

Akinetic Mutism Associated with Bicingular Lesions: Clinicopathological and Functional Anatomical Correlates

György Németh, Katalin Hegedüs, and László Molnár

Department of Neurology and Psychiatry, University Medical School, H-4012 Debrecen, Hungary

Summary. The clinical symptoms and neuropathological findings of three patients suffering from akinetic mutism were summarized. The patients showed almost absolute mutism and immobility and were unable to communicate in any way. The neurological signs varied from case to case. The pathological features common to all of the cases were bilateral lesions of the rostral part of the anterior cingulate gyri which overlapped onto the neighboring supplementary motor area, while differing as regards other damage. With the help of more recent neurobiochemical findings we tried to analyze the pathomechanism of akinetic mutism on the basis of the structures damaged. There seems to be an anatomic correspondence between the mesolimbocortical dopaminergic system and the circumscribed bilateral lesions of the medial prefrontal cortex. The study suggests that damage of the mesolimbocortical dopaminergic terminal fields in the anteromedial frontal cortex is essential for this specific type of akinetic mutism.

Key words: Akinetic mutism – Cingulate gyri – Mesolimbocortical dopaminergic system

Introduction

Akinetic mutism (AM) was the term given by Cairns et al. to the clinical picture observed in a patient with an epidermoid cyst of the third ventricle [6]. The patient showed almost absolute mutism and immobility except for eye movements as well as complete absence of communication. Akinetic mutism differs from coma, the apallic syndrome, and the locked-in syndrome with which it has often been confused.

Offprint requests to: L. Molnár

Pathophysiologically coma and apallic syndrome are other types of disturbances of consciousness and have to be distinguished from AM. On the other hand in the locked-in syndrome the patient's awareness is fully preserved which can be demonstrated by voluntary blinking and eye movements [34].

The condition of AM has been reported in a variety of articles related to different localizations of lesions including bilateral damage of the globus pallidus [8, 10], the diencephalic-mesencephalic reticular formation [9, 16, 19, 31, 36, 37, 38], or the basis of the brainstem [8, 35, 36]. Clinico-anatomical cases of bilateral lesions of the cingulate gyrus have rarely been reported, to our knowledge 14 cases have been described [1, 3, 5, 11, 12, 17, 22, 28, 32, 33, 39]. The clinical consequences have always been AM.

A total of 23 cases of clinically recognized AM have been autopsied during the last 10 years in our Department, and in 3 of them common pathological lesions were localized in the cingulate gyri and the neighboring area. The criteria of AM were total immobility (but not plegia) except for eye movements and blinking and complete absence of all types of communication. The 3 cases reported in this paper met the criteria of AM. The nature and extent of lesions in the cingulate gyri responsible for AM are still disputed. In our study we have been especially attentive not only to clinicopathological observations but to both the crucial clinical problems of behavior and their impact on some aspects of research in neurotransmission.

Case Reports and Neuropathological Findings

Only cases 2 and 3 will be described in greater detail as case 1 presented no circumscribed lesions in order to draw any relevant conclusions.



Fig. 1. 58-year-old man. Bilateral tumorous infiltration of the frontal lobes which involves both cingulate gyri. Heidenhain $\times 1$

Case 1. A 58-year-old man with a 3-week history of progressive drowsiness and instability of gait was admitted to our Department on March 19, 1977. The findings of a general physical examination performed on admission were normal. Neurological examination revealed rigid muscle tone, normal tendon reflexes without pyramidal signs and normal eye movements. He did not move spontaneously and showed only very few but adequate responses to painful stimuli. He was unable to speak, and there was no possibility of communication with him although he seemed to be alert. The EEG showed diffuse 10 cycles/s activity but was areactive to various stimuli. The patient remained immobile and in spite of the total absence of any initiative, either motor or verbal, he continued to give the impression of following every activity taking place around him with an alert look. In this state he died suddenly 4 days after admission.

Pathological Findings: general autopsy disclosed thrombosis of the right femoral vein, massive pulmonary thromboembolism, and massive sclerosis of the arteries. The brain weighed 1,420 g. It was edematous with bilateral tonsillar herniation. Frontal section of the brain revealed at the level of the frontal poles of the lateral ventricles a massive bilateral tumorous infiltration which had spread to both the cinguli gyri and midline regions and extended caudally at the level of the corpus mamillare. Microscopic examination of the tumor mass revealed the characteristic features of glioblastoma multiforme (Fig. 1).

Case 2. A 71-year-old woman with a 3-year history of left hemiparesis and hypertension was hospitalized on August 18, 1981. The day before admission she became unable to speak and to move her right limbs. On admission her blood pressure was 270/150 Hgmm, and general physical examination revealed no abnormalities. Neurological examination revealed bilateral optic atrophy, she made no sound and lay inert, and

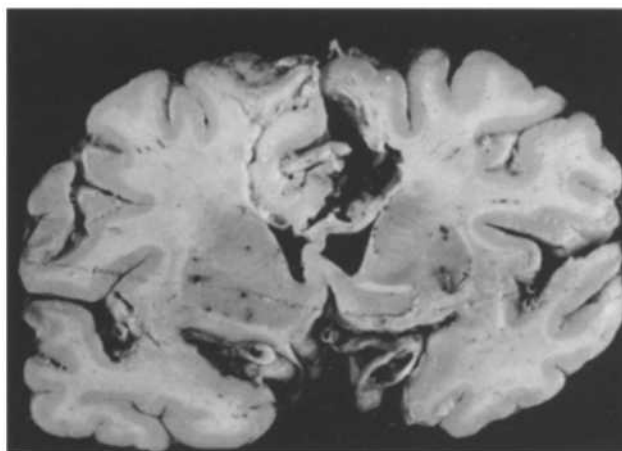


Fig. 2. 71-year-old woman. Bilateral softening in territory of the anterior cerebral arteries

there were no movements of a voluntary character. A painful stimulus produced weak, slow withdrawal of the left limbs. On the left side the tendon reflexes were slightly increased, and there were no pyramidal signs. The flexor muscle tone was increased in all four limbs. There was no possibility of achieving any type of communication. The patient made no voluntary, only automatic eye movements. Cisternal puncture yielded clear CSF with no abnormalities. The EEG presented theta-alpha waves bilaterally without focal signs, and was areactive to various stimuli. Fluctuations occurred in this AM state. After a few days there was an incomplete manifestation: the patient responded at times, though slowly and imperfectly, by speech and voluntary movements. This condition was observed for 2 days, and she remained in this AM state until she died of bronchopneumonia 15 days after admission.

Pathological Findings: general autopsy disclosed extensive bilateral bronchopneumonia. Except for severe dilatation of ventricles, and coronary sclerosis, her heart showed no abnormality. The brain weighed 1,255 g. There was severe arteriosclerosis of the circle of Willis. The left anterior cerebral artery was occluded with a thrombus and the right anterior cerebral artery was severely stenotic. On the right side old infarcted cystic lesions were present in the anterior cingulate gyrus, the caudal part of the superior frontal gyrus, leaving undamaged the frontal pole and the frontal basal areas. On the left side infarction had destroyed the parasagittal area of the frontal lobe extending more caudally, partly overlapping the posterior cingulate gyrus. On this side the precentral and postcentral gyri were damaged, too (Fig. 2).

Case 3. A 62-year-old man with a typical picture of AM was admitted to our Department on September 12, 1978. Some 15 days earlier he had been hospitalized with acute hypertension (300/100 Hgmm), massive bloody CSF and in a comatose state. On admission to our clinic his blood pressure was 180/100 Hgmm, and general examination was negative. Neurological examination revealed anisocoric pupils (left > right), right flaccid hemiplegia without pyramidal signs, and bilateral grasping reflexes. Lumbar puncture yielded xanthochromic CSF. In the angiogram of the left common carotid artery an aneurysm was observed at the beginning of the anterior cerebral artery. An EEG was not performed. The patient remained immobile and presented a state of total inertia except for the

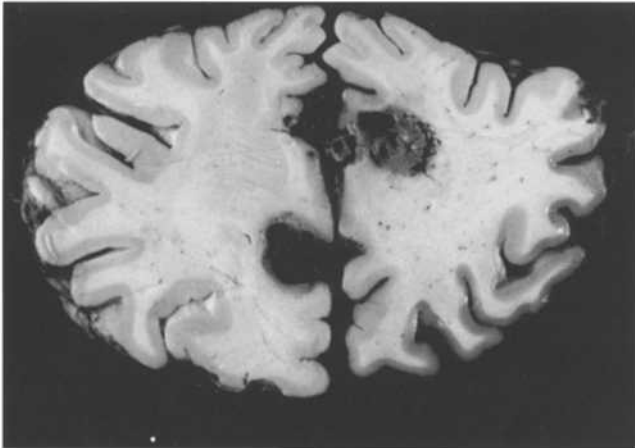


Fig. 3. 62-year-old man. Circumscribed hemorrhages due to rupture of an aneurysm of the right anterior cerebral artery

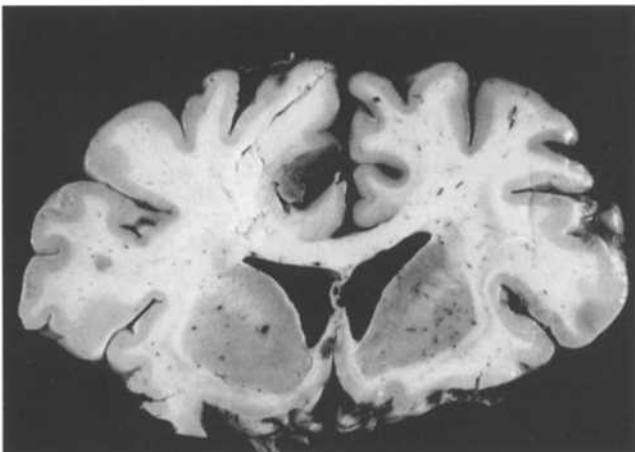


Fig. 4. The same 62-year-old man as in Fig. 3. Circumscribed infarction with hemorrhagic components in the territory of the left anterior cerebral artery

eyes which from time to time followed movements in the environment, thereby showing that he was alert. Only repeated verbal stimuli elicited a reply in the form of incomprehensible monosyllables. In this state he died suddenly 5 days after admission.

Pathological Findings: severe arteriosclerosis, right bronchopneumonia, thrombosis of the right femoral vein, and massive pulmonary thromboembolism. The brain weighed 1,310 g. An extended subarachnoid hemorrhage was present over both the cerebral hemispheres. On the right anterior cerebral artery 3 mm distally from the anterior communicating artery an aneurysm was found. On the mesial surface of both frontal lobes about 1 cm wide hemorrhages could be seen. On the right side only the rostral part of the anterior cingulate gyrus located around the genu of the corpus callosum was affected, leaving undamaged the caudal part of the anterior cingulate gyri. On the left side the hemorrhage destroyed at the level of genu a very circumscribed area of the anterior cingulate gyrus beneath the cingulate sulcus. The lesion overlapped slightly onto the neighboring cortical areas involving the supplementary motor area (Brodmann 32) rostrally (Figs. 3, 4).

Discussion

As previously mentioned the term AM has sometimes been used too extensively and improperly. Kemper and Romanul [20] and Molnár [29] stress the necessity of separating conditions which differ from AM. Generally the term AM designates a special type of disturbance of consciousness. In the available literature on most of the anatomical observations of AM associated with the bilateral anterior cingulate gyri (Brodmann area 24) however, the lesions were too extensive or multiple, therefore preventing a well-defined clinicopathological relationship. In all of the cases to date the lesions involved other brain structures, too: the territory of the anterior cerebral artery – most frequently the medial surface of the superior frontal gyri – and some parts of the limbic system such as the septum pellucidum, fornix, gyrus rectus, and the gyrus orbitalis. The destruction of the anterior portion of the caudate nuclei, the corpus callosum, the asymmetrical or unilateral invading of the globus pallidus and putamen and the anterior-medial thalamic nuclear groups was also observed.

The circumscribed lesions and common features of our cases, especially cases 2 and 3, partly supported the fact that the damage must be localized in the anterior part of the cingulate gyri bilaterally. In case 2 the lesions were most similar to those which can be found in the literature but slightly more restricted. Although in case 3 there was a massive subarachnoid hemorrhage which would explain the sudden onset of the illness and the comatose state on the first day, but not the AM state, which developed later. Comparing the three cases the only common pathological features were: (1) the lesion of the rostral part of the cingulate gyri just around the genu corporis callosi, and (2) the damage of the adjacent frontal lobe namely the supplementary motor area.

After cingulectomies or cingulotomies some degree of docility, indifference, and slight loss of depth in general interests and pursuits have been observed [40, 41]. There is considerable discrepancy between the clinical picture of our cases and the postoperative states of the cingulectomized patients. This discrepancy can be explained by two main facts. First, in the absence of anatomical verification in cingulectomies, the brain removal is imprecise and, possibly, often less extensive than our patients' cingulate lesion. The second fact which may account for the intensive behavioral changes in our patients is the presence of associated lesions. The most common clinical findings with lesions involving the supplementary motor area are the transient stage of apathy, akinesia, lack of drive and motivation, and disturbances of speech similar to transcortical motor aphasia

[18, 21]. Comparison of these facts suggests that simultaneous frontal (supplementary motor area) and limbic (cingulate) impairment is necessary to induce such a state as this type of AM. Therefore, it may be suggested that the cingulate lesion, when added to a frontal lesion could produce more pronounced symptoms – or a qualitatively different state such as AM – than those of frontal lesions alone or vice versa.

In true AM the akinesia and mutism appear without paralysis; therefore, the akinesia does not mean tetraplegia. This is supported by our present and previous studies and some observations in the literature [6, 22, 31]. It must be emphasized that these findings have also been observed in other localizations of bilateral lesions causing AM. These discrete lesions destroyed isolated structures, located within the pons or mesencephalon [8, 31, 36], diencephalon [6], or ventral pallidum [8, 10], without involving the pyramidal tracts.

The EEG in cases 1 and 2 showed diffuse bilateral theta-alpha waves areactive to various stimuli, similar to many other descriptions in the literature [7, 22, 31]. The EEGs were independent regardless of the level and the site of the lesion causing AM. This fact supports a neural mechanism for AM which does not depend on a special functional entity, at least pathophysiologically.

Our observations are consistent with animal models and human data suggesting that this type of AM may be related to loss of dopaminergic input to the anterior cingulate cortex or related cortex such as the supplementary motor area. It has been demonstrated that there are dopaminergic mesolimbocortical projections [23] which also exist in humans [2]. One of them originates in the pars compacta of the substantia nigra and in the ventral tegmental area of the mesencephalon and courses through the medial forebrain bundles and ultimately ends in the anterior cingulate gyri and the anteromedial prefrontal cortex [13, 15, 24]. In animals interruption of the dopaminergic axons traveling through the far-lateral hypothalamus in the medial forebrain bundles with 6-hydroxydopamine induced a behavioral syndrome similar to AM [26]. The impairments can be reversed by the systematic administration of the dopamine receptor stimulant apomorphine [25, 27]. Patients with bilateral, restricted ventral tegmental lesions in the mesencephalon [31] or with damage in the hypothalamus which involves both medial forebrain bundles [37] sparing the dorsal part of the upper brainstem tegmentum also exhibit the clinical picture of AM. In the latter case after treatment with bromocriptine (direct dopamine receptor agonist) there was marked improvement and the authors con-

cluded that if their patient's lesion involved the anterior cingulate gyri, he probably would not have responded to direct dopamine agonists because dopamine receptor targets would have been destroyed [37].

Dopaminergic receptor activity in the anterior part of the cingulate gyri regulates movement, decodes various types of sensory stimuli, a process necessary for proper sensory motor integration, and thus makes the selection of meaningful behavior in a complex environment possible [4, 14, 30].

If the data of our study are considered in their overall context three main observations emerge:

1. In all of our cases the affected regions are associated with those structures in which dopaminergic neurons of the mesolimbocortical system have been found.
2. On the other hand, no clear-cut anatomic observations can be made in humans concerning the extension of the medial surface lesion of the cortex which is necessary for the development of AM.
3. In lesions of different locations which result in AM those structures which play a role in the development of comatose states remain intact.

After integration of the functional-anatomical and human clinicopathological data the problem is to distinguish disorders of elementary neurological functions from the disorders of consciousness. The neurological signs – e.g., hemiparesis etc. – are accidental; they vary from case to case. Consciousness as a form of cerebral integration depends more probably on the synergy of different systems in complex interactions which sort and regulate sensory information deriving from the body or the outer world or result from action which it has itself provoked.

On the basis of pathogenesis AM is a specific type of disturbance of consciousness. It seems that AM constitutes a single entity from the functional point of view but, since it can occur after different lesion sites, it is different from the anatomical point of view. In AM a specific communicating system is damaged in isolation at various levels of the neuraxis. The significance of the functional patterns demonstrable at different levels of the nervous system will be understood only if it is appreciated that they are characteristic of the entire specific communicating system from the brainstem level to the cortex.

References

1. Amyes EW, Nielsen JM (1955) Clinicopathologic study of the anterior cingulate region. *Bull Los Angeles Neurol Soc* 20:112-130
2. Baldessarini RJ, Tasy D (1979) Relationship of the actions of neuroleptic drugs to the pathophysiology of tardive dys-

- kinesia. In: Smytkes IR, Bradhy RJ (eds) *International review of neurobiology*. Academic Press, New York
3. Barris WR, Schumann HR (1953) Bilateral anterior cingulate gyrus lesion: syndrome of the anterior cingulate gyri. *Neurology (Minneapolis)* 3:44–80
 4. Björklund A, Lindvall O (1984) Dopamine-containing systems in the CNS. In: *Handbook of chemical neuroanatomy*, vol 2: Björklund A, Hökfelt T (eds) *Classical transmitters in the CNS. Part I*. Elsevier, Amsterdam New York Oxford, pp 55–123
 5. Buge A, Escourolle R, Rancurel, Poisson M (1975) "Mutisme akinétique" et ramollissement bicingulaire. *Rev Neurol* 131:121–128
 6. Cairns HWB, Oldfield RC, Pennybacker JB, Whitteridge D (1941) Akinetic mutism with an epidermoid cyst of the 3rd ventricle. *Brain* 64:273–291
 7. Cairns HWB (1952) Disturbances of consciousness with lesions of brainstem and diencephalon. *Brain* 75:109–145
 8. Cravioto H, Silberman J, Feigin I (1960) A clinical and pathological study of akinetic mutism. *Neurology (Minneapolis)* 10:10–21
 9. Daly DD, Love JG (1958) Akinetic mutism. *Neurology* 8:236–242
 10. Denny-Brown D (1962) *The basal ganglia and their relation to disorders of movement*. Oxford University Press, London
 11. Faris AA (1969) Limbic system infarction. A report of two cases. *Neurology (Minneapolis)* 19:91–96
 12. Freemon FR (1971) Akinetic mutism and bilateral anterior cerebral artery occlusion. *J Neurol Neurosurg Psychiatr* 34:639–698
 13. Fuxe K, Hökfelt T, Johansson O, Jonsson G, Lidbrink P, Ljungdahl A (1974) The origin of the dopamine nerve terminals in limbic and frontal cortex. Evidence for mesocortical dopamine neurons. *Brain Res* 82:349–355
 14. Fuxe K, Agnati LF, Kalia M, Goldstein M, Anderson K, Härfstrand A (1985) Dopaminergic systems in the brain and pituitary. In: Flückinger E, Müller EE, Thomer MO (eds) *The dopaminergic system*. Springer, Berlin Heidelberg New York Tokyo, pp 11–25
 15. Glowinski J, Tassin JP, Thierry AM (1984) The mesocortico-prefrontal dopaminergic neurons. *Trends Neurosci* 7:415–419
 16. Hegedüs K, Németh G (1984) The adult form of subacute necrotizing encephalopathy. *Surg Neurol* 21:572–276
 17. Jurgens U, Cramon D von (1982) On the role of the anterior cingulate cortex in phonation. *Brain Long* 15:234–248
 18. Jonas S (1981) The supplementer motor region and speech emission. *J Commun Dis* 14:349–373
 19. Jouvet M (1969) Coma and other disorders of consciousness. In: Vinken PJ, Bruyn GW (eds) *Handbook of clinical neurology*, vol III. Elsevier, Amsterdam, pp 62–79
 20. Kemper TL, Romanul FCA (1967) State resembling akinetic mutism in basilar artery occlusion. *Neurology (Minneapolis)* 17:74–80
 21. Laplane O, Talairach J, Meininger V, Bancaud J, Orogozo JM (1977) Clinical consequences of corticectomies involving the supplementer motor area in man. *J Neurol Sci* 34:301–314
 22. Lechi A, Pilleri G, Carreras M (1975) Akinetic mutism due to glioma of the midline. *Arch Psychiatr Nervenkr* 220:1–5
 23. Lindvall O, Björklund A, Moore RY, Steneri J (1974) Mesencephalic dopamine neurons projecting to neocortex. *Brain Res* 81:325–331
 24. Lindvall O, Björklund A, Divac I (1978) Organization of catecholamine neurons projecting to the frontal cortex in the rat. *Brain Res* 142:1–24
 25. Ljungberg T, Ungerstedt U (1976) Sensory inattention produced by 6-hydroxydopamine-induced degeneration of ascending dopamine neurons in the brain. *Exp Neurol* 43:585–600
 26. Marshall JF, Teitelbaum P (1977) New considerations in the neuropsychology of motivated behavior. In: Iversen LL, Iversen SD, Synder SH (eds) *Handbook of psychopharmacology*. Plenum Press, New York, pp 201–229
 27. Marshall JF, Gotthelf T (1979) Sensory inattention in rats with 6-hydroxy-dopamine-induced degeneration of ascending dopaminergic neurons: apomorphine induced reversal of deficits. *Exp Neurol* 65:398–411
 28. Maughi E, Mironi F, Saginario M, Valla S (1953) La sindrome del mutismo acinetico. *G Psychiatr Neuropatol* 87:239–244
 29. Molnár L (1983) Blick- und Bewußtseinsstörungen bei Malazie der Brücke. In: Neumärker KJ (ed) *Hirnstammläsionen. Neurologische, psychopathologische, morphologische und computertomographische Aspekte*. Ferdinand Enke, Stuttgart, pp 164–168
 30. Moore RY, Bloom FE (1978) Central catecholamine neuron systems: anatomy and physiology of the DA systems. *Annu Rev Neurosci* 1:129–169
 31. Németh G, Hegedüs K, Molnár L (1986) Akinetic mutism and locked-in syndrome: the functional-anatomical differentiation. *Funct Neurol* 1:128–139
 32. Nielsen JM, Jacobs LL (1951) Bilateral lesions of the anterior cingulate gyri. Report of a case. *Bull Los Angeles Neurol Soc* 16:231–234
 33. Ogata J, Fikiyama K, Iwata Y (1966) Akinetic mutism in extensive cerebral softening. Clinical and pathological observation. *Clin Neurol (Tokyo)* 6:125–130
 34. Plum F, Posner JB (1966) *The diagnosis of stupor and coma*. Davis, Philadelphia
 35. Reuther R, Dorndorf W (1973) Ventrales Pons-Syndrom (akinetischer Mutismus) bei Verschluss der A. basilaris. *Nervenarzt* 44:419–423
 36. Reznik M (1983) Neuropathology in seven cases of locked-in syndrome. *J Neurol Sci* 60:67–78
 37. Ross ED, Stewart RM (1981) Akinetic mutism from hypothalamic damage: successful treatment with dopamine agonists. *Neurology (Minneapolis)* 31:1435–1439
 38. Segarra IM (1970) Cerebral vascular disease and behavior. I. The syndrome of the mesencephalic artery (basilar artery bifurcation). *Arch Neurol (Chicago)* 22:408–418
 39. Skultety FM (1968) Clinical and experimental aspects of akinetic mutism. *Arch Neurol* 19:1–14
 40. Showers MIC (1959) The cingulate gyrus. Additional motor area and cortical anatomic regulator. *J Comp Neurol* 112:231–301
 41. Tow PM, Whitty CWM (1953) Personality changes after operations of the cingulate gyrus in man. *J Neurol Neurosurg Psychiatr* 16:186–193

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