Altered Mental Status in Patients With Cancer

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Objective: To identify the causes of an altered mental status in a cancer population.

Methods: We studied 140 confused patients with cancer (100 prospectively and 40 retrospectively) between January 1, 1991, and June 30, 1992, to determine clinical findings, causes, and outcome.

Results: All patients had non-central nervous system cancers. The most common primary cancer types were lung (20%), gastrointestinal tract (18%), leukemia and lymphoma (17%), and breast (11%). Median patient age was 73 years, and 49% were men. Disseminated systemic metastases were present in 50% of patients; 34% were confused at hospital admission and 66% developed confusion during hospitalization. Symptoms included lethargy or coma in 61% of patients, agitation in 44%, disorientation in 83%, lateralizing signs in 41%, delusions or hallucinations in 28%, and seizures in 9%. A single cause of the altered mental status was found in 33% of patients, whereas 67% had multiple causes. Drugs, especially opioids, were associated with altered mental status in 64% of patients, metabolic abnormalities in 53%, infection in 46%, and recent surgery in 32%. A structural brain lesion was the sole cause of encephalopathy in 15% of patients. Although delirium improved in 67% of patients, it was a poor prognostic factor for overall outcome. Thirty-day mortality was 25%, and 44% of patients died within 6 months, usually from progression of the underlying cancer. Prolonged delirium suggested infection or coagulopathy. Younger patients and those with hypoxemia or kidney or liver dysfunction were more likely to die ($P<.05$).

Conclusion: Patients with cancer usually have multiple causes of delirium, many of which are treatable, with rapid improvement in their cognitive status.

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Delirium—from the Latin delirare, a farming term meaning to go out of the furrow but implying to lose one's wits—is common, but its cause is often difficult to identify. Sometimes florid but more often subtle, it is present in 10% to 25% of all hospitalized patients and in 14% to 40% of patients hospitalized with cancer and is associated with an increased mortality rate. Delirium prolongs hospital stay, causes morbidity, and, especially in patients with cancer, has a poor prognosis. Frequently, delirious patients are mistaken for being terminally ill, but if their mental status can be restored with proper treatment, they often recover remarkably. The disorder is often unrecognized by the patient's physicians and nurses, but even when recognized, its pathophysiologic origin is poorly understood. Early recognition of delirium and its underlying causes can shorten hospital time, restore function, and be lifesaving. Confusion is the most common reason for neurologic consultation at Memorial Sloan-Kettering Cancer Center (MSKCC), New York, NY. The patient with cancer often has complicated medical and surgical problems, which can predispose to delirium. Furthermore, the potential causes of encephalopathy, such as opportunistic central nervous system infection or metastatic disease, differ from those usually encountered in a general patient population. We set out to describe delirium in patients with cancer and to examine its causes and factors related to outcome.

RESULTS

The 40 patients studied retrospectively and 100 patients studied prospectively had identical characteristics and, therefore, were grouped together. There were 69 men (49%) and 71 women (51%). Median patient age was 73 years (range, 26-92 years). Forty-eight patients (34%) had altered mental status on hospital admission and 92 (66%) developed it during hospitalization. One hundred twenty-eight patients (91%) were maximally encephalopathic...
PATIENTS AND METHODS

PATIENTS

We studied 140 consecutive adults (aged >18 years) with systemic cancer admitted to MSKCC who were evaluated by a neurologist for impairment of mental status that developed during hospitalization or was present at admission. All patients had delirium as defined in the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (Table 1). One hundred patients were studied prospectively from July 1, 1991, to June 30, 1992, and 40 patients seen between January 1, 1991, and June 30, 1991, were retrospectively identified from the database of the Department of Neurology at MSKCC. All patients were seen by a neurologist within 24 hours of a request for mental status evaluation and were followed up until hospital discharge or resolution of delirium. We excluded patients admitted to the hospital for terminal care and those with primary brain tumors or acquired immunodeficiency syndrome.

All patients underwent a complete neurologic evaluation; routine laboratory studies; and, when necessary, cerebrospinal fluid examination, cranial computed tomography, or magnetic resonance imaging. For patients studied prospectively, the Mini-Mental State Examination was performed at each neurologic visit, and a score less than 28 was interpreted as abnormal. Outcome was determined by the consulting neurologist, and survival was assessed through the hospital’s database 30 days and 6 months after diagnosis of delirium.

DIAGNOSIS OF DELIRIUM

Based on information acquired at the initial visit, each patient was assessed with respect to (1) extent of cancer; (2) cancer treatment, including surgery or chemotherapy at the same hospital admission and previous or current brain irradiation; (3) drugs being taken at admission or administered during hospitalization, including opioids, corticosteroids, benzodiazepines, histamine; blockers, antihistamines, anticholinergics, and anticonvulsants; and (4) neuroradiologic results.

CLINICAL MANIFESTATIONS

Of 140 patients, 3 (2%) were comatose, 83 (59%) were lethargic, and 54 (39%) were awake at presentation. On examination, only 24 patients (17%) were fully oriented. Agitation was present in 62 patients (44%), delusions or hallucinations were experienced by 39 (28%), and 13 (9%) had at least 1 seizure. A few patients were lethargic when not stimulated but became agitated when aroused. Inattention was present in 85 (92%) of 92 patients tested prospectively. Calculation was tested in 89 patients and was normal in only 7 (8%), moderately impaired in 29 (33%), and severely impaired in 53 (60%). Only 15 (23%) of 64 patients could follow 3-step commands, and 18 (28%) could not follow single-step commands. The Mini-Mental State Examination score was impaired in 68 (91%) of 75 patients tested completely. The median Mini-Mental State Examination score was 12 at first evaluation and 23 at last assessment. Asterixis was present in 30 (36%) of 140 patients, and frontal lobe release signs (eg, snout and grasp) were found in 54 (39%). Lateralizing signs were present in 57 patients (41%).

TUMOR TYPE

Lung cancer was the most frequent primary tumor (20%), followed by gastrointestinal tract cancer (18%), breast cancer (11%), leukemia (9%), and lymphoma (9%). Systemic metastatic disease was present in 102 patients (73%), and only 17 (12%) had no metastases; cancer stage was unknown in 21 patients (15%). Previously diagnosed brain or leptomeningeal metastases existed in 13 patients (9%) and were newly diagnosed in 23 (16%).

Causes of delirium were assigned to 1 of 7 categories, and their relation to the delirium was ranked; this approach was modified from Francis et al.8 The 7 categories are as follows: (1) drug (withdrawal, intoxication, or adverse effect if the drug is known to cause altered mental status and the patient improved with cessation or dose reduction or confusion started within 7 days of cessation in a patient with known alcohol or illicit drug use), (2) systemic infection, (3) organ dysfunction (eg, renal or hepatic failure), (4) hypoxia (eg, hypoxemia or hypoperfusion), (5) fluid or electrolyte imbalance (eg, hyponatremia or hypercalcemia), (6) structural brain lesion (eg, metastasis or infarct), and (7) sensory or environmental (eg, intensive care unit or preexisting dementia).

Based on clinical assessment and medical chart review, each potential cause was categorized as (1) definite if it was temporally related, it had laboratory confirmation (eg, toxic level or positive blood culture), the patient improved with treatment or cessation of the offending agent, and no other cause was present; (2) probable if all the previous criteria were met but another main cause was present or laboratory confirmation was not achieved; (3) possible if it was temporally and clinically related but without laboratory confirmation or improvement was not observed with treatment or treatment was not administered; and (4) contributory if it was only temporally related and there were more evident causes for altered mental status or the abnormalities present could facilitate but not directly cause delirium.

STATISTICAL ANALYSIS

Two sets of risk factor analysis were performed. The first used the 30-day mortality rate as the dependent variable and the second used worsened mental status at last neurologic evaluation as the dependent variable. The unadjusted odds ratio for each risk factor was calculated using a logistic regression model (stepwise forward analysis). All independent variables were adjusted for age. All variables with P<.10 were included in the model, and variables with covariance greater than 0.4 were excluded from the model. The significance level was P<.05.

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The causes of delirium are shown in Table 2. Most patients had multiple causes, and the median number of probable causes was 3 per patient. Drugs were associated in 64% of patients but were a definite cause in only 4%; the implicated drugs are listed in Table 3. Hypoxia was found in 60 patients (43%), and organ dysfunction occurred in 75 (54%). Electrolyte disturbance contributed in 46% of patients but was a definite cause in only 1%. Delirium occurred in the postoperative period in 32% of patients; other functional or environmental disturbances played a role in 29 (21%). Infection was present in 65 patients (46%), but sepsis was the single cause in only 1%. Central nervous system structural disease contributed to encephalopathy in 36% of patients and was a definite cause in 15%. Eleven percent of patients had cranial radiotherapy previously or during the same hospital admission, and 11% had chemotherapy during the same admission; either factor was considered only potentially contributory.

The causes of delirium are presented in Table 4. Only 44 patients (31%) had one specific cause of delirium. Hypoperfusion was the sole cause in 6 patients but was contributory in another 32, hypoxemia was contributory in 30 patients and the only cause in 2. Twenty-five patients had multiple organ dysfunction, especially renal and liver failure, as contributory factors to delirium. Central nervous system metastases were responsible for delirium in 19 patients (14 cerebral, 4 leptomeningeal, and 1 both) and contributed to encephalopathy in an additional 17 (14 cerebral and 3 leptomeningeal). Fourteen patients with cerebral metastases had additional focal lesions causing delirium; 2 had posterior circulation stroke and 12 had other lesions, such as meningitis. In 65 patients, systemic infection was a cause of confusion, but it was the sole cause in only 2.

**ABNORMALITIES IN AUXILIARY TESTS**

All patients had abnormal laboratory test results. On average, 50% of the 34 tests most commonly ordered had abnormal results for each patient, but many of the abnormalities were mild and not considered a cause of delirium. Considering only tests that were performed in more than 80% of patients, the most common abnormalities were low albumin (84%), low total protein (74%), low hemoglobin (74%), abnormal glucose (71%), elevated blood urea nitrogen (65%), and abnormal sodium and alkaline phosphatase (60% each) levels. Hypercalcemia was present in 11 patients (8%). Ninety percent of 33 tested patients had reduced creatinine clearance, and an elevated lactate level was seen in 25 (89%) of 28 patients tested. A positive blood culture was present in 9 (7%) of 131 patients. Neuroimaging (magnetic resonance imaging or computed tomography) was performed on 117 patients (84%): 24 (21%) had normal results, 49 (42%) had brain atrophy, 26 (22%) had metastases, and 18 (15%) had other structural abnormalities such as stroke or white matter changes. Twenty-five percent of patients without lateralizing signs had structural lesions on neuroimaging. Cerebrospinal fluid was examined in 53 patients (38%): 8 (15%) had positive cytology and 1 (2%) had infectious meningitis.
Delirious patients had an average length of hospital stay of 30 days compared with 9 days for other patients at MSKCC during the same period. Ninety-four patients (67%) recovered, and 5 were still delirious at hospital discharge; same-admission mortality was 29% (41 patients), including all 3 comatose patients. Thirty-day mortality was 25%, and 6-month mortality was 44%. Average time to death after onset of encephalopathy was 183 days. Patients admitted to the hospital for surgery who developed delirium had a significantly lower 30-day mortality than other patients at MSKCC during the same period (P =.02), increased serum urea nitrogen level (P =.03), increased alkaline phosphatase level (P =.02), increased serum urea nitrogen level (P =.01), and low arterial oxygen saturation (P =.04).

### OUTCOME

Delirium is a common symptom in hospitalized patients, particularly those who are extremely ill. In a retrospective study, Clouston et al found that delirium was the most common cause for neurologic consultation at MSKCC, accounting for 17% of consultations. This is a minimal incidence because it does not include confused patients for whom a neurologic consultation was not requested or those whose confusion was unrecognized by their physicians.

Acute encephalopathy has been studied in general hospital populations, but patients with cancer are likely to have different causes, and the outcome may also differ, eg, the delirium may improve, but the mortality rate from the underlying malignancy may be high. In our population, patients with cancer had a significantly lower 30-day mortality than other patients at MSKCC during the same period. Ninety-four patients (67%) recovered, and 5 were still delirious at hospital discharge; same-admission mortality was 29% (41 patients), including all 3 comatose patients. Thirty-day mortality was 25%, and 6-month mortality was 44%. Average time to death after onset of encephalopathy was 183 days.

Patients admitted to the hospital for surgery who developed delirium had a significantly lower 30-day mortality rate and better mental status on last neuropsychologic examination. Chemotherapy and brain radiotherapy were significantly related to worsened mental status on last neuropsychologic examination. Multivariate analysis identified 2 independently associated variables for persistent delirium: the presence of infection (P =.04) and elevated prothrombin time (P =.005). For 30-day mortality rate, the multivariate analysis demonstrated an increasing mortality rate with younger age (P =.03), increased alkaline phosphatase level (P =.02), increased serum urea nitrogen level (P =.01), and low arterial oxygen saturation (P =.04).

### COMMENT

Delirium is a common symptom in hospitalized patients, particularly those who are extremely ill. In a retrospective study, Clouston et al found that delirium was the most common cause for neurologic consultation at MSKCC, accounting for 17% of consultations. This is a minimal incidence because it does not include confused patients for whom a neurologic consultation was not requested or those whose confusion was unrecognized by their physicians.

Acute encephalopathy has been studied in general hospital populations, but patients with cancer are likely to have different causes, and the outcome may also differ, eg, the delirium may improve, but the mortality rate from the underlying malignancy may be high. In our population, no particular type of cancer predisposed to the development of delirium.

The clinical diagnosis of delirium was not difficult in most patients because lethargy and poor attention were common. Lateralizing signs were found in 41% of patients, and of those, 42% had cerebral metastases. However, 25% of patients without lateralizing signs who had neuroimaging also had focal cerebral lesions that caused or contributed to their delirium, and almost half of these patients had newly diagnosed brain metastases. Thus, the absence of lateralizing signs does not exclude structural brain disease in cancer patients. Furthermore, because most patients had multiple causes of delirium, the identification of a reasonable cause (eg, liver dysfunction) does not preclude other contributory factors, such as a structural cerebral lesion. All cancer patients with delirium should undergo neuroimaging unless an acute delirium is completely reversed using a medical intervention, eg, glucose administration for hypoglycemia.

Only one third of our patients had normal cognitive function on hospital admission. Although some might have had subtle cognitive changes that were not appreciated by the examining physician, all had significant deterioration of their mental function during hospitalization. Forty percent of patients admitted to the hospital with normal mental status underwent a surgical procedure, which preceded the appearance of delirium. As in other studies, surgery was an important predisposing factor, but it was also associated with a high probability of recovery from the encephalopathy.

Unlike the delirium seen in a general hospital in which 25% to 50% of patients have preexisting dementia as a contributory cause, only 7% of our patients were demented. Forty-nine patients (42% of those imaged) had some degree of cerebral atrophy on computed tomographic scans or magnetic resonance images, often attributed to previous cranial irradiation (11%), chemotherapy (11%), or concurrent corticosteroid administration (21%). Some of these patients might have had subtle cognitive impairment that was not appreciated by the admitting physician before the acute delirium that precipitated neurologic consultation.

More than two thirds of patients (69%) had multiple causes of their delirium. This is similar to what has been identified in general hospital inpatients; however, in those patients, factors such as malnutrition, use of physical restraints, fracture, and bladder catheters were among the precipitants leading to delirium. In patients with cancer, the most common causes included drugs, systemic infection, and metabolic dysfunction, particularly hypotension, hypoxia or hypoperfusion, and renal failure. A decreased serum albumin level was seen in more than 80% of patients.
of our patients, which might be a measure of malnutrition that has been associated with delirium; however, cachexia was not recorded. Wernicke encephalopathy is a rare and correctable cause of confusion in patients with cancer but was not observed in our cohort. Structural brain disease was identified in 50 patients and was the sole cause of altered mental status in 21 (Table 4). Although brain metastases were the most common cause of intracranial lesions, stroke and other central nervous system lesions were seen in 14 patients. In 65 patients, infection was present at diagnosis of encephalopathy, but only 1 had meningitis as a cause of delirium. Drugs were a common contributing factor to confusion, and the most common offending agents were opioids used for acute and chronic pain. Corticosteroid use contributed to delirium in 30 patients but seemed to protect against early mortality. Chemotherapy rarely contributed to delirium in our patients. We did not observe a high incidence of previous or concurrent use of biological agents as reported by Meyers and Abbruzzese as a cause of cognitive abnormalities in ambulatory cancer patients.

Delirium was associated with greater morbidity and mortality rates than seen in the general hospitalized population. Our confused patients were hospitalized 3 times longer than the overall population at our institution. Twenty-five percent of our patients with encephalopathy died within 30 days and 44% within 6 months of onset of delirium; 29% of patients died during the index hospital admission. Death was primarily due to advanced cancer, and the delirium was usually a direct reflection of advanced disease causing organ failure, infection, and cerebral metastases. Nevertheless, two thirds of patients recovered cognitive function when the causes of their delirium were treated. This was particularly true for patients with cerebral metastases and could be attributed to the institution of corticosteroid treatment, with rapid improvement in neurologic function. In addition, patients can improve even if all causes of their delirium cannot be corrected equally. For example, the confused postoperative patient with hepatic failure receiving opioids for pain relief might become mentally clear with adjustment of the pain medications and resolution of the early postoperative period. Furthermore, simple interventions, which can prevent delirium in general hospitalized older patients, might also be applicable to patients with cancer.

Older age is a risk factor for the development of encephalopathy, and cancer usually affects an older population. In our series, youth was significantly associated with the 30-day mortality rate in contrast to the population. However, in our series, youth was significantly associated with the 30-day mortality rate in contrast to the population. Nevertheless, it is usually reversible once the causes are identified and treated. Restoring cognitive function, even at the end of life, is often difficult for patients and their families and can even facilitate critical medical decision making. Furthermore, some patients will go on to survive for months to years after an episode of confusion. Consequently, aggressive pursuit of all causes of delirium and correction of as many contributory factors as possible is important and worthwhile even in patients with disseminated malignancy.

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