Delirium: A Neurologist's View—The Neurology of Agitation and Overactivity

Louis R. Caplan, MD

Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Delirium *is a term used variously to characterize a change in behavior. Neurologists most often use the term to describe a patient who has acutely developed a hyperactive agitated state. In many patients, agitation and overactivity are explained by toxic and metabolic factors and infections. Lesions, especially strokes, in some brain regions have been reported to cause sudden agitation and a hyperactive state, often with an increased amount of speech output, the topics of which flit from one subject to another. Strokes and other lesions that involve the temporal lobes, fusiform and lingual gyri, caudate nucleus, and anterior cingulum have been reported to cause an acute hyperactive state similar to that found in patients with delirium tremens related to alcohol withdrawal.*

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"When *I* use a word," Humpty Dumpty said, in a rather scornful tone, "it means just what I choose it to mean–neither more nor less." "The question is," said Alice, "whether you *can* make words mean so many different things." "The question is," said Humpty Dumpty, "which is to be master–that's all."

Through the Looking-Glass
Lewis Carroll

"For when the cause of the complaint's unsure 'Twould be a miracle to find a cure."

The Adventures of Don Quixote
Miguel de Cervantes

One of the most common reasons for neurologic consultation these days is "a change in mental status." This overused, dreadful term is often applied by nonneurologists to any change in cognition and behavior, from underactivity to overactivity with agitation, and to decreased consciousness—all sometimes subserved under the variously used term *delirium*. During the past 2 decades, the topic of delirium has been given considerable attention in the medical, geriatric, and psychiatric literature as a major problem, especially in older hospitalized patients.[1,2] In most of these published reports and reviews by nonneurologists, the focus and emphasis have been on the

epidemiology, underlying conditions, precipitating factors, and management. Delirium has often been considered as a single disease entity or condition.

I think it important for neurologists and other medical specialists to realize that the term *delirium* is often defined and used differently by neurologists as compared with other medical specialists. The approach to the patient, the differential diagnosis, clinical imaging and laboratory evaluation, and management differ considerably depending on how delirium is defined and categorized. Herein I review the neurology of agitation and overactivity, emphasizing the known causative anatomic lesions.

The Neuroanatomical Basis of Hyperactivity

Dr. C. Miller Fisher was probably the first to tackle the complex problem of the anatomic basis of activity. He reviewed his extensive personal experience with 2 behavioral states that present as polar opposites: abulia and agitated behavior.[3] Abulic patients have less than normal activity. They are apathetic, lack initiative and motivation, and show little exploratory behavior. They may simply sit without doing anything for extended periods of time. They sometimes do not respond to queries or commands but may respond correctly after repetitive urging. They are often slow to respond and their responses are characteristically terse and brief. Family members sometimes described these abulic patients as "a bump on a log." Fisher contrasted these very inactive patients with others who were hyperactive and agitated. These individuals were characteristically restless, excited, and hyperalert and had an increased amount of speech (logorrhea) and behavior.[3]

Brain lesions in abulic patients were located in the rostral mesencephalic tegmentum, substantia nigra, medial thalami, striatum, and frontal lobes. These lesions often involved or interrupted the ascending reticular activating system in the rostral brainstem or their target destinations in the frontal lobes. Fisher posited that lesions of a mesencephalofrontal activating system that was mostly dopaminergic were the basic pathologic anatomy of hypoactive, abulic states. In contrast, when hyperactive agitated patients had focal brain lesions, the location was most often in the posterior portions of the cerebral hemispheres in the temporal, occipital, and inferior parietal lobes.[3] Many agitated patients had infarcts or inflammatory lesions that involved limbic cortex in these regions.

Clinico-anatomical correlation is usually clearest in patients with well-localized brain infarcts. Other stroke lesions—subarachnoid and intracerebral bleeds—and other neurologic conditions—tumors, infections, trauma, inflammations—are often not as well localized, have a general impact on adjacent brain structures, and are often accompanied by edema and altered intracranial pressure.

Localization of Lesions in Reported Series of Patients With Focal Brain Infarcts

Clinico-anatomical correlation is usually clearest in patients with well-localized brain infarcts.[4] Other stroke lesions (subarachnoid and intracerebral bleeds) and other neurologic conditions (tumors, infections, trauma, inflammations) are often not as well localized, have a general impact on adjacent brain structures, and are often accompanied by edema and altered intracranial pressure. Congenital and developmental and degenerative processes also do not lend as well to clinico-anatomical correlation. For these reasons I emphasize the data available in patients with well-described vascular lesions and localized brain infarction.

Posterior portions of the cerebral hemispheres in patients with top of the basilar artery embolism. At the 1962 annual meeting of the American Neurologic Association, Horenstein and colleagues[5] reported on 9 patients who presented with sudden-onset visual loss accompanied by hyperactive agitated behavior. They described the behavior of their patients as "restlessness, agitation, forced crying out, and extreme distractability."[5] These patients were very talkative, and their conversations tended to flow from one topic to another. All had infarcts that were in the unilateral or bilateral territory supplied by the posterior cerebral arteries. The infarcts most often involved the fusiform and lingual gyri.[5] Later, Medina and associates[6] described the clinical and pathologic findings in a 78-year-old man who had the sudden onset of an agitated, excited state. The man was previously quiet, stable, and kind despite a prior stroke that caused transient left hemiparesis, left hemisensory loss, and a persistent left hemianopia. His niece found him suddenly agitated. He cursed and struck her. On admission to the hospital he was extremely agitated, perspiring profusely, screaming, biting, and spitting. He was also blind and had defective memory. He remained agitated and shouted most responses to

queries until his death approximately 5 months after his stroke. Necropsy showed an old infarct in the territory of the inferior division of the right middle cerebral artery (MCA) involving the superior temporal gyrus and the inferior parietal lobe. The left posterior cerebral artery (PCA) territory was also infarcted, including the entire lingual gyrus and portions of the adjacent fusiform, parahippocampal, and calcarine gyri.[6] The left hippocampus and portions of the left thalamus were also involved, including the mamillary bodies and the pulvinar.[6] Other reports subsequently described patients who developed an agitated delirious state caused by embolism to the rostral basilar artery and its PCA branches.[7-9] Necropsy and neuroimaging in these patients showed bilateral infarcts invariably involving occipital and temporal lobe cortex below the calcarine sulcus, including the lingual and fusiform gyri. Bilateral visual field defects and memory loss usually accompanied the agitated, hyperactive state. Some patients also had infarcts in the rostral brainstem and superior cerebellar artery territory of the cerebellum; however, no patient with an infarct limited to the rostral brainstem had an agitated hyperactive state. The patients with bilateral rostral brainstem tegmental infarcts were, in contrast, often sleepy and had reduced behavior and activity. Infarction of the PCA territory on the lower bank of the calcarine sulcus was a necessary component of those patients with hyperactivity and agitation, all of whom had posterior circulation brain embolism.[7-9]

A hyperactive, agitated state also occasionally develops after vertebral artery angiography.[9,10] Patients become hyperactive and restless, have markedly reduced vision, and poor memory. In most patients the results of angiography are normal, and the confusional disturbance and other neurologic signs usually remit within hours. The patients have received a relatively large amount of iodinated contrast, and the syndrome is most likely caused by a dye reaction in the bilateral territories of the PCAs.

Unilateral temporo-occipital infarcts in the territory of a posterior cerebral artery. Devinsky and colleagues[11] reported the clinical and imaging abnormalities in 4 patients with left PCA territory infarcts and an agitated confusional state, and reviewed prior reports of confusional states in patients with unilateral PCA territory infarcts. All 4 patients had lesions of the left occipital and posteromedial temporal lobes. Three had left PCA territory infarcts that were most likely attributable to cardiogenic embolism. One patient most likely had dural sinus and cortical venous thrombosis with left posteromedial temporal lobe and occipital lobe infarction. Three of the patients had agitated states sometimes alternating with lethargy, 1 of whom had the sudden onset of "confusion, agitated disorientation, and aggressive behavior."[11] This patient shouted curses and threats and threw objects at the wall. He was "distractable and shifted the focus of his attention to virtually any novel stimulus."[11] Another agitated patient had speech that was "fluent but tangential with difficulty finding words."[11] In some patients the agitated confusional state was temporary. The authors reviewed prior published reports of patients with unilateral PCA territory infarcts who had acute confusional states; 18 of the 19 patients (95%) described in 10 different reports had left PCA territory infarcts, whereas only 1 had a right PCA territory infarct.[11] Fisher also commented that when an agitated delirium developed in patients with unilateral PCA territory infarct, the lesion was predominantly in the dominant left cerebral hemisphere.[3]

Infarcts in the territory of the inferior division of the MCAs. Boudin and associates[12] reported on 10 patients who had the sudden onset of confusion with agitated behavior. Two of the patients had right temporal lobe infarcts and died. In the other 8 patients the clinical findings and electroencephalogram (EEG) abnormalities suggested to the authors that the vascular lesions involved the right temporal lobe.[12] This report antedated modern neuroimaging.

Juillet and colleagues,[13] 1 year later, described 4 patients who had visual and mental confusion, often with agitation. In 2 of these patients the clinical and EEG abnormalities suggested right temporal lobe infarction.[13] in 1976, Mesulam and coworkers[14] reported 3 patients with infarcts in the territory of the right MCA who had acute confusion with agitation. The abnormal behavior in these patients began abruptly, and they showed extreme distractability, incoherent streams of thought, restlessness, agitation, and hyperactive behavior. In 1 patient an early-generation computed tomography (CT) scan showed a lesion in the inferior right frontal lobe, although this patient had no motor or sensory signs. In the other 2 patients a radionuclide scan showed lesions in the right temporal and inferior parietal lobes. Angiography in 1 patient showed an occlusion of the right angular artery branch of the MCA but was normal in the patient with the CT-documented frontal lobe infarct. These patients all had emboli to the right MCA. Although the authors posited that right parietal lobe infarction was the likely explanation for the

agitated state, the localization of the ischemic lesions in their patients was quite vague and all probably also had temporal lobe infarcts.[14]

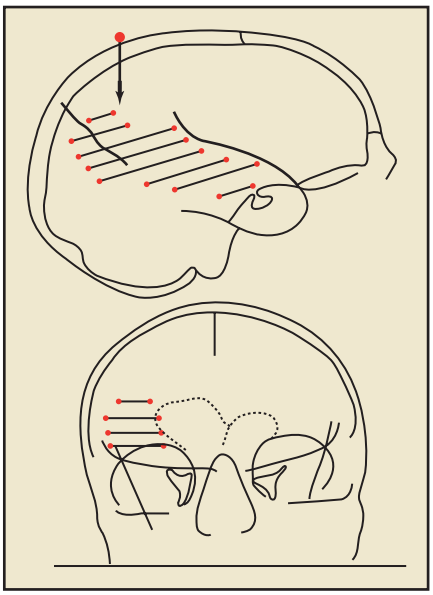
Schmidley and Messing[15] reviewed the clinical and imaging findings among 46 patients who had infarction in the territory of the right MCA. Two patients presented with agitation and confusion. Each had a left hemianopia and minor left limb motor signs. CT scans in 1 of these patients were normal, and a CT scan showed an enhancing right temporal-parietal infarct in the other.[15] Angiography in the agitated patient who had a normal CT scan result showed delayed filling of the temporal and inferior parietal branches of the inferior trunk of the right MCA. The other 44 patients had more severe motor and sensory signs, indicating that they had more anterior and/or deep infarcts.[15]

A clinicopathologic conference in Paris (Confrontation de la Salpêtrière) concerned a 68-year-old man who had the sudden onset of abnormal behavior.[16] This man was agitated and could not attend to tasks. He spoke incessantly and incoherently. He had a left hemianopia but no motor, sensory, or reflex abnormalities. CT scan revealed an infarct that involved the right inferior parietal and temporal lobes in the territory of the inferior division of the right MCA.[16]

My colleagues in the Stroke Data Bank project and I searched the Stroke Data Bank registry and our own patient files for patients with acute strokes that involved the inferior division of the right MCA.[17] The purpose was to characterize the findings in this syndrome. All 10 patients we reported had left visual field abnormalities. Motor abnormalities were slight and transient. Three of the patients had a severe agitated delirium at onset. One patient moaned continuously and repeatedly removed all treatment lines, tubes, and catheters despite 4-limb restraints. He became less restless after 12 hours but continued to call out apparently random names and spoke incoherently and his conversation incessantly flitted from one topic to another. Four other patients were restless and had difficulty concentrating for neurologic testing.[17] The restless, agitated patients had abnormal results with drawing and copying tasks. The anatomic localization of the infarcts shown on CT scans was plotted in the 5 agitated, restless patients versus the 5 other patients who were not agitated. Figures 1 and 2 show this reconstruction. The agitated patients all had right temporal lobe infarcts. The authors concluded that infarction of the right temporal lobe was the likely explanation for the agitation that may accompany right MCA territory infarcts.[17]

Mori and Yamadori[18] reviewed their experience with patients who had right MCA territory infarcts associated with acute confusional states and agitated delirium. They characterized the acute confusional state as a failure to maintain a coherent stream of thought or action with inattention and easy distractability. Among the 59 patients with right MCA territory infarcts, 25 had an acute confusional state and 6 had an acute state that they called an *acute agitated delirium*. This hyperactive state was characterized by extreme agitation, irritability, vivid hallucinations, delusions, insomnia, and signs of autonomic nervous system overactivity.[18] The 6 patients with agitation had infarcts in the distribution of the inferior division of the right MCA, involving the territories of the middle and posterior temporal artery branches in 5 of the 6 patients.[18] The anatomic locus that best correlated with the agitated delirious state was the right middle temporal gyrus.

Figure 1. *Location of right cerebral infarcts. Reprinted with permission from Caplan LR et al.[17]*



Agitation, anger, and paranoia are sometimes observed in patients with Wernicke aphasia. These patients most often have embolic infarctions involving the inferior branch of the left MCA and temporal lobe infarcts. Patients with aphasia who are irascible and show anger usually have Wernicke-type aphasia.[19] These behavioral changes are most likely related to dysfunction of limbic cortex and its connections that lie medial to the convexal temporal lobe infarcts that cause the aphasia. Excessive speech (logorrhea) has long been recognized as a common feature of the speech output in patients with Wernicke aphasia.

I vividly recall a patient of mine, an elderly grandmother who had the sudden onset of Wernicke aphasia. Her granddaughter who visited her said that in the past she was always docile and never raised her voice or showed anger. After her stroke she became easily agitated, threw objects, bit and spat at examiners, and began to curse profusely.

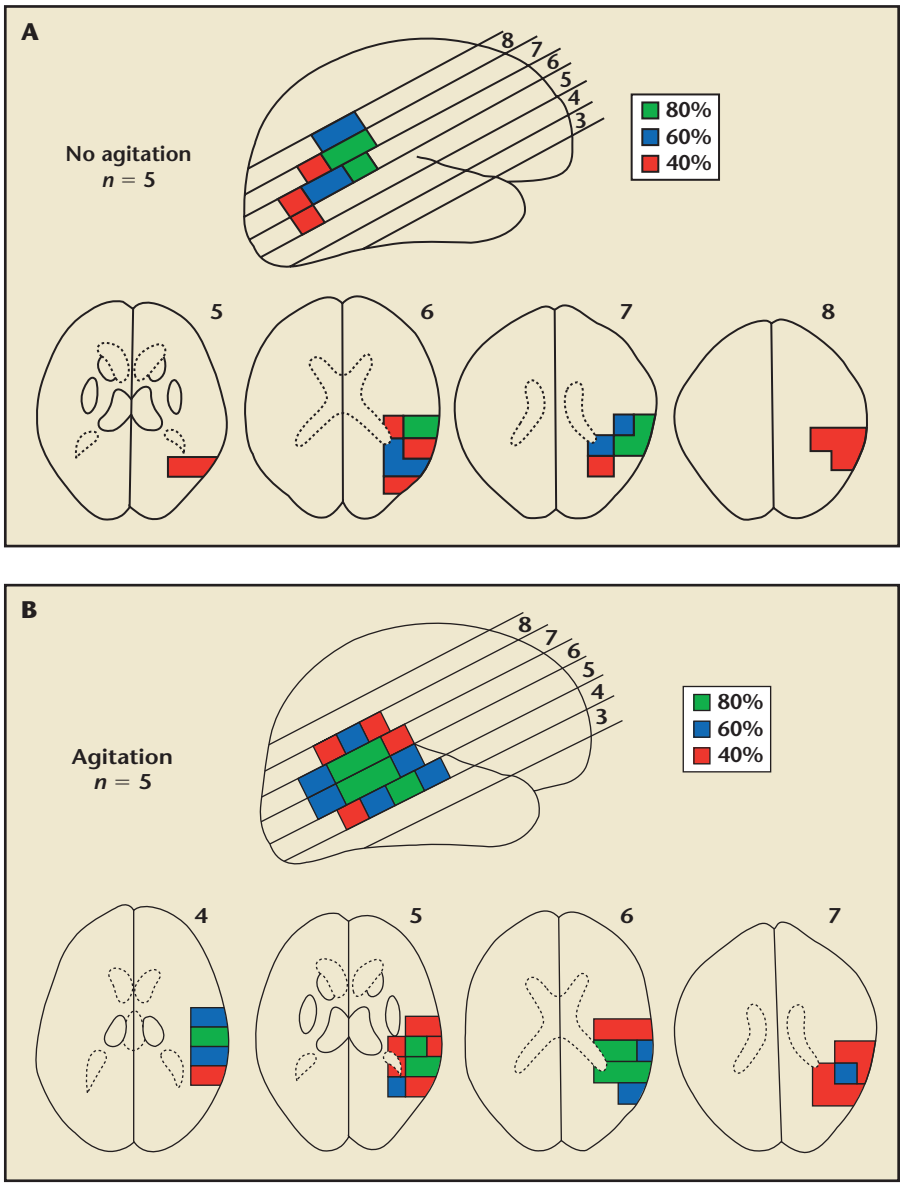


Figure 2. (A) *Location of the infarcts in the right hemisphere in those without agitation.* **(B)** *Location of the infarcts in the right hemisphere in those with agitation. Reprinted with permission from Caplan LR et al.*[17]

Bilateral temporal lobe involvement is especially likely to be associated with an agitated state. I recall 2 patient examples. One man seen during the early 1970s developed acute manic, hyperactive behavior while looking at a potential new home with his wife. All of a sudden he went running through the house opening windows and shouting. When brought to the hospital he required restraints, shouted repeatedly and incoherently, and bit, spat, and urinated on examiners. Angiography showed bilateral embolic occlusions of the inferior trunks of the MCAs. Another woman had undergone temporal lobe surgical removal during resection of an MCA aneurysm. Years later she developed a metastatic tumor in the opposite temporal lobe. She became restless, agitated, hypersexual, and aggressive when the second lesion developed.

There are conclusive data that infarcts and other lesions that include the portions of the temporal lobes subserved by the inferior branches of the MCAs, especially the right MCA, are an important cause of an agitated hyperactive restless state associated with logorrhea. Excessive loquaciousness may be a characteristic of temporal lobe dysfunction involving either hemisphere and may be present without aphasia. Bilateral lesions are more likely to cause agitated delirium than are unilateral lesions.

Caudate nucleus infarcts and hemorrhages. Mendez and associates[20] reported neurobehavioral abnormalities in 12 patients with caudate infarcts, 11 unilateral and 1 bilateral. Five of the 12 patients had "affective symptoms with psychotic features." One patient was described as extremely anxious and had difficulty sleeping and feelings of panic. She was suspicious and paranoid and heard voices that commented on "activities in the atmosphere." During examination she was very restless.[20] Patients with agitation and psychotic features had lesions that involved mostly the ventromedial portion of the caudate nucleus. Three other patients were disinhibited, inappropriate, and impulsive. One such patient was unkempt, distractable, loquacious, unconcerned, and sexually disinhibited. These 3 patients had large lesions that included most of the caudate nucleus and spread to adjacent structures.[20] The authors noted that the ventromedial caudate (the "limbic striatum"[21,22]) was topographically connected to orbitofrontal cortex.

My colleagues and I[23] reported the neurologic findings in 18 patients

with caudate infarcts. Infarcts often extended into the adjacent anterior limb of the internal capsule and the anterior portion of the putamen. The cause was most likely occlusion of lateral lenticulostriate arterial branches of the proximal MCA. Seven of these patients had transient or persistent restlessness and hyperactivity. Three of these 7 patients had left caudate infarcts, and the other 4 had right-sided lesions. In these patients apathy and abulia often alternated with hyperactivity. Two patients with right caudate infarcts had severe hyperactivity. They were restless, talked and moved incessantly, and often called out loudly. A later report described 34 new patients with caudate infarcts and reviewed the literature. These newly reported patients had behavioral findings that were similar to those of the original 18 patients.[24]

The anatomic connections of the caudate nucleus noted by Alexander and colleagues,[25] Nauta,[21] and Nauta and Domesick[22] explain the behavioral abnormalities. A lateral orbitofrontal circuit projects from the orbitofrontal cortex (Brodman area 10) to the ventromedial portion of the caudate nucleus. This portion of the caudate nucleus also receives input from temporal lobe visual and auditory association cortex. An anterior cingulate circuit originates in the anterior cingulum (Brodman area 24) and in limbic temporal lobe structures, including the hippocampi, amygdala, enterorhinal, and perirhinal cortex structures, and projects to the ventral striatum (nucleus accumbens septi, olfactory tubercle, and ventromedial caudate nucleus). The caudate nuclei have reciprocal connections with the ventral anterior and dorsomedial thalamic nuclei.[25] Although sleep abnormalities and apathetic abulic states do occur in patients with thalamic hemorrhages and infarcts, I am not aware of the presence of an agitated delirious state in patients with lesions limited to the thalamus.

Frontal lobe and other vascular lesions. Occasional reports describe patients with frontal lobe lesions who had some features of the behavioral abnormalities described in patients with agitated hyperactive delirious states. Hyland[26] reported a patient who had thrombosis of an azygous-type anterior cerebral artery (ACA) and developed a left hemiparesis accompanied by hypersexuality and incessant talking. In 1955, Amyes and Nielsen[27] discussed clinicopathologic correlations in 8 patients with vascular lesions that included the anterior cingulate area of the frontal lobes. Two of these patients were agitated during their course of illness. A 65-year-old woman who had developed a right hemiparesis with aphasia was "extremely agitated" during most of her hospital stay and needed to be restrained. Necropsy revealed an embolic occlusion of her left ACA with softening of the medial left frontal lobe. The left anterior cingulate gyrus and underlying white matter were necrotic. Another patient became agitated after infarcts that involved her bilateral basal frontal lobes related to a ruptured anterior communicating artery aneurysm.

Starkstein and colleagues[28] described 12 patients who developed manic-like behavior after brain lesions and reviewed prior literature. The lesions in these patients clustered in limbic and limbic-related areas that had strong frontal lobe projections. Starkstein and associates[29] later reported a second group of patients (a consecutive series of 8 patients) with mania after brain injuries.[29] All 8 patients were elated and had pressured speech and grandiose delusions. Seven were hyperactive and had insomnia and flights of ideas, 5 were irritable, and 6 were hypersexual. All of the lesions in these patients involved the right cerebral hemisphere. One patient had an infarct involving the head of the caudate, medial temporal gyrus, and basotemporal and dorsolateral frontal regions. Another had an infarct involving the head of the caudate, amygdala, hippocampus, and basotemporal cortex. Another patient developed an infarct after embolization of a right basotemporal vascular malformation. One patient had a right temporal lobe hemorrhage; 1 had bilateral orbitofrontal contusions; and 3 patients had subcortical lesions, including a contusion that on CT and magnetic resonance imaging was shown to involve the white matter of the anterior frontal lobe, an infarct of the ventromedial caudate head and adjacent anterior limb of the capsule white matter, and a larger infarct of the caudate nucleus and anterior limb.[29] Positron emission tomography scans in the 3 patients with subcortical lesions showed abnormal metabolism in the right lateral basotemporal regions.[29] The authors posited that dysfunction of the orbitofrontal region was a cause of somatic and mood abnormalities in patients with mania due to organic brain lesions.[30]

Arseni and Dănăilă[31] described hyperactive behavior in relation to pontine brainstem disease. Their patients showed logorrhea with a flow of ideas and content and hyperactivity. One patient with a basilar artery aneurysm and a clinical deficit localizable to the pons and upper brainstem showed logorrhea with a flow of ideas and content and hyperactivity.[31] The authors posited that a lesion that stimulated the ascending reticular activating system could cause increased speech and behavior.

They also emphasized that logorrhea and hyperkinesis did not always exist simultaneously. Among their 13 patients, 6 had both logorrhea and hyperactivity, whereas 1 patient had logorrhea without hyperactivity and 6 other patients were hyperkinetic but mute.[31] I have seen 1 patient with a dolichoectatic basilar artery and an infarct in the territory of a penetrating pontine artery branch who suddenly became loquacious and had persistent logorrhea after she developed a hemiparesis caused by her pontine infarct.[32]

Nonstroke Lesions

Infections, both systemic and those involving the central nervous system, are often associated with agitation especially at and near onset. Patients with bacterial meningitis often become symptomatic quickly and may appear restless and agitated when they first present. Similar presentations may occur in patients with subarachnoid hemorrhage, and those with primary intraventricular bleeding that spills into the cerebrospinal fluid, indicating that irritation of the meninges is a precipitant of agitation. Patients with viral encephalitis often present with agitation and restlessness and some become quite aggressive, angry, and hyperactive. Many types of encephalitis are rather diffuse. Herpes simplex (HSV) encephalitis most often affects the medial temporal and orbital frontal lobes, often bilaterally but sometimes on only 1 side.[33] Restlessness, hyperactivity, agitation, and seizures are common presenting features of HSV encephalitis.[33,34]

Limbic encephalitis, a presumably noninfectious condition often seen in patients with cancer, has a similar distribution to HSV encephalitis. These patients present less acutely than those with HSV encephalitis, but their early course is also often characterized by an agitated restless state.[35,36] More recently, a limbic, predominantly temporal lobe inflammatory condition sometimes associated with cancer has been attributed to anti–*N*-methyl-D-aspartate receptor antibodies in children and adolescents[37] and to antibodies against the α-amino-3 hydroxy-5-methyl-4-isoxazolepropionic acid receptor in adults[38] who have an inflammatory lesion that primarily affects the medial temporal lobes. Seizures, agitation, and behavioral changes are common early predominant features of these 2 forms of limbic encephalitis.

Head injuries may cause an agitated hyperactive state. Bakchine and coworkers[39] reported a manic-like state in a patient with bilateral orbitofrontal and right temporoparietal lobe contusions. This patient had a reduced amount of spontaneous behavior when left alone but became manic when stimulated. She had reduced sleep time and frequent outbursts of anger. When spoken to, she became logorrheic and constantly switched conversation from one topic to another. Lesions of the orbitofrontal cortex have been shown to cause distractability, overactivity, and motor disinhibition.

I have also seen agitation with hypersexuality, aggressiveness, and anger in patients with traumatic brain injuries that had involvement of the orbitofrontal regions. Accompanying basotemporal contusions could not be excluded from the neuroimaging tests performed.

Lesions of the orbitofrontal cortex have been shown to cause distractibility, overactivity, and motor disinhibition.

Toward the end of the 19th century, Gowers[40] noted that epileptic seizures were occasionally followed by a period of agitation with mania and aggressive behavior. Complex migraine attacks, especially in children and adolescents, often have a component of agitation and hyperactivity.[41] The brain location of the abnormalities is often in the posterior portion of the cerebral hemispheres, and visual abnormalities are a frequent co-occurrence. In young persons, the agitation may be a psychologic reaction to the neurologic dysfunction and not related to the brain localization. ■

Main Points

- The term *delirium* is best reserved for an acute change in behavior characterized by a hyperactive, restless, agitated state.
- Brain lesions, especially strokes in certain brain areas—most often limbic regions—are known to produce such hyperactive agitated states.
- The most common regions in which strokes and other pathology cause hyperactivity and agitation are the temporal lobes (right more than left), fusiform and lingual gyri, caudate nucleus, and cingulate cortex.

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