy of the left midbrain peduncle (A) and T1-hypointense lesions in the periaqueductal gray (B).

MRI scans showed recovery of the midbrain lesion followed by repeated microscopic hemorrhages. A radiologic diagnosis of cavernoma was retained.

Cases Reported in the Literature

Improvement of parkinsonian features following administration of levodopa has been reported in patients who had a focal midbrain lesion, but no data are available on the efficacy of apomorphine. Table 2 summarizes 10 cases for which improvement following levodopa administration (either acute or chronic challenge) is reported. In addition, reports on two patients with similar midbrain lesions who did not benefit from levodopa are also available (Table 3). In these cases, improvement following the administration of other drugs (including amantadine) was observed on occasion.

Patients who were improved by levodopa had a variety of focal lesions, including tumors (one angioma, one cystic astrocytoma), hemorrhage (two posttraumatic, three as a result of stroke), posttraumatic atrophy, wound, or lacuna (one case each). Patients who were not improved by levodopa had tumors (one protozoan abscess, one craniopharyngioma, one ependymal cyst), hemorrhage (one resulting from a cavernoma), or ischemic stroke (one case).

In patients improved by levodopa, the lesions were always located in the upper cerebral peduncle and extended to the thalamus (in three) or to the subthalamic region (in one). In patients who did not improve following levodopa therapy, the lesions were also located in the midbrain (unilaterally or in proximity of the midline) and extended to the caudate nucleus and putamen in one case. Anatomic locations were confirmed pathologically in one case⁹ and by brain imaging in the remaining cases (including ours).

In addition to these, a number of reports on parkinsonian syndromes or on "rubral" tremor following a mid-

brain lesion did not provide information regarding response to levodopa.^{1,10-12}

DISCUSSION

Cases available in the literature do not provide any reliable clinical anatomic correlates allowing us to predict when a parkinsonian syndrome, or a parkinsonian tremor, resulting from a focal lesion of the midbrain would respond to levodopa or to dopamine agonists.

The observed lesions in cases not responding to levodopa do not present any evident anatomic or clinical difference from those in which response to levodopa is observed (Tables 2 and 3). Remarkably, the clinical efficacy of dopamine agonists has been assessed in a limited number of patients; this is probably the result of insufficient potency of classic dopamine agonists and unavailability of apomorphine in clinical practice until recently. In addition, in a significant number of patients with midbrain lesions, antiparkinsonian medications (either levodopa or dopamine agonists) were not tested at all. Because the present cases are the only ones in which apomorphine has been assessed, no direct comparison with other reported cases can be drawn on this point.

In healthy people and in early stages of Parkinson's disease, levodopa is transformed to dopamine in dopaminergic terminals located in the neostriatum. It is

TABLE 1. Patient 3: variation of response to acute challenge before and after the midbrain lesion

UPDRS-III improvement	February 1994	November 1995
Levodopa/carbidopa (250/25)	43.2%	13.5%
Apomorphine		
1.5 mg	15.1%	14.6%
3 mg	18.8%	16.8%
4.5 mg	22.4%	24.3%
6 mg	24.1%	24.3%

UPDRS, Unified Parkinson's Disease Rating Scale.

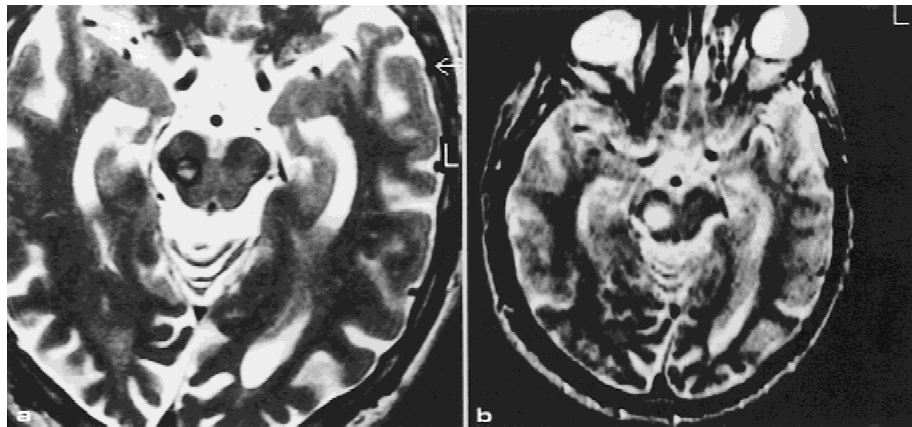


FIG. 3. MRI observation of patient three 6 months after the midbrain hemorrhage (A). T2-weighted image demonstrates a hyperintense lesion in the right midbrain (B).

thought that in Parkinson's disease, when a complete degeneration of dopaminergic terminals is attained, levodopa is decarboxylated to dopamine in nondopaminergic striatal cells.¹³ Apomorphine, instead, is a direct dopamine agonist which stimulates both D1- and D2-like dopamine receptors; this action is thought not to depend on the existence of dopaminergic terminals to be efficacious.¹⁴ Thus, levodopa challenge is related to presynaptic uptake function whereas apomorphine challenge tests postsynaptic function. This information is required to draw conclusions on the occurrence and on the extent of dopaminergic denervation in the neostriatum. Such information is only partially (or not at all) available in cases preceding our series. Therefore, the real status of dopaminergic degeneration in those patients cannot be fully ascertained.

In a series of six patients with peduncular tremor, who improved following levodopa but not following dopamine agonists, a marked decrease of ¹⁸F-fluorodopa uptake was found in the neostriatum ipsilateral to the lesion, while no increase of D2-like dopamine receptor binding (as seen by 76 Br-bromolisuride) was observed.³ This led the authors to hypothesize that their observation reflected a severe striatal dopaminergic denervation secondary to a lesion of the ipsilateral nigrostriatal neurons. A PET study in another patient with a bilateral lesion restricted to the substantia nigra also revealed a marked reduction of ¹⁸F-fluorodopa uptake in the neostriatum.¹⁵ This patient too responded to levodopa. Taken together, these observations suggested that in patients with a midbrain lesion, who respond to levodopa, neostriatal dopaminergic terminals are decreased but spared enough to allow conversion of levodopa to dopamine.

In the present series, patients with midbrain lesions did not improve following levodopa administration. Although higher levodopa doses could have provided increased benefit, in each of these cases apomorphine was

immediately helpful. This may indicate that dopaminergic terminals located in the neostriatum were degenerated to a large extent, whereas post-synaptic sites were receptive to dopamine agonists. Changes in the sensitivity to dopamine receptors stimulation over time may partly explain the discrepancy between levodopa and apomorphine responses. An alternative interpretation is that dopaminergic nigrostriatal neurons had not degenerated but were functionally inactivated. The latter possibility is consistent with the observation that parkinsonian features recovered completely in patient 1, almost completely in patient 2, and are still rapidly improving in patient 3. All patients had an acute onset of symptoms.

Why an acute dysfunction of dopaminergic nigrostriatal neurons should bring about loss of response to levodopa following an acute event as in our cases, but not following a chronic progressive degeneration as in idiopathic Parkinson's disease, is an intriguing question. Rats with an acute degeneration of the nigrostriatal pathway produced by 6-hydroxydopamine show contralateral rotations following injection of apomorphine and ipsilateral rotations following administration of levodopa.^{16,17} Levodopa taken up by intact nigrostriatal terminals is responsible for the ipsilateral rotation. In people, no clinical equivalent to the rotation observed in lower species has been demonstrated. In addition, animal models of acute or subacute functional inactivation of nigrostriatal neurons are also available. Subacute administration of MPTP to black mice has been shown to produce a transient inactivation of nigrostriatal neurons.¹⁸ Energy-dependent fast axonal transport does not take place in viable, but inactivated, neurons until they recover. A similar event may have occurred in the patients in the present series.

These cases suggest that unbalanced response to levodopa and apomorphine (meaning that response to levodopa is lost whereas that to apomorphine is maintained)

TABLE 2. Cases with improvement following levodopa administration (side of lesion and of clinical sign is indicated whenever available)*

Anatomic structures (etiology)	Clinical picture	Levodopa efficacy	Other drugs	Reference
Right midbrain (mesencephalic angioma)	Left resting, postural and action tremor (3-8 Hz) Dyskinesia in the left hemisoma Extrinsic and intrinsic right third cranial nerve palsy	Good (660 mg)	Ineffective • Tetrabenazine • Diazepam • Clonazepam • Orphenadrine	19
Left cerebral peduncle posttraumatic focal atrophy)	Left-sided spastic hemiparesis Delayed spastic right hemiparesis Delayed dysmetria and dysarthria Delayed bilateral Babinski's sign Delayed resting, postural and action tremor of head, neck, and arms	Excellent (800 mg)	Ineffective • Propranolol (240 mg) • Primidone (1000 mg) Amantidine (200 mg)	2
Right upper peduncle and thalamus (traumatic hematoma)	Left resting, postural and action tremor Left hemiplegia Diplopia Peripheral right seventh cranial nerve palsy	Excellent (600 mg)	Ineffective • Clonazepam • Oxitripam • Primidone	
Upper peduncle (bullet wound)	Delayed left cerebellar syndrome Resting (4-6 Hz), postural and action tremor Hemiparesis Hypoesthesia Left third cranial nerve palsy	Excellent (300 mg)	Not reported • Piribedil (120 mg)	Patient 1 ³
Upper peduncle (hemorrhagic stroke)	Resting (7 Hz) and postural tremor Dystonia Bradykinesia Spastic hemiparesis	Mild (600 mg)	Not reported • Bromocriptine (7.5 mg)	Patient 2 ³
Upper peduncle and thalamus (hemorrhagic stroke)	Resting tremor (3.5-4 Hz) Hemiparesis Bilateral rigidity and bradykinesia Right third cranial nerve palsy	Moderate (500 mg)	Not reported • Piribedil (300 mg)	Patient 3 ³
Upper peduncle and thalamus (hemorrhagic stroke)	Resting, postural and action tremor Hypertonia Dystonia Right rest tremor Bradykinesia Transient right third cranial nerve palsy?	Moderate (500 mg)		Patient 4 ³
Upper peduncle and subthalamic region (traumatic hemorrhage)	Resting (5 Hz), action and postural tremor Dysmetria (lower limb) Hypertonia	Mild (600 mg)		Patient 5 ³
Left frontal lobe (cystic astrocytoma)	Right resting and postural tremor Micrographia Right rigidity	Good with delayed response (375 mg)	Good • Trihexyphenidyl (6 mg) • Amantadine (300 mg)	21
Bilateral substantia nigra: pars compacta and pars reticulata on the left, pars compacta on the right (lacuna)	Bilateral (predominant right side) bradykinesia and rigidity No tremor	Excellent (550 mg)	Not reported • Selegiline (5 mg) • Lisuride (0.4 mg)	15

* Quality of improvement following levodopa or other drugs (with maximum daily dosage) is indicated.

may be a specific feature of some parkinsonian syndromes resulting from acute midbrain lesions. This is in keeping with the observation that improvement following levodopa is a specific feature of idiopathic Parkinson's disease. We suggest that patients with focal midbrain lesions leading to parkinsonian features should be studied with acute and chronic drug challenge (levodopa and dopamine agonists) and be followed up to detect time-related clinical changes. Unbalanced response to levodopa and apomorphine challenge may predict recovery in such patients.

LEGENDS TO THE VIDEOTAPE

Segment 1: This segment shows patient 2 untreated. This woman had a left incomplete third nerve palsy, a right hemiparesis, resting and action tremor.

Segment 2: This segment shows patient 2 after acute challenge tests with Sinemet 250/50. One hour after an acute challenge with 250/25 mg levodopa/carbidopa a minimal reduction of resting tremor in the upper limb is observed. Resting tremor in the lower limb is unchanged. Thirty minutes after receiving 1.5 mg apomorphine the

TABLE 3. Cases without improvement following levodopa administration (side of lesion and of clinical sign is indicated whenever available)*

Anatomic structures (etiology)	Symptoms	Levodopa	Other drugs	Reference
Round lesion (1 cm) in the left midbrain slightly crossing the midline (toxoplasma abscess)	Left resting (3-4 Hz), postural and action tremor Dysarthria Left ptosis (extrinsic third cranial nerve palsy) Slow saccades Right hemiplegia Weakness of the left seventh cranial nerve	No effect	Ineffective • Clonazepam • Primidone Mild improvement • Trihexyphenidyl • Isoniazide	22
Substantia nigra, caudate nucleus, and putamen (craniopharyngioma compressing the brain stem)	Bilateral tremor Bilateral temporal hemianopsia Bilateral and axial rigidity and bradykinesia Generalized weakness	No effect (1 g)	Ineffective • Amantadine (200 mg) • Bromocriptine (60 mg/)	9
Right midbrain next to the midline (ependymal cyst)	Bilateral (predominantly right bradykinesia and rigidity) Bilateral resting and action tremor	No effect (600 mg)	Clear improvement Apomorphine (1,5 mg, acute challenge)	Present report, Patient 1
Left midbrain and pons (ischemic stroke)	Right hemiparesis Left third cranial nerve palsy (intrinsic and extrinsic) Delayed resting, postural, and action tremor on the right Right rigidity	No effect (250 mg)	Clear improvement • Apomorphine (4.5 mg, acute challenge)	Present report, Patient 2
Right midbrain (hemorrhage: cavernoma)	Worsening of rigidity and bradykinesia Postural instability	Loss of effect (1000 mg)	Clear improvement • Apomorphine (4.5 and 6 mg, acute challenge)	Present report, Patient 3

* Quality of improvement following other drugs (with maximum daily dosage) is reported.

patient is mildly sedated; improvement of resting tremor in the upper limb is observed. Thirty minutes after receiving 4.5 mg apomorphine, resting tremor is markedly decreased in the upper and lower limbs, whereas postural and action tremor remains. Voluntary movements of the right upper limb are performed more easily and faster as a result of a reduction of the associated parkinsonian features.

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