# Brain Magnetic Resonance Imaging Findings in ECT-Induced Delirium

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*A prolonged (interictal) but reversible delirium was induced by electroconvulsive therapy (ECT) in 10 of 87 (11%) elderly depressed patients. Brain magnetic resonance imaging (MRI) revealed several structural abnormalities, particularly basal ganglia and moderate to severe subcortical white-matter lesions, in the patients who developed delirium. These findings are consistent with several lines of data that have implicated the basal ganglia and subcortical white matter in the development of delirium from other causes and suggest that lesions in these areas may predispose one to developing an interictal delirium during a course of ECT.*

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While electroconvulsive therapy (ECT) is an effective treatment for severe depression in the elderly,[1] it has been suggested that these patients may be at a relatively higher risk for developing encephalopathic side effects from the treatment.[2] This risk has been attributed, in part, to a presumed increase of preexisting structural brain abnormalities in elderly individuals,[3] although this contention has never been directly studied. Nor has the question of whether lesions in particular brain regions predispose patients to a particular type of cognitive side effect (for example, delirium or amnesia) been investigated.

A possible insight into these questions may have been provided by recent data indicating that agitated delirium frequently follows acute cerebral infarctions that involve the basal ganglia and subcortical white matter.[4,5] In addition, recent reports indicate that lesions of the basal ganglia and subcortical white matter revealed by brain magnetic resonance imaging (MRI) may occur in elderly depressed patients who develop delirium in association with antidepressant drug therapy.[6] We decided, therefore, to examine the potential relationships of basal ganglia lesions and other structural abnormalities to the development of an interictal delirium during a course of ECT. We use the term "interictal delirium" to refer to a

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delirium that develops during a course of ECT and persists on days that the patients do not receive ECT.

## METHODS

### Subjects

This report is part of an ongoing, prospective MRI investigation of structural brain abnormalities in depressed elderly patients. From July 1, 1985, to December 31, 1987, 87 elderly patients (60 years old or older) received a brain MRI scan prior to undergoing ECT at Duke University Medical Center. The patients received the MRIs either as part of a research protocol (written informed consent was obtained in each case) or as part of a work-up to rule out organic causes of depressive symptoms.

There were 57 women and 30 men among the 87 elderly patients. They had a mean age of 71.5 years (range, 60 to 90). All subjects were right-handed. Twelve patients had a clearly established history of dementia according to *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III)* criteria prior to the onset of the current depressive episode. In each case, the cognitive deficits persisted after the resolution of the affective disorder. Two patients had diagnoses of dementia and a history of a cerebral vascular accident. No patient received the diagnosis of delirium prior to the initiation of ECT.

The following medical illnesses were present in the 87 elderly patients: hypertension or coronary artery disease (n=60), chronic obstructive pulmonary disease (n=6), diabetes mellitus (n=9), history of cancer (n=4), history of a cerebral vascular accident (n=2), Parkinson's disease (n=3), degenerative joint disease (n=5), and alcohol or drug abuse (n=6). None of the patients who had a diagnosis of alcohol or drug abuse developed delirium.

### Brain MRI Procedure

All brain MRI studies were performed on a 1.5-Tesla system. Technical parameters included a 128×256 matrix, a 20-cm field of view, and two excitations. Spin-echo pulse sequences were used to generate both T1-weighted (TR, 500 msec; TE, 20 msec) and T2-weighted (TR, 2000 msec; TE, 40 msec; TE, 80 msec) images. For both T1-weighted and T2-weighted images, a series of 5-mm thick sections with a 2.5-mm interscan gap was performed in the axial plane (parallel to the orbitomeatal line, 0°).

This imaging protocol was modified slightly for six patients who were participating in another research study as well. For these patients, contiguous, 5-mm thick, T1-weighted images were obtained in the coronal plane (perpendicular to the canthomeatal line).

The brain MRI scans were analyzed independently by a board-certified neuroradiologist and a neurologist who was also a psychiatrist; both were blind to the clinical interpretation of each patient's MRI scan and to whether that patient had developed a delirium. Each patient's MRI study was assessed for the presence and severity of several abnormalities: leukoencephalopathy, subcortical gray-matter lacunae, lateral ventricular enlargement, cortical atrophy, and abnormalities of other brain areas, such as the brain stem and cerebellum.

Evaluation for leukoencephalopathy included noting the occurrence of periventricular hyperintensity and deep white-matter hyperintensity. Both periventricular hyperintensity and deep white-matter hyperintensity were rated from the T2-weighted images using a modification of the 4-point scale described by Fazekas et al.[7] When grading periventricular hyperintensity, 0 indicated an absence of periventricular hyperintensity; 1, caps or a pencil-thin lining; 2, a smooth halo; and 3, an irregular periventricular hyperintensity extending into the deep white matter. When grading separate deep white-matter hyperintensity signals, 0 indicated such signals were absent; 1, the presence of punctuate foci; 2, the presence of small confluent areas; and 3, the presence of large confluent areas.

Abnormalities (lacunae) of the subcortical gray matter (basal ganglia and thalamus) were rated from the T2-weighted images as either present or absent. Lateral ventricular enlargement was evaluated based on a 5-point scale: 0 indicated no ventricular enlargement; 1, slight enlargement; 2, mild enlargement; 3, moderate enlargement; and 4, severe enlargement. Ventricular enlargement was rated only if it was considered more extensive than would be expected for the patient's age. Cortical atrophy was assessed using a 5-point rating scale: 0 indicated no atrophy; 1, slight atrophy; 2, mild atrophy; 3, moderate atrophy; and 4, severe atrophy.[2]

Predefined axial and coronal visual standards for each grade of atrophy, lateral ventricular enlargement, periventricular hyperintensity, and deep white-matter hyperintensity lesions were established for comparison. Interrater differences were resolved by a final consensus rating.

### ECT Technique

Psychotropic medications (antidepressants, lithium, benzodiazepines, and other sedatives) were tapered and discontinued prior to ECT in 77 patients. The duration of the drug washout before ECT ranged from one to 14 days. Ten patients required sedative or neuroleptic agents for insomnia or agitation after beginning ECT. Of these, nine patients received an anxiolytic, and one received a neuroleptic. Only one patient who was taking a psychotropic medication during ECT developed an interictal delirium. The ECT technique was similar for each patient. ECT was

administered three mornings a week (Monday, Wednesday, and Friday). Patients were premedicated with an anticholinergic, either glycopyrrolate (0.0044 mg/kg) or atropine (0.1 mg/10 kg). Anesthesia was induced with methohexital 1 mg/kg iv, followed by succinylcholine 1 mg/kg iv. All patients were oxygenated before ECT by breathing 100% oxygen through a mask. Once apneic, their respirations were maintained at a rate of 20 to 25 respirations per minute with positive pressure ventilation by bag until spontaneous respiration returned. Patients were monitored by electrocardiogram and a one-channel electroencephalogram (EEG).

For unilateral nondominant ECT, the d'Elia placement technique was used. The total number of treatments and the choice of electrode placement was determined by the attending physician; the average number of ECT treatments was nine (range, five to 18).

A moderately suprathreshold ECT stimulus was administered with an SR1 brief-pulse device. For each ECT treatment, seizure duration was determined from a one-channel EEG using standard criteria to ensure that all patients received seizures of an adequate length.[8]

### Clinical Data

All patients received a comprehensive physical examination with standard laboratory evaluations when they were admitted to the hospital. Subsequently, each patient received a neuropsychiatric evaluation, including a neurologic exam and mental-status examination by a member of the ECT service prior to beginning ECT.

The mental-status examination was derived from the composite Mental Status Examination developed by Strub and Black.[9] This examination is performed in an orderly way and includes the assessment of basic processes: the levels of consciousness, attention, and vigilance are assessed first, and the higher cognitive functions are tested last. This systematic examination should be particularly sensitive at detecting the cognitive changes associated with delirium.[9] Patients were assessed for delirium prior to ECT, and none were found to meet the *DSM-III* criteria for that disorder.

Following ECT, patients were assessed for delirium with the mental-status exam and *DSM-III* criteria by physicians on each patient's treatment team and on the ECT service. To differentiate interictal delirium from the acute confusion that follows (and typically clears on the day of) ECT treatment,[10] the diagnosis of delirium was made on days that patients did not receive ECT. Using the mental-status exam, we evaluated biweekly each patient who developed an interictal delirium. Delirium was judged resolved when the subjects' performances on the mental-status exams had returned to pre-ECT levels and they no longer met criteria for delirium.

Summers et al.[11] have reported that preexisting, chronic medical illnesses and exposure to psychoactive drugs may be associated with disorientation or decreased intellectual functioning during a course of ECT. To investigate these variables, the charts of all 87 patients were reviewed for the presence of significant medical illnesses. According to the method developed by Summers,[12] prior exposure to psychoactive drugs was estimated by calculating a "drug-risk number" for all patients before beginning ECT. Higher drug-risk values reflect increased exposure to drugs that have central nervous system anticholinergic properties. In addition, elevated drug-risk values have been associated with delirium that develops following cardiotomy and cataractectomy.

### Statistical Tests

All comparisons were made using the two-tailed Yates'-corrected chi-square test. Calculations were carried out on a SYS-STAT statistical program.

## RESULTS

Interictal delirium developed in 10 (11%) patients during their course of ECT (table 1). In each case, evaluating the patient's history, physical examination, and appropriate laboratory studies revealed no identifiable etiology for the delirium.[13,14]

None of the subjects who developed delirium had experienced cardiac or neurologic complications during ECT treatments. Nine patients who developed delirium were able to continue with a full course of ECT therapy. For seven of these patients, the frequency of treatments was decreased to once or twice a week to reduce the risks associated with delirium (for example, falling or wandering). ECT treatments were discontinued in one patient because of interictal delirium. Within one week of completing the course of ECT, all patients appeared to be free of delirium. At that time, all patients were judged by the clinical treatment team to have experienced a good or an excellent clinical remission of their depressive symptoms according to a 7-point clinical global rating scale.[15]

Patients who developed interictal delirium did not differ from those who did not with respect to age, sex, average number of ECT treatments, types of anticholinergic medications before ECT ($\chi^2$=0.329, df=1, p=.566) or history of dementia prior to ECT ($\chi^2$=1.19, df=1, p=.275) (table 1).

The groups did not differ in the occurrence of significant medical illnesses (coronary artery disease, hypertension, chronic obstructive pulmonary disease, diabetes, dementia, cancer, cerebral vascular accident, and alcohol or drug abuse) or other neurologic illnesses. The groups

TABLE 1. Descriptive characteristics of 87 elderly patients who did and did not develop ECT-induced interictal delirium

| Characteristic | Patients With Delirium (n=10) | Patients Without Delirium (n=77) |
|---|---|---|
| **Demographic Feature** | | |
| Age | | |
| mean | 76.1 | 70 |
| range | 72 to 81 | 60 to 90 |
| Sex | | |
| female | 7 | 52 |
| male | 3 | 25 |
| **Clinical Feature** | | |
| History of dementia | | |
| number of patients | 3 | 9 |
| percent of patients | 30 | 12 |
| Mean±SD drug-risk number[a] | 12.4±2.1 | 12.3±2.5 |
| ECT treatments | | |
| mean | 8.5 | 9.1 |
| range | 5 to 18 | 5 to 18 |
| Pre-ECT anticholinergic medications | | |
| atropine | | |
| number of patients | 3 | 13 |
| percent of patients | 30 | 17 |
| glycopyrrolate | | |
| number of patients | 7 | 64 |
| percent of patients | 70 | 83 |
| Electrode placement | | |
| bilateral | | |
| number of patients | 2 | 8 |
| percent of patients | 20 | 10 |
| right unilateral | | |
| number of patients | 5 | 60 |
| percent of patients | 50 | 78 |
| Switched from right unilateral to bilateral | | |
| number of patients | 3 | 9 |
| percent of patients | 30 | 12 |

[a]Higher drug-risk numbers reflect greater previous exposure to drugs with anticholinergic properties.[12]

had comparable mean drug-risk numbers on the day prior to beginning ECT (table 1).

The two groups of patients did not differ with respect to stimulus-electrode placement. Three patients who developed an interictal delirium were switched from right-unilateral to bilateral stimulus-electrode placement to enhance therapeutic efficacy. Two of these patients were diagnosed as having an interictal delirium prior to switching electrode placements.

Brain MRI revealed several abnormalities in both groups of patients (table 2), and statistical analyses revealed that the abnormalities differed significantly between groups. In particular, lesions of the basal ganglia were observed in nine patients (90%) who developed interictal delirium, compared with only 30 patients (39%) who did not. Only one patient who did not have lesions of the basal ganglia (n=48) developed delirium. These differences were significant ($\chi^2$=7.37, df=1, p=.007).

Nine patients who developed interictal delirium (90%) had periventricular hyperintensity and deep white-matter lesions that were rated as moderate to severe. In the group who did not develop delirium (n=77), only 39 patients (51%) had moderate to severe periventricular lesions, and only 35 patients (45%) had moderate to severe deep white-matter lesions. These differences were significant (periventricular hyperintensity, $\chi^2$=4.064, df=1, p=.044; deep white-matter lesions, $\chi^2$=5.36, df=1, p=.021). The lesions of the basal ganglia and of the subcortical white matter appeared as foci of increased signal hyperintensity on the T2-weighted images.

TABLE 2. Brain magnetic resonance imaging findings in 87 elderly depressed patients

| Brain Abnormalities | Patients With Delirium (n=10) | | Patients Without Delirium (n=77) | |
|---|---|---|---|---|
| | n | % | n | % |
| Basal ganglia lesions* | 9 | 90 | 30 | 39 |
| Cortical atrophy | | | | |
| absent or slight | 0 | 0 | 8 | 11 |
| mild | 2 | 20 | 24 | 31 |
| moderate | 8 | 80 | 28 | 36 |
| severe | 0 | 0 | 17 | 22 |
| Lateral ventricular enlargement | | | | |
| absent or slight | 4 | 40 | 37 | 48 |
| mild | 5 | 50 | 17 | 22 |
| moderate | 1 | 10 | 21 | 27 |
| severe | 0 | 0 | 2 | 3 |
| Periventricular hyperintensity | | | | |
| absent | 0 | 0 | 5 | 6 |
| mild | 1 | 10 | 33 | 43 |
| moderate | 6 | 60 | 24 | 31 |
| severe** | 3 | 30 | 15 | 20 |
| Deep white-matter hyperintensity | | | | |
| absent | 0 | 0 | 16 | 21 |
| mild | 1 | 10 | 26 | 34 |
| moderate | 8 | 80 | 19 | 24 |
| severe*** | 1 | 10 | 16 | 21 |
| Thalamic lesions | 2 | 20 | 16 | 21 |
| Pontine lesions | 4 | 40 | 23 | 30 |

*p=.004, **p=.021, ***p=.015

The groups did not differ in the occurrence of moderate to severe cortical atrophy ($\chi^2$=.941, df=1, p=.332) or moderate to severe lateral ventricular enlargement. Nor did they differ on the occurrence of either pontine or thalamic lesions (table 2).

## DISCUSSION

Interictal delirium developed during the course of ECT in 10 (11%) of 87 elderly depressed patients. In all cases, no other specific etiologies for delirium were found, and the deliria appeared to resolve within one week following the course of ECT. All patients who developed delir-

ium were judged by the clinical treatment team to have experienced a good or an excellent response to the treatment. In this preliminary study, ECT-induced delirium in the elderly appeared to be transient and reversible, and it did not interfere with a therapeutic response.

In our study, patients who did and who did not develop interictal delirium did not differ with respect to age, sex, average number of ECT treatments, history of dementia, type of pre-ECT anticholinergic medications, drug-risk number, or history of significant medical illnesses. While rarely studied, many investigators feel that electrode placement can play a role in the development of an interictal delirium during ECT.[16] In our study, the groups did not differ with respect to stimulus-electrode placement. Although in our preliminary study the groups did not differ significantly on any of these clinical or ECT parameters (table 1), the potential contribution of these clinical and ECT parameters to the development of ECT-induced interictal delirium and the mechanisms by which any of these parameters can interact with structural brain changes require further study.

Basal-ganglia and moderate to severe subcortical white-matter lesions occurred more frequently in the patients who developed interictal delirium. These findings are consistent with several lines of data that have implicated these subcortical structures in the development of delirium from other etiologies.

Mori and Yamaddri[5] found that 25 of 41 patients developed delirium after a right-middle cerebral artery infarct. In 24 of the patients who developed delirium, the infarct involved the basal ganglia. Caplan et al.[4] described agitated, confused behavior in four of eight patients who experienced an infarction in the right caudate and in three of 10 patients who experienced an infarction in the left caudate. Finally, Figiel et al.[6] described the occurrence of basal ganglia and subcortical white-matter lesions in five elderly depressed patients who developed antidepressant-induced delirium.

The precise etiology of these subcortical white-matter and basal-ganglia lesions revealed by MRI is not known. However, current clinical and neuropathological data suggest that in the elderly, these lesions may reflect abnormal water (hydrogen) content or structural changes (for example, dilated perivascular spaces, edema, or frank lacunar infarctions)[17,18] resulting from arteriosclerotic involvement of the small penetrating arterioles that irrigate the basal ganglia and subcortical white matter.[2]

Lesions of the subcortical white matter have been visualized on the MRI scans of healthy subjects. However, we[19] and others[20] have found that basal ganglia and severe white-matter lesions are uncommon in healthy subjects. Because severe white-matter and basal-ganglia lesions were common in our elderly depressed patients referred for ECT, this raises the question of whether these lesions have clinical significance. We have previously reported that lesions in these areas might be a marker for the development of late-onset depression.[2,3] Further study is required to determine whether these lesions are associated with the pathophysiology of affective disorder in some patients.

We can only speculate on the pathophysiologic mechanism or mechanisms whereby lesions of the basal ganglia and subcortical white matter may be associated with ECT-induced, interictal delirium. The basal ganglia and subcortical white matter have extensive connections with cortical areas known to be important to attentional processes.[21,22] Perhaps in some patients lesions of the basal ganglia and subcortical white matter disrupt or disconnect these pathways (for example, the corticostriate and corticoreticular pathways or the ascending reticular formation), resulting in an increased vulnerability to disturbances of attention and vigilance, which are the hallmarks of delirium. However, not every patient with lesions in these areas developed delirium. Further work examining the metabolic, neurochemical, and physiochemical correlates of such lesions could allow us to further identify patients who are susceptible to developing ECT-induced, interictal delirium.

In summary, brain MRI scans of depressed elderly patients who developed ECT-induced interictal delirium showed a high rate of basal-ganglia lesions and moderate to severe lesions of the subcortical white matter. These findings are consistent with several lines of data implicating these structures in the development of delirium from other causes. Additional work in a larger sample is required to determine the extent to which basal-ganglia and subcortical white-matter lesions, along with other clinical variables, might be risk factors for the development of ECT-induced interictal delirium.

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