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*Neurorehabil Neural Repair* 2001 15: 151  
DOI: 10.1177/154596830101500208

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## Case Report

# Chronic Akinetic Mutism After Mesencephalic–Diencephalic Infarction: Remediated with Dopaminergic Medications

Michael P. Alexander

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**Objective:** Akinetic mutism (AKM) is an uncommon disorder with a complex neuropathology. There is no generally accepted treatment, and it is not known if late treatments are effective. The relationship between AKM and abulia is uncertain. **Methods:** The effects of dopaminergic treatment of a patient with chronic AKM after discrete bilateral infarctions of the mesencephalic ventral tegmental area and the lateral hypothalamus were studied with motor measures, the Functional Independence Measure (FIM), and neuropsychological tests. **Results:** Treatment with a combination of carbidopa/levodopa and pergolide produced prompt amelioration of AKM with dramatic and rapid improvement in FIM. An apathetic, amotivational state persisted despite resolution of akinesia and normal frontal executive functions. **Conclusions:** AKM may respond to dopaminergic treatment even after months of severe akinesia. The mechanism of abulia is more complex than simply a partial dopaminergic deficiency state and may persist even when AKM is treated and frontal cognitive functions are normal. **Key Words:** Akinetic mutism—Dopamine—Abulia.

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Akinetic mutism (AKM) is an uncommon neurologic condition characterized by paucity and slowness of movement and speech despite retained capacity to move and to speak (1). Although the pathologic anatomy of AKM has been identified, many diseases that may cause it are known, and some treatments have been reported, several aspects of AKM are not optimally clarified (2). The clinical recognition of AKM is not always straightforward. When there is also paresis, the contribution of

akinesia to disability may not be recognized. Potential markers for specific treatments have not been established, nor is it clear whether chronic AKM responds to treatment. It has been suggested that the amotivational state (abulia) that sometimes accompanies frontal lobe damage is a lesser form of AKM (2), but it is unknown whether they necessarily have the same pathophysiology. If abulia represents lesser injury to the same neural system as AKM, they might have a common treatment.

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Presented in part at the American Academy of Neurology, Seattle, May 1995.

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## Case Report

This 36-year-old, right-handed, college-educated woman had a stepwise neurologic deficit that progressed over 15 days. History is significant only for infrequent common migraine headaches and two normal term pregnancies. Her only medication was an oral contraceptive

that she had been using for 2 years. After 3 days of severe headache, she collapsed at home, was briefly unresponsive, and was admitted to the hospital. She was alert, cognitively intact, but had left lower facial weakness. EEG, unenhanced computed tomography (CT), and lumbar puncture were normal. The next day she was less responsive but otherwise unchanged. Magnetic resonance imaging (MRI) demonstrated bilateral paramedian midbrain–thalamic infarcts. Magnetic resonance angiography (MRA) suggested a narrowed distal basilar artery. Complete coagulation profile, transthoracic echocardiogram, chest radiograph, mammogram, and pelvic ultrasound were normal. Over the next 2 days, she became drowsier, and vertical gaze paresis and left-sided weakness developed. Conventional arteriography demonstrated narrowing of the midbasilar and no filling in the distal basilar. Heparin was begun. For 6 days, she showed rapid improvement. On day 14, she again became lethargic with worsened left hemiparesis. MRI demonstrated a new, left pontine infarct. Repeated conventional arteriography showed increased narrowing of the basilar artery. She remained minimally responsive. On day 32, a right temporal brain/meningeal biopsy was negative. A feeding tube was placed, and she was discharged to a rehabilitation hospital 40 days after the initial symptoms.

On admission to rehabilitation, she was described as mute, lying in bed in essentially decorticate posture, with no movement. She was bed-bound and dependent in all care. She underwent 3.5 months of daily intense multidisciplinary therapy. Relaxation, neuromuscular reeducation, passive ranging, serial casting to all four limbs, repeated phenol blocks, and trials of diazepam (up to 15 mg, t.i.d.), dantrolene (up to 125 mg, qd), and baclofen (Lioresal; up to 30 mg, t.i.d.) produced little change in function. Vigorous attention to positioning improved swallowing, and the *g*-tube was removed after 3 months. At discharge (5 months after onset), she still had minimal speech and movement. Medications were dantrolene, 25 mg qd; baclofen, 20 mg, b.i.d.; and oxycodone with acetaminophen (Percocet; 1–4 qd) for limb pain.

At home she required daily services for self-care, suspension transfers, and positioning. Six days weekly, she had 3 h of outpatient therapy. Treatment continued to focus on relaxation, maintenance of range, positioning, and strengthening. She had botulinum treatments at the left hand and wrist and left ankle with modest results. Dantrolene and baclofen were increased with no improvement but with decreased responsiveness.

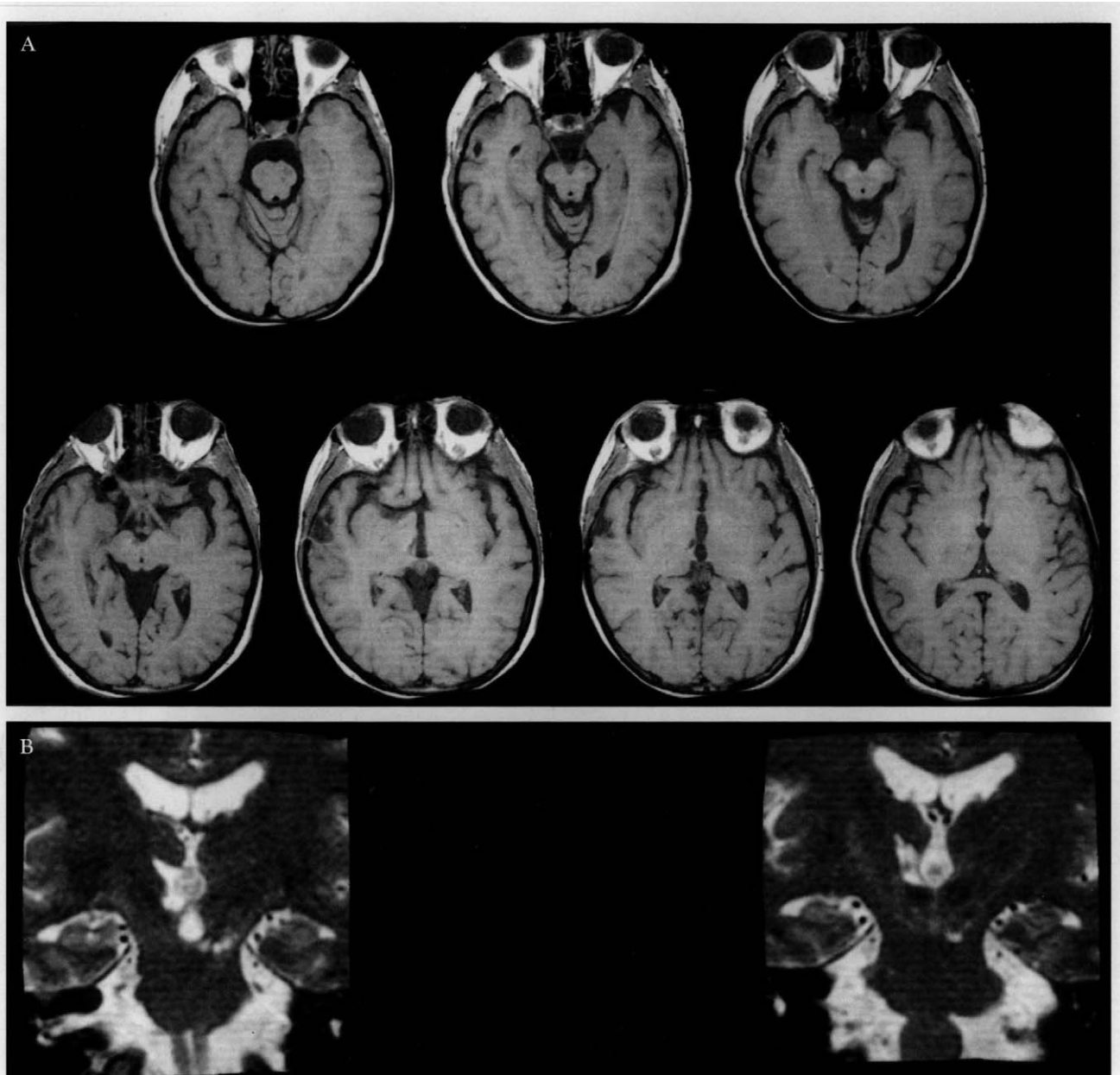
She was admitted to a second rehabilitation hospital in hope of identifying interventions that would allow less intense home services. She had almost no spontaneous speech and very terse responses to questions, with response latencies routinely >20 s. Speech was aprosodic and hy-

pophonic. Allowing for her extremely slow responses, language and memory seemed normal. Visual fields and pupillary size and responses were normal. All pursuit and horizontal saccadic eye movements were normal, but she could produce no vertical saccadic movements. Vertical doll's-eyes responses were present. She had moderate lid retraction, very reduced blink rate (<1/min), and very exaggerated glabellar response. She had masked facies and left lower facial weakness to command. There was low-amplitude titubation. She was generally akinetic, particularly on the left, and tended to rest in bed or chair in a near-decorticate position. When prompted, she had good power on the right, although all requested movements were delayed and had reduced amplitude, with a coarse proximal tremor. She required 29 min to do 10 finger-to-nose circuits at a distance of 30 cm. She could isolate all small-finger movements, although she required much prompting to continue. Power in the left leg was good, although again delayed and also with a significant action dystonia. The left arm was fisted in decorticate position with decreased passive range at all joints. Sensation was normal. Tendon reflexes were brisk and equal; both toes went down.

Her functional status on admission after 6.5 months of intense therapy (~600–700 h) was still limited. She transferred from bed to chair with maximal assistance. She sat with maximal assistance for support and stood with moderate assistance using the left ankle–foot orthosis (AFO), but she had no postural reflexes and could not ambulate or advance her wheelchair. She could do feeding, grooming, and oral hygiene with maximal assistance; all other self-care was dependent. Speech intelligibility was poor: 32% at sentence level. Her overall Functional Independence Measure (FIM) was 42 (3).

Standard rehabilitation interventions were continued, and carbidopa/levodopa was begun at 10/100 b.i.d. Within days her movement and speech began to improve. She was increased to a daily dose of 60/600 over 2 weeks. Pergolide was begun 0.05 mg, b.i.d.. Dantrolene was stopped without any clinical change. Speech latencies were <10 s; intelligibility at sentence level had improved to 55%. Titubation and right arm tremor were reduced. Speed of movement increased; 10 cycles of finger-to-nose, as previously described, required 16 s (45% faster). She sat independently and stood with supervision, no AFO required, although postural stability was still poor. She advanced her wheelchair independently and walked 150 feet with a rolling walker with minimal assistance. Her upper body self-care required at most supervision, and lower body, moderate assistance. Her overall FIM was now 87. She was transferred to a subacute facility for further therapy.

Four weeks later, taking carbidopa/levodopa 60/600 daily in five doses, and pergolide, 0.10 t.i.d., spontaneous movement and speech were much more frequent. Re-



**Figure 1.** Magnetic resonance imaging performed several months after onset:  $T_1$  study (A; 2-mm slices and 1-mm gap) demonstrates infarctions in (a) the left pons, basis, and tegmentum; (b) bilateral midbrain (upper center and lower left scans); (c) bilateral hypothalamus; and (d) the right thalamus, partly paramedian and partly in dorsomedial nucleus. Detail from  $T_2$  coronal study (B) demonstrates the right thalamic infarction and also demonstrates the hypothalamic lesions medial and anterior to red nucleus and substantia nigra.

response latencies were near normal. Voice volume and intelligibility were normal although still aprosodic. She ambulated independently, ate, and did most self-care independently. She went home to live with her family with minimal home services.

Over the next 8 months, the three medications were systematically adjusted. Increasing baclofen to 20 mg,

q.i.d., produced no improvements in her persistently tight left arm. Decreasing it to 10 mg, b.i.d., produced increased gait instability because of left-ankle action dystonia and clonus. Reduction of carbidopa/levodopa to 25/100, b.i.d., quickly produced worsening akinesia, postural instability, and increased tremor. At pergolide, 0.30 t.i.d., and carbidopa/levodopa, 25/100 five times daily,

she ambulated completely independently without any assistive device. She was essentially independent in self-care, more talkative, and doing some household chores. Her family noted that she appeared unmotivated to increase her independence.

She was lost to follow-up for 11 months. Her family brought her for reevaluation because of her apathy and poor motivation. Dosages of medications had not been changed. Examination was unchanged. Increasing either pergolide or carbidopa/levodopa caused orthostatic hypotension. When either was reduced, tremors and balance worsened. Fluoxetine was added at 10 mg qd with no effect. After it was increased to 20 mg qd, her motivation to do home activities seemed better, but she also had a marked increase in irritability. The dose was reduced to 10 mg qd. At last follow-up, she had not attempted any return to employment. She expressed little interest in household activities, in increasing her role in her family, doing the home activities that she is able to do, or pursuing any leisure activities. She often simply sits for hours.

### *Neuropsychological Assessments*

At 7 months after onset, she was oriented, had normal naming and repetition, normal praxis, and normal delayed recall of a four-word list. Performance was quite delayed, and she often required multiple prompts to produce any response. Because of severe akinesia and mutism, formal testing was not possible before treatment. Her first comprehensive evaluation was 13 months after onset. Language, fund of knowledge, verbal subtests of the WAIS-R, Wisconsin Card Sort, Raven's Progressive Matrices, and verbal fluency were entirely normal.

Follow-up evaluation (28 months after onset) demonstrated little change, although some time-dependent tasks were faster. The Stroop test was normal. Word-list generation (FAS) was average. List learning was mildly impaired (7-11-14-14-13), but semantic clustering was used as a learning strategy. Delayed recall (12) was slightly low, but recognition was normal (16 of 16).

At the final neuropsychological evaluation at 39 months after onset, results were essentially normal. She remained slow on some tasks, especially perceptual-motor tasks. She had material-specific memory deficits for visual nonverbal material. All executive cognitive tasks were normal. The patient was, however, quite aware of, and her family complained of, her lack of interests and poor motivation. She denied any depression, and there were no vegetative symptoms of depression. Her manner was jocular and breezy.

## **Discussion**

AKM is a disorder in activation to move and to speak despite conscious awareness, perhaps even the "desire" to speak or move, and no impairment in power, coordination, or tone that restricts movement (1). AKM has been reported as a consequence of lesions in numerous brain regions: (a) bilateral medial frontal (4-7), even when restricted to anterior cingulate gyri (ACG) (8-10); (b) the anterior hypothalamus (11,12) (usually tumors); (c) with acquired hydrocephalus (13-17); (d) severe diffuse axonal injury of trauma (during recovery) (18,19); (e) bilateral globus pallidus (20-22); (f) the paramedian mesencephalic-diencephalic region (usually infarctions) (23-28).

Lesions in any of these areas can damage part of a neural system critical for activating movement (including speech) and probably cognition without affecting the patterns or content of either. Damage directly to dopaminergic neurons in the midbrain or to their ascending projections may be the most common pathophysiology of AKM. There is substantial overlap in the midbrain of the dopaminergic neurons projecting to striatum and those projecting to cortex (29), but the cortical projections are more medial and dorsal than the striatal; that is, they are centered in the ventral tegmental area (VTA) (30). This mesocortical system projects through the medial forebrain bundle (MFB) (31). The MFB runs through the lateral hypothalamus into the septal area and then into the infraventricular white matter before projecting to the ACG and other, predominantly medial frontal structures (32). MFB pathways are strictly uncrossed (29). Lesions in the nonnigral ventral tegmental area (VTA, region A10) cause dopamine depletion in frontal cortex only, and damage to the MFB produces akinesia (31).

The terminations of the mesocortical pathway in frontal lobes are primarily the supplementary motor area (SMA) and the ACG, and bilateral damage to the ACG and SMA produces AKM. ACG and SMA share many connectivity properties (33, 34). In addition to the dopaminergic afferents from the VTA (29), both have bilateral efferents to frontal and premotor cortex and major projections to the striatum (33, 34) running in the periventricular white matter (35). Damage to medial frontal cortex or to its deep projections produces impaired activation. Unless very extensive, even bilateral SMA and ACG damage does not typically cause severe global akinesia, but in some cases, the clinical presentation can be quite similar clinically to that of the midbrain lesions (36).

Dopaminergic inputs to the striatum arise from more lateral midbrain structures, primarily the zona compacta of the substantia nigra (29, 37), and pass through the ventral posterior limb internal capsule (30). Damage re-

stricted to the cells of origin produces profound akinesia (37). The striatum projects to the globus pallidus. Damage to the globus pallidus produces severe akinesia (38), and stimulation of globus pallidus can eliminate akinesia (39). Much of the internal segment of the globus pallidus output is to the thalamus: VA, VL, and CM nuclei, and the IL region. Damage to the pallidothalamic pathways as they cross the ventral internal capsule or in the intramedullary thalamus may also produce akinesia (40).

The ascending systems are strictly uncrossed. The cortical efferents are bilaterally distributed. The pallidal efferents are uncrossed. Complete AKM requires bilateral lesions, although they need not be symmetrical. In this case, damage was asymmetrical. The precise basis is uncertain but includes at least the right VTA, ascending dopaminergic pathways in the left lateral hypothalamus, and the medial pallidothalamic pathways.

That AKM responds to various medications has also been known for years (41). L-DOPA, bromocriptine, lisuride, metoprolol, methylphenidate, and amphetamine have all been used, but the best agents, optimal doses, and duration of treatment are unknown. Successful treatment has been reported in TBI (18, 42), herpes simplex encephalitis (43), hydrocephalus after ventricular shunt failures (13, 14, 16, 17), basal tumors (12), hypoxia (42), and various causes of chronic hepatic encephalopathy (44). Bromocriptine is the most commonly reported agent. Once successfully treated, sensitivity to dose reduction has been variable. Given the remarkable number of possible lesions within a very small anatomic region that can cause AKM, it is not surprising that drug treatment has had variable results. Damage to the afferent (dopaminergic) system should be preferentially responsive to dopa agents.

In this case, AKM was not clinically recognized for 8 months after onset, perhaps because left hemiparesis developed at the same time. Two features of the examination might have suggested coexistent AKM. First, preservation of isolated finger movements, even with long delay after requested movement, is atypical in corticospinal pattern paresis. Second, loss of vertical gaze points to a paramedian injury that often produces AKM. Although the initial dose was low and peripheral dopamine metabolism was surely not blocked at the starting doses, a striking clinical response was seen within days of starting carbidopa/levodopa after months of unchanging deficit. Additional benefit was seen with pergolide. In this case, treatment will probably be permanently required, as attempts to decrease either drug caused worsened deficits within days. Dopaminergic treatment should be considered even in very chronic cases of AKM.

Despite excellent motor recovery with treatment and no evidence of executive cognitive deficits, she has re-

mained apathetic and emotionally indifferent (i.e., abulic). The lack of response of the motivational deficits under dopaminergic treatment suggests that abulia need not be simply a milder form of AKM. It is still possible that dopamine deficiency does underlie both disorders, but that the motor-response impairment (AKM) is more directly mediated by dopamine and, thus, more directly treated with dopaminergic agents. A similar observation of differential response to treatment has been made in cognitive functions (45). In a group of patients with cognitive impairments, but not AKM, after traumatic brain injury, bromocriptine improved a subset of executive functions but did not affect working memory, an allegedly dopamine-dependent operation (46). Various cognitive, motor, and emotional capacities may share a requirement for ascending dopaminergic input but remain anatomically segregated, use different dopamine receptor systems, or differ in the extent of direct modulation by dopamine. In this patient, it can be concluded that abulia is not due to a simple dopamine deficiency and is not just part of AKM, as the latter improved so dramatically, and the former not at all. It is also not due to a general executive-system impairment, as standard assessments of executive cognitive functions are intact. Apathy is likely a very complex disorder with cognitive, emotional, visceral, and activational components (9). If they have an effect, dopaminergic agents may treat only the activational component. Perhaps in this patient, the lesion in the right anterior thalamus has disrupted the emotional components and is the source of the persistent apathy.

#### Acknowledgment

Supported in part by program project grant NS 26985 to the Boston University School of Medicine, Memory Disorders Research Center.

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