Hydrocephalus in Radiation Leukoencephalopathy

Results of Ventriculoperitoneal Shunting

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Objective: To assess the clinical benefit of ventriculoperitoneal shunting in patients suffering from radiotherapy-induced leukoencephalopathy.

Design: Retrospective review of a single institutional experience.

Patients: Thirty-one patients with the postradiotherapy syndrome received ventriculoperitoneal shunts. All had a history of cranial irradiation, progressive ventriculomegaly visible on neuroimaging scans, and neurologic decline; other causes of hydrocephalus were excluded. All 31 patients had cognitive deficits: 30 had gait disturbance and 24 were incontinent.

Results: Twenty-four (80%) of 30 assessable patients achieved symptomatic improvement an average of 1.6 months after ventriculoperitoneal shunting. Incontinence and gait problems were more likely to improve than cognition. Sixteen (53%) of 30 patients achieved a good overall functional outcome, and incontinence was the only feature significantly associated with good outcome ($P=.04$). Neither cerebrospinal fluid–opening pressure nor tap tests predicted improvement from ventriculoperitoneal shunting. Median duration of improvement was 6 months, and median survival after receiving the shunt was 14.5 months. Shunt-related complications occurred in 10 (33%) of 30 patients, with 1 fatal outcome.

Conclusions: Our results from ventriculoperitoneal shunting in selected patients with radiation-induced hydrocephalus suggest potential benefit. Improvement is incomplete and temporary, but can improve quality of life. Reliable predictors of successful shunt outcome were not identified.

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Central nervous system (CNS) toxic effects from therapeutic or prophylactic cranial radiotherapy has become an increasing problem as survival improves among patients with primary cerebral and systemic cancers. Delayed neurologic sequelae of radiotherapy have several manifestations, of which radiation leukoencephalopathy is one of the most common. Clinical symptoms of radiation leukoencephalopathy are impairment of memory, abulia or apathy, gait disturbance, tremulousness, and urinary incontinence.1-6 The disorder ranges from mild to severe and can be inexorably progressive, leading to death in many. Neuroimaging features typically consist of cortical atrophy, ventricular dilatation, and periventricular white matter changes.7,8 Because white matter changes are such a prominent radiographic abnormality, many have attributed this clinical syndrome to white matter damage1,6; however, cortical dysfunction and communicating hydrocephalus may contribute to the pathogenesis of this condition.3 In many patients, ventriculomegaly is prominent and often out of proportion to the degree of cortical atrophy, and clinical symptoms strongly resemble idiopathic normal pressure hydrocephalus.9,10 Furthermore, pathological similarities between radiation leukoencephalopathy and normal pressure hydrocephalus have been noted.1

DeAngelis et al3 reported an incomplete, but substantial, response to ventriculoperitoneal shunting in 3 of 4 patients with radiation leukoencephalopathy, especially in regard to gait problems and incontinence. However, Asai et al1 reported no improvement in cognitive function or ventricular size from cerebrospinal fluid (CSF) diversion in 14 patients with a similar syndrome; the authors did not comment on any improvement in gait.
PATIENTS AND METHODS

PATIENT SELECTION

We reviewed the neurosurgical records at Memorial Sloan-Kettering Cancer Center, New York, NY, and identified 306 adult patients who received ventriculoperitoneal shunt ing between January 1, 1985, and December 31, 1995. Patients with obstructive hydrocephalus or another cause of secondary communicating hydrocephalus, such as leptomeningeal metastasis, recent craniotomy, history of significant head trauma, intracranial infection, or subarachnoid hemorrhage, were excluded. Twenty-eight patients were identified who had a history of cranial radiotherapy and progressive neurologic decline, involving cognition, gait, or sphincter control. All patients had serial magnetic resonance imaging (MRI) scans reviewed by our neuroradiologists and interpreted as showing progressive ventriculomegaly consistent with communicating hydrocephalus. An additional 3 patients, who were identified from oncological clinic records, did not receive a shunt at Memorial Sloan-Kettering Cancer Center, but were followed up at this center before and after receiving the shunt. Frequency of postshunt follow-up was not standardized, but all patients were evaluated by a neurologist within 2 months of ventriculoperitoneal shunting and at variable intervals afterward.

GRADING SCALES

Each patient had a Karnofsky performance score11 assigned before and after maximal improvement following ventriculoperitoneal shunting. Scores were either recorded in the patients’ record or assigned by one of us (B. T.), based on the patients’ functional abilities as described in the records. Changes in Karnofsky performance score before and after the shunt were recorded. Improvement in each major category of neurologic dysfunction was also graded. Cognitive improvement was scored as 0 if there was no or minimal change in cognitive function, 1 if there was subjective improvement in memory or some identified improvement in spontaneity and lethargy, and 2 if there was objective clear improvement in memory function demonstrated in the results of a Mini-Mental State Examination or neuropsychological test or the resolution of abulia or apathy. Gait changes were scored as 0 for no improvement or minimal improvement, 1 for mild to moderate improvement as assessed by the patient’s attending neurologist, and 2 for major improvement. Improvement in sphincter control was graded as 0 for no change, 1 for improved bladder and bowel control, and 2 for resolution of incontinence. An overall outcome score was assigned to each patient that heavily favored functional improvement (Table 1). This overall scale was intended to indicate those patients whose improvement led to increased independence or ease of management by their caregivers. The scales were applied rigidly, and, when there were discrepancies, the patient was assigned the lowest possible score.

STATISTICAL METHODS

Patient age, tumor diagnosis, radiation type and dose, interval from radiation completion to date of shunt placement, prior chemotherapy treatment, clinical features, Karnofsky performance score before shunt placement, CSF-opening pressure, tap test results (a positive result represented temporary improvement of gait after serial lumbar punctures, each removing at least 30 mL of CSF), and change in ventricular size after receiving the shunt were analyzed as possible prognostic factors using Spearman rank correlation coefficients for the following outcome results: overall functional outcome, gait improvement, cognitive improvement, sphincter control improvement, patient survival, and duration of improvement. As a method of multivariate analysis, any factor found to predict overall functional outcome was further evaluated using Fisher exact tests to assess impact on individual outcomes for gait, cognition, and incontinence.

RESULTS

DEMOGRAPHIC AND CLINICAL FEATURES

Thirty-one patients (16 women and 15 men) were identified and included in this analysis. One patient did not have adequate follow-up to be assessable for outcome analysis, but was included for description of the initial features of radiation leukencephalopathy. The mean patient age at the time of ventriculoperitoneal shunting was 61.9 years (range, 37-77 years), and the mean Karnofsky performance score was 50 (range, 30-80). The underlying tumor diagnoses were primary CNS lymphoma (n=9), malignant glioma (n=8), brain metastases (n=7), low-grade glioma (n=3), and meningioma (n=2). Two patients did not have intracranial tumors; 1 received prophylactic whole-brain radiotherapy for small cell lung cancer, and the other had prophylactic craniospinal radiotherapy for high-grade systemic lymphoma. Twenty-four of the patients received whole-brain and 7 patients received partial-brain radiotherapy. Radiation dose was available for 26 patients: 25 patients received 3000 cGy or more, with 21 receiving 4000 cGy or more and 1 patient received 2500 cGy. Fractionation schedules were documented in 14 of these 26 patients, with 12 receiving fraction sizes of 200 cGy or less, 1 receiving 250 cGy per fraction, and the other, 300 cGy per fraction. Twenty-one of the 31 patients received chemotherapy as part of initial or recurrent therapy. Ten of these 21 patients received high-dose systemic methotrexate, intrathecal methotrexate, or both, and 6 received nitrosourea.

Initial clinical evaluation disclosed cognitive impairment in all patients, gait disturbance in 30 patients, and urinary incontinence in 24 patients; these 24 pa-
tients had deficits in all 3 areas (Hakim triad). The most commonly described clinical features are shown in Table 2. Only 11 subjects received formal neuropsychological testing, with the most frequent abnormalities occurring in executive functions (n=10), short-term memory (n=9), visuospatial functions (n=4), language function (n=2), and psychomotor speed (n=2). Gait difficulties were usually characterized as wide-based and poorly balanced, with retropulsion when standing. Urinary incontinence was most frequently of the urgency type. In all patients, the onset of symptoms was insidious, making it difficult to assess exact onset. Two patients deteriorated suddenly after several months of slow decline. In the remainder, physical decline was slowly progressive during several months to years. The interval between completion of radiotherapy and insertion of the ventriculoperitoneal shunt ranged from 2 to 120 months (median, 19 months).

Neuroimaging with computed tomographic (CT) or MRI scans was performed in all patients before CSF diversion. All had evidence of cortical atrophy and enlarging ventricles out of proportion to the degree of atrophy. Twenty-four of 31 patients had periventricular white matter abnormalities, which were present in all 23 subjects who received MRI scans before shunting (Figure 1). Only 2 patients, both with glioblastoma multiforme, had evidence of tumor recurrence on the preshunt scan. In neither case was the recurrence in a location to produce the clinical symptoms or to impinge on the ventricular system.

Before ventriculoperitoneal shunting, all 31 patients had no clinical improvement, and 1 patient worsened after lumbar puncture.

OUTCOME RESULTS

Ventriculoperitoneal shunting resulted in some improvement in 24 (80%) of 30 assessable patients (see “Grading Scales” section for explanation of grades). Overall functional improvement was considered good (grade 2 to grade 3) in 16 patients (53%), modest (grade 1) in 8, and negligible (grade 0) in 6. The mean Karnofsky performance score after shunt placement was 60 (range, 30-80) and had improved by 20 or more points in 10 patients. Two patients with grade-1 outcomes did not have sufficient clinical information to be assigned a performance score. Cognitive improvement was modest, with only

Table 1. Overall Outcome Grading Scale

<table>
<thead>
<tr>
<th>Outcome Classification</th>
<th>Definition</th>
<th>Grade</th>
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</thead>
<tbody>
<tr>
<td>No improvement</td>
<td>No change in Karnofsky performance score (KPS), no clinical improvement, or both</td>
<td>0</td>
</tr>
<tr>
<td>Mild improvement</td>
<td>Increase in KPS of 10, or 1 or 2 of the following: (a) Improvement bladder control, (b) Mild-to-moderate gait improvement, (c) Subjective memory improvement, (d) Reduced lethargy or apathy</td>
<td>1</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>Increase in KPS of 20, or 3 or more of the following: (a) Improved bladder control, (b) Mild-to-moderate gait improvement, (c) Subjective memory improvement, (d) Reduced lethargy or apathy; or 1 of the following: (1) Resolved incontinence, (2) Improvement to independent gait or cane from walker-dependent gait or worse, (3) Resolution of gait imbalance if independent, (4) Significant objective improvement of cognitive functions on formal mental status or neuropsychological testing, (5) Resolution of abulia or apathy</td>
<td>2</td>
</tr>
<tr>
<td>Marked improvement</td>
<td>Increase in KPS of 30 or greater, or 2 or more of the following: (a) Resolved incontinence, (b) Improvement to independent gait or cane from walker-dependent gait or worse, (c) Resolution of gait imbalance if independent, (d) Significant objective improvement of cognitive functions on formal mental status or neuropsychological testing, (e) Resolution of abulia or apathy</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2. Clinical Features at Ventriculoperitoneal Shunt Placement

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive impairment (n = 31)</td>
<td>26</td>
</tr>
<tr>
<td>Impaired short-term memory</td>
<td>9</td>
</tr>
<tr>
<td>Abulia or apathy</td>
<td>7</td>
</tr>
<tr>
<td>Psychomotor slowing</td>
<td>17</td>
</tr>
<tr>
<td>Gait abnormalities (n = 30)</td>
<td>14</td>
</tr>
<tr>
<td>Wide base</td>
<td>11</td>
</tr>
<tr>
<td>Retropulsion or lateropulsion</td>
<td>9</td>
</tr>
<tr>
<td>Imbalance</td>
<td>8</td>
</tr>
<tr>
<td>Shuffling</td>
<td>7</td>
</tr>
<tr>
<td>Magnetic gait</td>
<td>7</td>
</tr>
<tr>
<td>Impaired turning</td>
<td>7</td>
</tr>
<tr>
<td>Function (n = 31)</td>
<td>3</td>
</tr>
<tr>
<td>Independent or cane-assisted walking</td>
<td>16</td>
</tr>
<tr>
<td>Walker-dependent mobility</td>
<td>12</td>
</tr>
<tr>
<td>Bed-bound patient</td>
<td>3</td>
</tr>
<tr>
<td>Sphincter control (n = 24)</td>
<td>24</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>6</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>6</td>
</tr>
</tbody>
</table>
12 patients reporting a notable change. Two patients received formal neuropsychological evaluation after the shunt was placed; 1 showed some improvement in psychomotor speed, but no change in memory, and the other had mild improvement in verbal short-term memory, but no change in visual memory or executive functions. The results of formal Mini-Mental State Examinations were documented in 5 patients, and, although no scores worsened after the shunt was placed, no patient's score improved by more than 3 points. Improvement in abulia or apathy was more common (5 of 9 patients) than changes in memory function (8 of 26 patients with subjective or objective memory improvement). Gait was more likely than mental state to improve after ventriculoperitoneal shunting. Twenty patients (67%) showed gait improvement (14 patients had a modest improvement and 6 patients had a marked improvement). Of the 15 patients with a walker-dependent gait or worse, 4 achieved independent ambulation or cane-dependent gait. Incontinence was the most likely symptom to reverse after shunt placement. Of the 22 patients with urinary incontinence, 11 (50%) had complete resolution and an additional 6 (27%) had improved bladder control after ventriculoperitoneal shunting. Fecal incontinence resolved in all 6 affected patients.

Clinical improvement after ventriculoperitoneal shunting often began within days, but maximal improvement usually took several weeks. The mean time to maximal change was 1.6 months (range, 0.5–4.0 months). The median duration of improvement was 6 months (range, 1.5–89.0 months). Reduction in ventricular size was reported in 9 of 30 patients when postoperative scans were reviewed. However, clinical improvement did not correlate with ventricular decompression (Figure 1). Median survival after receiving the shunt was 14.5 months (range, 5 to >120 months). Five patients remain alive. The cause of death was known in 12 of the 26 deceased patients; 5 deaths resulted from tumor recurrence, 5 deaths resulted from progressive radiation leukoencephalopathy, 1 death was from carmustine-related pulmonary toxicity, and 1 death was from Candida ventriculitis infection. Autopsy results were available for 2 patients who died from radiation leukoencephalopathy. Pathological inspection of the brain revealed cortical atrophy, ventricular dilatation, and old bilateral subdural membranes in both patients. The white matter was softened with yellow discoloration, especially around the ventricles; in 1 patient, the ventral medulla was also affected. Microscopic examination revealed a necrotizing periventricular leukoencephalopathy in both patients. Myelin pallor was prominent and myelin loss, axonal dropout, and extensive gliosis were seen. Vascular changes, primarily small vessel sclerosis, were present, but not overly prominent. There was no evidence of recurrent tumor. One patient (age, 75 years) had concurrent Alzheimer-type changes with senile plaques in the hippocampus and entorhinal cortex and mild congophilic angiopathy, but not enough to meet pathological criteria for Alzheimer disease.

**PROGNOSTIC VARIABLES**

Age, sex, underlying tumor diagnosis, type and dose of radiotherapy, use of adjuvant chemotherapy, and Karnofsky performance score before shunt placement were not found to significantly influence shunt outcome in our patients. Clinical features when the shunt was placed were evaluated for prognostic significance. Dementia and gait disorder were too prevalent to be discerning prognostic variables. There was a trend for the presence of urinary incontinence to predict a good overall functional outcome on univariate analysis ($P=0.04$), but not with multivariate analysis. The Hakim triad tended to predict a good outcome, but this was not statistically significant ($P=0.07$). Tap tests did not predict a favorable result from CSF diversion. Of the 11 patients with a positive tap test, only 6 had a significant functional improvement (grade 2 or 3). The tap test had a sensitivity of 54%, specificity of 50%, and positive predictive value of only 54% in pre-
dicting favorable shunt outcome. Similarly, the CSF-opening pressure did not predict outcome.

COMPLICATIONS

Complications of ventriculoperitoneal shunting occurred in 10 (33%) of 30 patients. Six patients developed subdural fluid collections; 4 of these patients required neurosurgical drainage and shunt revision with a higher pressure valve. One patient of the 10 developed symptomatic intracranial hypotension requiring revision to a higher pressure system. The remaining 3 patients developed shunt infections that were easily treated with antibiotics in 2 patients, but led to the death of 1 patient from C. ventriculitis infection.

Our study is a retrospective review of patients with radiation-induced leukoencephalopathy who were selected for ventriculoperitoneal shunting. These patients were referred for a shunt because they had symptoms suggestive of hydrocephalus and had ventricular enlargement disproportionate to the amount of generalized atrophy. We did not identify all patients with radiation leukoencephalopathy at Memorial Sloan-Kettering Cancer Center and, therefore, cannot compare patients who received a shunt with those who did not. However, we believe our observation of clinical improvement after shunt placement is valid and important for several reasons. First, the natural history of untreated radiation-induced leukoencephalopathy is of a progressive, relentless illness that eventually leaves the patient bedridden, incontinent, and severely demented. Second, there is no effective treatment for this condition, and we are reporting the first therapy that may offer amelioration of symptoms and prolongation of independent function. Last, reversal of symptoms with shunt placement strongly implicates hydrocephalus as a partial mechanism of radiation leukoencephalopathy. This has not been described and lends some insight into the pathophysiological nature of this condition.

Patients with radiation leukoencephalopathy have the typical clinical syndrome of normal pressure hydrocephalus with cognitive impairment, ataxia, and urinary incontinence. Ventricular dilatation, disproportionate to the amount of generalized atrophy, is observed on CT and MRI scan images, and, in our series, most patients improved after receiving a ventriculoperitoneal shunt. Unfortunately, like normal pressure hydrocephalus, no preoperative clinical features or tests predicted with high degree of specificity those patients with radiation leukoencephalopathy who will benefit from a shunt.8,12,13 Among our patients, only the presence of urinary incontinence was significantly associated with good functional outcome. Furthermore, gait, sphincter control, and level of alertness were the symptoms most improved after ventriculoperitoneal shunt placement, whereas, memory dysfunction usually had minimal improvement, if at all. Consequently, a ventriculoperitoneal shunt is unlikely to help the patient suffering from cognitive impairment alone, and other symptoms should be present before recommending it to a patient with radiation leukoencephalopathy.

While the clinical features point to hydrocephalus as a contributing mechanism of radiation leukoencephalopathy, the pathophysiological nature of altered CSF dynamics is unknown and CSF dynamics have not been studied in these patients. One possibility is that cranial radiotherapy produces fibrosis of the arachnoid granulations, impairing CSF flow and inhibiting reabsorption.14 In our 2 autopsied patients, old bilateral subdural membranes were apparent in both, suggesting that scarring over the convexities may, in fact, play a role. However, marked parenchymal damage is also apparent throughout the white matter. A gradient of demyelination with variable axonal destruction is seen most severely in the periventricular regions and diminishes with increasing distance away from the ventricles.15 The cortex reveals no damage microscopically, but an abnormal blood-brain barrier has been demonstrated in the gray matter of rats after irradiation.16 This parenchymal damage explains the incomplete resolution of symptoms seen after ventriculoperitoneal shunting and suggests that the cognitive difficulties are primarily caused by tissue injury.

The exact combination of factors necessary to produce radiation leukoencephalopathy is also unknown. It is clear that whole-brain radiotherapy is a major risk factor, although 7 of our patients developed this syndrome after partial-brain irradiation.5,17 Total dose and large fraction size (≥200 cGy) are associated with an increased incidence of radiation leukoencephalopathy, but symptoms can develop with smaller and presumed safe fractions as seen in most of our patients.2,18,19 Older age is also a risk factor. Asai et al.1 reported that 72.9% of patients older than 50 years who received whole-brain radiotherapy developed substantial cerebral atrophy with white matter changes, whereas this complication occurred in 39.2% of patients younger than age 50. Adjuvant chemotherapy can increase the risk of radiation leukoencephalopathy, especially with known neurotoxic agents, such as methotrexate and nitrosourea.2,10,12 Fifteen of our patients received either methotrexate or a nitrosourea, which likely augmented the toxic effects of their cranial radiotherapy. In addition, there are individual host factors that clearly predispose a patient to radiation leukoencephalopathy, but are as yet unidentified. Not all patients treated in an identical fashion carry equivalent risks for radiation leukoencephalopathy. Some lifestyle issues, such as smoking, have been identified in other clinical settings11 of radiation-induced tissue damage, but are not obvious risk factors for CNS injury.

Radiation leukoencephalopathy has a poor prognosis.1,12,14,15 The median survival of our patients was only 14.5 months after ventriculoperitoneal shunt placement, and almost half died from complications of radiation leukoencephalopathy. Earlier reports of beneficial treatment, either with corticosteroids or shunting, have been limited to case reports or small series of patients.1,3 We have compiled the largest series to date of this syndrome. While this is a highly selected group of patients, 80% of patients achieved some symptomatic relief, and 53% had substantial benefit. We do not know if receiving a ventriculoperitoneal shunt prolonged life in our patients, but it clearly improved the quality of life for many. The com-
Complication rate of 33%, with 1 death, was significant, but most complications were manageable. Although our results are preliminary, ventriculoperitoneal shunting is the only therapy to reverse symptoms from radiation leukoencephalopathy. It should be considered for any patient with treatment-induced leukoencephalopathy who has this syndrome, especially those with gait or bladder difficulties.

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REFERENCES