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Saint Francis Health System
Founded by The William K. Warren Foundation

August 20, 2003

Mr. John W. Vardiman
Attorney-at-Law
Williams and Connolly
725 Twelfth Street N.W.
Washington, D.C. 20005

Dear Mr. Vardiman:

This is a follow-up to my previous reports on Senator Gene Stipe. As you know, he is 76 years old. I saw him as a patient initially on October 17, 2002. At that time, his concerns were about his hypertension and diabetes mellitus. Also, his wife had recently expired after a lengthy illness and he was experiencing depression.

My diagnoses at that time included essential vascular hypertension, non-insulin dependent diabetes mellitus, hyperlipidemia, mild left lower extremity paresis etiology uncertain (possibly related to his childhood poliomyelitis), recurring falls, carcinoma of the prostate and a history of chemotherapy for his prostate carcinoma.

I was also concerned about his congitive state. I first met him in 1956. I have visited with him occasionally over the years. I have known him to be an extremely intelligent, observant person. On October 17, his cognition seemed slow, his memory seemed impaired and he seemed to be struggling with simple decisions. I thought that on the basis of his multiple ailments and his depression over his wife's illness, that he had become cognitively impaired and perhaps had some early dementia. I did not record my concerns regarding his cognition at that time because of my concern for his privacy. Unfortunately, with the passing of time, these conditions have worsened. When I have encountered him out in public in recent times, it has seemed to me that he has experienced significant and sustained cognitive decline.

Unfortunately, he fell on October 28, while walking in his driveway due to lower extremity weakness. He sustained a comminuted fracture of his proximal left humerus. Follow-up x-rays three days later showed interval displacement of his proximal humerus into a 100% displaced alignment. On November 4, he had an open reduction and internal fixation with an intramedullary nail of the fracture.

I subsequently spoke to him about my concerns regarding his lower extremity weakness, frequent falls, memory loss and cognitive impairment. I suggested arranging an appointment for him at The Northwest Senior Health Memory Disorders Center in Sprindale, Arkansas. It is the only comprehensive memory disorder clinic that I am aware of in this part of the country. They have an extensive program for evaluating cognitive impairment. He was agreeable and the arrangements were made. They performed an extensive examination and assessment over a three week period. Their examination was multidisciplinary including physical examination, diagnostic imaging, psychosocial evaluation, neurological examination and neuropsychological assessment.

Their neurocognitive evaluation included clinical interview, mental status examination, behavior observations, chart review, *Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), The Neurobehavioral Cognitive Status Examination (COGNISTAT),* Vocabulary from the *WAIS-III, Trail Making Test A and B, Controlled Oral Word Association Test (COWAT), Clock Drawing Task,* selected measures from the *Halstead-Reitan Neuropsychological Battery, Geriatric Depression Scale,(GDS), Clinical Dementia Rating Scale (CDR)* and the *U.C.L.A. Neuropsychiatric Inventory (NPI-Q).*

Some of the abnormal findings included a four-to-five year history of memory loss, depression, a positive Rhomberg test, decreased arm swing (more prominent on the left), a low average serum B_{12} level, and an abnormal C.-T. scan of the head.

Neuropsychological evaluation revealed a multi-focal deficit profile, especially in the area of visuospatial construction. There was delayed free recall of verbal information. Recall of visually presented information was severely impaired. There was evidence of decreased processing speed and cognitive flexibility plus subtly impaired orientation. It was noted that these deficits are present despite his extensive education. In addition to the above cognitive deficits, he was also found to have depression.

The presence of these signs and symptoms of dementia and cognitive impairement prompted a vigorous pursuit of the etiology or etiologies. The C.-T. scan of his head showed a communicating hydrocephalus which was thought to be the primary cause of his cognitive deficits. Hydrocephalus is a condition of increased pressure within the skull and brain due to an increased amount of fluid within the rigid, non-expandable skull. This condition will produce progressive atrophy or destruction of the brain if not treated. Even after treatment, the loss of function that has occurred will probably not return. Accordingly, an urgent appointment was made with Dr. Benjamin T. White, neurosurgeon and assistant professor of neurosurgery at the University of Oklahoma Health Science Center in Oklahoma City.

Dr. White's diagnosis was a "normal pressure hydrocephalus". He has scheduled Senator Stipe for a **ventricular peritoneal shunt.** This involves placing a tube extending from an area within his brain to within the abdominal cavity. That will enable the excessive fluid to escape from within the skull and empty out into the peritoneal (abdominal) cavity where the body can deal with it easily. This procedure will hopefully prevent or slow further damage to Senator Stipe's cognitive function, strength and balance, but it will probably not correct the damage that has already occurred. The hydrocephalus is probably also a contributor to his incontinence.

Dr. White has advised Senator Stipe to not travel by air for two to four weeks following the surgery.

If there is further information that I can supply, please let me know.

Sincerely,

L. M. Milton, M. D.

L. M. Milton, M. D.

LMM/ek
D.&T.: 08-20-03

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Saint Francis Health System
Founded by The William K. Warren Foundation

August 28, 2003

Mr. John W. Vardiman
Attorney-at-Law
Williams and Connolly
725 Twelfth Street N.W.
Washington, D.C. 20005

Dear Mr. Vardiman:

Dr. Benjamin White, neurosurgeon, performed a spinal puncture on Senator Stipe and removed a large volume of spinal fluid. Senator Stipe seems to have experienced some benefit from the procedure. Dr. White plans a ventricular-peritoneal shunt soon. At this time, we are not sure how much improvement in his memory, cognitive function and gait he will experience after the procedure. Hopefully, it will at least prevent further decline.

If there is further information that I can supply, please let me know.

Sincerely,

L. M. Milton, M.D.

L. M. Milton, M. D.

LMM/ek
D.&T.: 08-28-03

Christopher M. Loftus, M.D., F.A.C.S.
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Christopher E. Wolfla, M.D.
Associate Professor

Benjamin T. White, M.D.
Assistant Professor

Johnnie H. Honeycutt, M.D.
Assistant Professor

The University of Oklahoma
Health Sciences Center
DEPARTMENT OF NEUROSURGERY

September 15, 2003

Jack Vardaman
Attorney-at-Law
725 12th Street N.W.
Washington, D.C. 20005

Re: STIPE, GENE
DOB: 10/21/1926

Dear Mr. Vardaman:

Mr. Stipe is under my care for a normal pressure hydrocephalus. Normal pressure hydrocephalus is a degenerative condition seen most often in older individuals. It is a condition that has a very slow onset and it is likely that he has had this condition for several months to even several years while the symptoms have been slowly progressive. I recently saw him back in follow up and he does tell me that he feels like his walking is more steady, so hopefully we are seeing the benefit of his ventricular peritoneal shunting.

Again, please do not hesitate contacting my office if you need more information.

Sincerely,

Benjamin T. White, M.D.
Assistant Professor
Department of Neurosurgery
University of Oklahoma Health Sciences Center

BTW/sgs

Treatment Considerations for Alzheimer's Disease and Related Dementing Illnesses

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Normal Pressure Hydrocephalus and Dementia—Evaluation and Treatment

Dennis A. Turner, MD, and Robert E. McGeachie, MD†*

A variety of techniques are used for the initial evaluation of dementia, including a clinical history, physical examination, radiologic studies, and laboratory tests. This article will concentrate on part of the initial evaluation, namely, that concerned with the possibility of normal pressure hydrocephalus (NPH) as a factor contributing to the cognitive dysfunction. Normal pressure hydrocephalus remains one of the few diagnostic categories that may lead to an effective treatment, thus underscoring the importance of a careful evaluation. We will review the pertinent history that may help raise the suspicion of NPH contributing to the dementia, as well as the usefulness of adjunct radiologic and laboratory tests. Newer diagnostic studies, such as magnetic resonance imaging (MRI) and CSF infusion studies will also be discussed in this context.

This article will help point out the possible interpretation of the history and diagnostic tests, as well as describe a logical path to follow in the patient evaluation. However, CSF shunting remains the only definitive method to prove or disprove the clinical hypothesis of normal pressure hydrocephalus. In many cases the shunting procedure does not appear to lead to clinical improvement, suggesting that even the best combination of clinical tests may be inaccurate and subjective in interpretation. However, better diagnostic studies and CSF diversion procedures may considerably enhance both the accuracy of the diagnosis and the likelihood of clinical improvement.

CLINICAL SYNDROME

Clinical Triad of Dementia, Gait Ataxia, and Incontinence

A triad of clinical symptoms has been suggested as the essence of the NPH syndrome.[1, 14, 20] This triad consists of dementia, gait disturbance, and urinary incontinence. The order of appearance as well as the duration of

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†Assistant Professor, Department of Radiology, University of Minnesota, Minneapolis, Minnesota

symptoms appears to have considerable importance in terms of outcome. The dementia was originally described[1] as memory loss and subsequent confusion, as well as slowness and paucity of thought. The dementia in these three cases appeared rather mild and diffuse, and seemed to stem mainly from the memory loss and slowness of response. This type of memory loss and general slowness also occurs with tension hydrocephalus, when presenting in the classic form in the adult. However, the types of dementia that may co-exist or be observed with NPH are various and have not often been clearly described in terms of neuropsychologic testing.[9, 31, 39]

A clear gait disturbance was also an important aspect of the original patients, which has subsequently been confirmed with additional reviews of patients.[1, 14, 19, 48] The gait disturbance usually involves slow, shuffling steps and a wide-based ataxia, often associated with heightened reflexes in the lower extremities. The gait difficulty also included an incoordination of the lower limbs when upright and a decreased speed of taking strides. On more detailed quantitative gait testing,[49] the slowness and unsteadiness were convincingly improved after a CSF shunting procedure, thus pointing to this problem as an essential part of the hydrocephalic changes in brain function.

The third part of the triad was urinary incontinence. All of the initial three patients demonstrated both fecal and urinary incontinence and were unaware of the resultant loss of control. Other patients defined as NPH have included a number of patients without clear urinary incontinence, indicating that this may be a variable feature of the clinical syndrome.[3, 4, 20, 29, 43, 49]

Additional patients have included a much wider range of clinical symptoms, with many patients undergoing evaluation for NPH and CSF shunting that do not exhibit the classic triad of gait disturbance, urinary incontinence, and dementia.[7, 9, 14, 31, 40, 42, 45] Thus, patients may exhibit gait abnormalities alone and many series include patients with dementia alone. The dispersal of clinical characteristics over time points to a wider application of CSF shunt procedures. Clearly, by the outcome measure of clinical improvement following CSF shunting, many patients exhibiting dementia alone do not improve, compared with the increased likelihood that patients with gait disturbance alone will improve. Thus, the ranking of symptoms that would suggest the likelihood of clinical improvement with CSF diversion is usually in the order of gait abnormality, urinary incontinence, and dementia. A higher degree of improvement may also be suggested if the symptoms appear in that order, especially as compared with dementia first.[49]

Etiology of Clinical Symptoms

The anatomic similarity between these diverse symptoms associated with NPH appears to be the predilection of the hydrocephalic process to exert significant tension against the frontal lobes, thus stretching the white matter fibers connecting the cortex with deeper structures. The most medial fibers from motor cortex involve the control of urinary and leg function, and these may be impaired bilaterally in a symmetrical fashion. In

addition, tension on the walls of the third ventricle may severely affect memory function and produce a slowness of response, accentuated by the frontal lobe pressure bilaterally from the ventricular expansion. Thus, heightened ventricular tension can lead to this triad of symptoms, with the most reliable symptom being gait disturbance.[14]

CSF CIRCULATION AND PATHOPHYSIOLOGY OF VENTRICULAR ENLARGEMENT

CSF Formation and Absorption

The circulation of CSF remains a complex and somewhat controversial topic, even after many years of investigation. Much of the total volume of CSF (at least half) appears to emanate from a combination of bulk flow and active pumping mechanism (an ultrafiltrate) across the choroid plexus and ventricular surfaces. The choroid plexus is a distributed system throughout all cerebral ventricles, but primarily in the two lateral ventricles. Even after extirpation of the bulk of the choroid plexus in both lateral ventricles, however, CSF formation and circulation continue. Thus, a considerable amount of CSF appears to be constituted from alternative sources, the most important of which is direct bulk flow from the extracellular fluid of the brain across the ependymal lining of the cerebral ventricles. The modern concept of the third circulation is that a major function of the CSF pathway is drainage of the brain extracellular space, similar to the lymphatic system in the peripheral circulation.[39]

After formation at various sites within the brain and cerebral ventricles, CSF flows through the cerebral aqueduct and through the exit foramina of the fourth ventricle. Once in the subarachnoid space, the CSF courses through the subarachnoid cisterns around the brain stem and over the cerebral convexities to the midline. The CSF then returns to the venous system through the arachnoid villi, which filter the CSF and prevent backflow of venous blood into the subarachnoid space. If obstruction occurs at any of these levels, alternative pathways appear to partially compensate for the change in CSF flow. Such alternative pathways include a reverse flow of extracellular fluid back into capillaries and veins from the ependymal surface outward, as well as new arachnoid villi opening along the spinal root sleeves.

One controversial alternative pathway of CSF flow, suggested by animal studies and of unknown importance in humans, is through the olfactory nerve and cribriform plate into the cervical lymph circulation. It is unclear from radioisotope studies of hydrocephalic patients if this is ever a significant compensatory pathway in humans. Another alternative flow pathway of CSF in hydrocephalic states may be through the fourth ventricle and into the central canal of the spinal cord, which occurs in dogs after kaolin injection. Again, it is unclear if this pathway of alternative flow is relevant to the human NPH situation. However, compensation occurs through a number of potential routes, suggesting that a rearrangement of CSF absorption follows obstruction in humans as well as experimental animals.[22, 51]

Pathophysiology of Ventricular Enlargement

Depending on brain compliance and the pulsatile nature of the CSF dynamics within the cerebral ventricles, the ventricles may dilate in response to an obstruction to CSF flow. This dilation is due to the transfer of the force of ventricular expansion to the brain. After ventricular dilation, the pressure within the ventricular lumen may decrease, often to near normal levels, similar to a balloon after inflation. Thus, the degree of ventricular expansion depends on the initial pressure level, the pulse pressure of the intraventricular space, and the compliance or "give" of the brain substance. The nomenclature of NPH stems from the deceptively normal pressure measured at rest from either the ventricular space or during a lumbar puncture, although often the CSF pressure may be elevated during long-term recording at periodic intervals. Thus, continued tension against the brain substance across the ependymal surface of the ventricles may cause persistent brain dysfunction and subsequent neurologic deficit, even though the intraventricular pressure may have returned to almost normal. This persistent tension appears to be a critical factor in the evolution of neurologic deficits in this syndrome, and the relief of such tension is important to the outcome of CSF shunting.

Other mechanisms that have been discussed as important in communicating or "normal" pressure hydrocephalus include a partial absorption block in the CSF circulation pathways (such as in the subarachnoid space or the arachnoid villi). One classic prototype of NPH is ventricular enlargement after a severe subarachnoid hemorrhage, in which there occurs a partial obstruction of the reabsorption of CSF into the venous sinuses.[21] After partial resolution of the initially high pressure, a "normal" pressure state is eventually reached, similar to the usual cases of NPH in which no etiologic factors can be identified.

Another potential etiologic factor for ventricular enlargement is an increased pulse pressure within the ventricles, even though the mean pressure may not be elevated. An elevated pulse pressure may be due to either decreased brain compliance or an increased outflow resistance. Several animal studies have indicated that the heightened pulse pressure alone, without an increase of the mean pressure, may lead to ventricular dilation. This finding has been substantiated in small clinical series of intracranial pressure measurements.[15] Thus, the main two mechanisms leading to the clinical symptoms have been suggested as a partial absorption defect and an increased CSF pulse pressure.

The symptoms of memory loss, gait disturbance, and incontinence also occur after subarachnoid hemorrhage, similar to NPH in general. Thus, when no antecedent subarachnoid hemorrhage or other etiology is known, it is often assumed that a partial absorptive block of the CSF circulation may be likely. Other potential explanations for the subtle development of increased ventricular wall tension and ventricular enlargement in NPH include changes in brain compliance to normal CSF pressure, an antecedent but unrecognized hemorrhage or infection in the CSF space, and loss of absorptive reserve for unknown reasons. The outcome in patients following CSF shunting for NPH appears in general to be significantly improved if an antecedent etiology is known, such as subarachnoid hemorrhage or

trauma, due to the higher likelihood of a partial CSF absorption block being present.[49]

INITIAL DIAGNOSTIC TESTING

Lumbar Puncture Pressure Measurements

The evaluation for normal pressure hydrocephalus in a patient with a suspicious clinical history of two or more elements of the triad of gait abnormality, dementia, and urinary incontinence may include a variety of bedside, laboratory, and radiologic tests. An initial brain CT or MRI scan (as discussed below) may be valuable in excluding other causes of this same clinical picture, including cerebrovascular accident, bilateral chronic subdural hematoma, parasagittal meningioma, and glioblastoma. If the scan suggests increased ventricular tension on the brain, without lateral shift or evident mass, then a lumbar puncture may be helpful in considering both the potential cause of the increased ventricular size (such as following a subarachnoid hemorrhage) and the pressure of the CSF. Indeed, if the pressure is elevated significantly (greater than 200 mm CSF with the patient at rest), then there is a high likelihood that a CSF shunting procedure may help the clinical symptoms, and the patient may not require further preoperative evaluation. In this situation, the patient would fall into a clear tension hydrocephalus group, where the pathogenesis and treatment are in general better understood than in the normal pressure situation.[7, 24, 33, 34, 49]

If the lumbar puncture pressure is within the normal range, additional tests are suggested, particularly if the clinical situation does not follow the classic distribution described above. Thus, after the initial scan of the brain, a lumbar puncture may be helpful at deciphering the proper course of action with regard to a CSF shunting procedure. Additional tests on the CSF, including cell count and protein, may indicate other etiologies of the ventricular enlargement, such as chronic meningitis, previously inapparent subarachnoid hemorrhage, carcinomatosis of the CSF space, or inflammatory disease. The extension of the single lumbar puncture for diagnosis is the consideration of multiple, serial lumbar punctures for a short-term therapeutic trial. After several lumbar punctures the CSF pressure may be lowered considerably, particularly if continued CSF leakage occurs from the multiple dural punctures. However, the role of serial lumbar punctures remains undefined, and is not often performed because of the short-term relief afforded to the patient and the discomfort caused by the procedure.

Ventricular Pressure Recordings and Infusion Tests

The impaired absorption capacity of the CSF system may be evaluated with paired ventricular and lumbar catheters.[5] Initially, the resting pressure is measured within the ventricle for a period of time, searching for periods of increased pressure. Then a constant pressure is maintained, and the flow rate into the lumbar catheter and out of the ventricular catheter is measured, which allows the calculation of the net conductance to CSF outflow (ml per min per mm Hg). The predictive value of a small conductance (or inversely, a high resistance) was excellent, and a level above which no

patient improved following CSF shunting could be defined.[5] This is one of the few studies that definitely provides a link to impaired absorption of CSF flow in NPH patients, with correlation of improvement following CSF shunting to this impairment.

Other studies on CSF have included the measurement of pulse pressure within the ventricle.[15, 26] The pulse pressure is the difference between the diastolic and systolic intraventricular pressure. In both animal studies and humans, the analysis of this parameter in patients with suspected NPH has been suggested to help evaluate appropriate candidates for CSF shunting. Thus, a high pulse pressure may indicate increased ventricular tension in certain cases, analogous to animal models of ventricular enlargement. Clearly, the height of the pulse pressure is linked to a variety of factors, particularly brain compliance, which may be decreased in cases of NPH.

BRAIN IMAGING

Cerebral Blood Flow and Radioisotope Cisternography

An additional type of study has attempted to differentiate the blood flow patterns visualized in Alzheimer's type dementia from that seen with NPH. Two different types of blood flow studies have been utilized, the first being positron emission tomography (PET) scanning[30] and the other Xenon-enhanced computed tomography scanning.[33] Although in both instances there was a pattern difference between the two types of dementia, this difference was not related in the reports to outcome following CSF shunting. Additionally, because the intracranial pressure is defined as normal in NPH, then blood flow pattern differences may be more attributable to large or small vessel disease as a co-morbidity rather than to the primary etiology of NPH.

The evaluation of CSF flow characteristics with a radioactive tracer, such as indium or technetium labeled DPTA, is one of the older techniques for the diagnosis of NPH.[24, 26] This test involves the lumbar injection of the tracer, and the subsequent imaging of the flow of the tracer, either into the cerebral ventricles or over the convexity and to the parasagittal region, where reabsorption occurs. Pooling of the tracer within the ventricles and stasis have been suggested as positive abnormalities defining NPH. In effect this tracer test evaluates the possibility of impaired CSF absorption through the CSF movement and stasis. In comparison, the normal pattern would be brisk reabsorption of the tracer back into the venous circulation, via a route over the cerebral convexities. However, the correlation of the abnormal pattern with outcome has not been uniformly helpful, which will be discussed further.

Pneumoencephalography

Pneumoencephalography (PEG) provided the earliest anatomic picture of the deformities of the CSF spaces in NPH. Although PEG is seldom performed in the United States, many of the anatomic descriptions using this modality form the basis of findings seen with CT scanning and magnetic resonance imaging.[26, 41] These findings include enlargement of the lateral

ventricles with decreased sulcal air over the cerebral convexity, expansion of the temporal horns, and a corpus callosal angle of less than 120 degrees. With hydrocephalus the angle becomes acute, whereas cerebral atrophy results in an even elevation of the corpus callosum, giving a larger or flatter angle.

Computed Tomography

CT scanning has been the mainstay of the radiologic evaluation of the brain in dementia. This serves the very important function of excluding other structural causes for dementia such as neoplasm, subdural hematoma, and multiple infarcts. In patients without focal neurologic findings, the study may be done without intravenous contrast. The most problematic cases occur in the differential diagnosis between NPH and cerebral atrophy.

A key finding in both conditions is enlargement of the lateral ventricles. A variety of studies has shown that the lateral ventricles and the cerebral sulci increase in size with age. This has recently been reviewed.[35] A myriad of techniques has been used to measure ventricular dimensions, including line, area, and volume computations. Measurements are rarely used in clinical practice. However, two relatively simple ratios have been defined and normal limits have been calculated.[21, 23] Measurement of the size of cerebral and cerebellar sulci is highly technique dependent and subjective estimates will usually suffice.

Enlargement of the lateral ventricles associated with hydrocephalus of all types, as a rule, is greater than that due to cerebral atrophy.[37] The ventricles in hydrocephalus tend to have more bulbous and rounded frontal horns (Fig. 1). The angle on CT scanning, which in the horizontal plane is analogous to the callosal angle on PEG, is more acute in hydrocephalus than in atrophy,[25] although often this measurement is not helpful in differentiating the two. In communicating hydrocephalus the third ventricle and fourth ventricle are often enlarged in comparison to an atrophic process, while the basal cisterns and cerebral sulci are not greatly enlarged. Relative expansion of the lateral ventricles compared to cerebral sulci in this situation is in favor of NPH over atrophy. The temporal horns are often expanded more in hydrocephalus than in atrophy.

Although enlargement of the temporal horns favors hydrocephalus, two caveats exist. Occasionally in NPH or hydrocephalus, even obstructing, enlargement of the temporal horns is minimal. Also, Alzheimer's disease may be associated with enlargement of the temporal horns, usually in association with cortical atrophy in the region of the temporal lobes in addition.[36] In obstructive hydrocephalus and occasionally in NPH, areas of lucency are seen on the CT scans around the frontal horns. This problematic finding will be discussed further under magnetic resonance imaging.

In summary, hydrocephalus is favored if the degree of the enlargement of the lateral ventricles is moderate to marked and out of proportion to enlargement of the cerebral sulci, the temporal horns are enlarged, the third and fourth ventricles are enlarged, and the ventricular system has a distended bulbous configuration (Fig. 1). There is no objective method to absolutely differentiate hydrocephalus from atrophy, however.

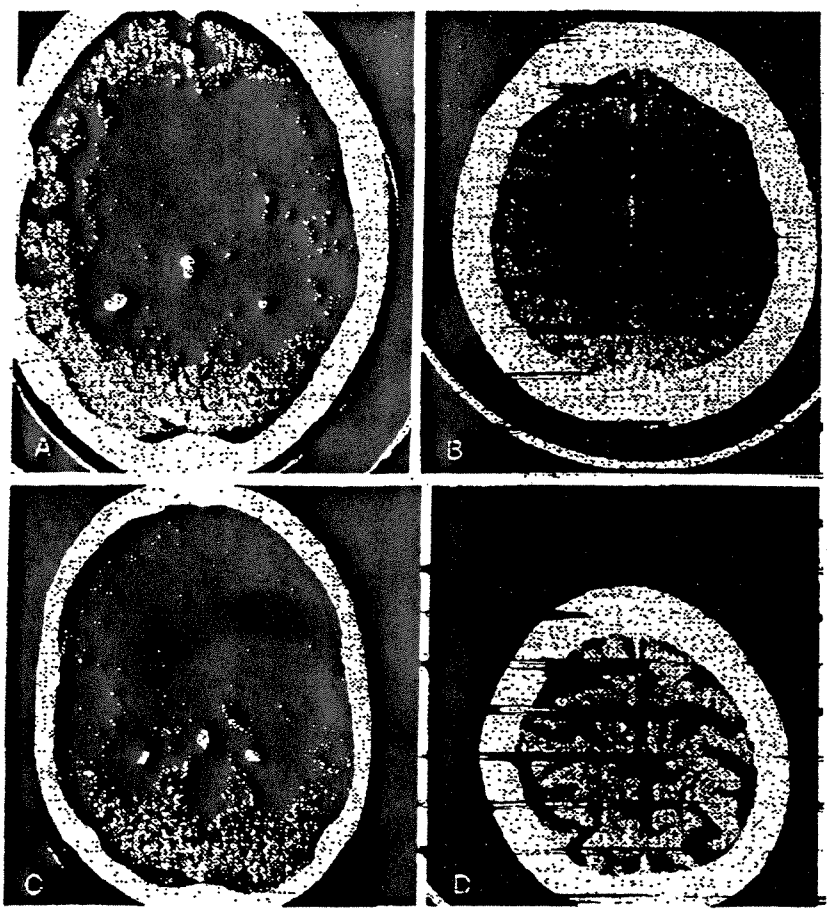

Figure 1. Four axial CT scans without contrast, demonstrating normal pressure hydrocephalus (NPH) responding to shunting (*A* and *B*) and a patient with cerebral atrophy (*C* and *D*). Differentiation by CT is often difficult. NPH (*A*) shows larger, more bulbous frontal horns than in atrophy (*C*). The cerebral sulci are smaller in NPH (*B*) than in atrophy (*D*). The lower CT sections demonstrated slightly larger temporal horns and third and fourth ventricles in NPH.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is quickly replacing CT scanning for evaluation of the brain in a wide variety of disorders, including dementia and NPH. Advantages of MRI over CT scanning include the ability to image in different planes, increased sensitivity to structural abnormalities of the brain, the ability to visualize CSF flow effects, and the ability to visualize iron and other paramagnetic substances. Disadvantages of MRI include increased cost, less availability, longer examination times, and

occasional need for sedation or anesthesia. MRI is also insensitive to the presence of calcium; however, this would rarely be a major factor in the evaluation of dementia. The basic principles of MRI are complex and the interested reader is referred to a recent review.[17] The pathologic and anatomic findings described on CT scanning largely translate to MRI and points relatively unique to MRI will be emphasized.

Magnetic resonance imaging enables one to perform imaging easily in different planes. Examinations of the brain commonly include a sagittal T1 weighted series of images and either coronal or axial double echo images. On a sagittal view, distention of the anterior inferior recesses of the third ventricle, depression of the posterior hypothalamus toward the upper surface of the pons, and depression of the fornices have been felt to favor the diagnosis of hydrocephalus over atrophy (Fig. 2).[11] Specialized techniques have been developed to quantify ventricular and subarachnoid space volumes.[5] Preliminary studies are also being performed to assess the value of quantitative measurements on white matter, gray matter, and ventricular and subarachnoid space volumes.

The greater ability of MRI to diagnose other abnormalities that may be in the differential diagnosis of dementia is a distinct advantage over CT scanning. MRI is particularly superior to CT in revealing the anatomy of the brain stem, cerebellum, and temporal lobes. Occasionally suggestive atrophy patterns may be seen, as in Pick's disease, trauma, and multi-infarct dementia. MRI's sensitivity to the presence of brain iron may also be useful in a variety of degenerative disorders.[18]

Magnetic resonance imaging is very sensitive to abnormalities in the white matter, commonly those manifested by a decrease of myelin content and increased water content. The significance of these findings in relation to patients with dementia is an area of controversy. Normal patients commonly show a tiny focus of increased signal abutting the lateral ventricles, particularly the frontal horns. This becomes more common and increases in extent of involvement along the lateral ventricles in elderly patients and occurs in patients without evidence of dementia.[52] Several etiologies of abnormal signal exist that are relevant to elderly patients exhibiting dementia. A thin ring of increased signal surrounding the ventricles may be seen in clear-cut cases of obstructive hydrocephalus (Fig. 3).[53] This likely represents decreased forward flow of CSF into the ventricles from the brain extracellular space. The same phenomenon likely occurs in some patients with NPH, although the relative occurrence and the significance in relation to response to CSF shunting is questionable.[28] In addition, a periventricular halo of increased signal has also been reported to occur in Alzheimer's disease.[12] Ischemic changes or atrophic changes involving demyelination or partial infarction of the white matter secondary to occlusion and narrowing of small perforating arteries is felt to be a common cause of abnormal signal in the white matter in the elderly. This is more common in hypertensive and diabetic patients and has been suggested to be loosely correlated with cognitive function.[18, 50, 51] Our opinion is that a periventricular halo is of questionable significance in relationship to the possibility of NPH and that extensive white matter disease should suggest a vascular etiology for the dementia.

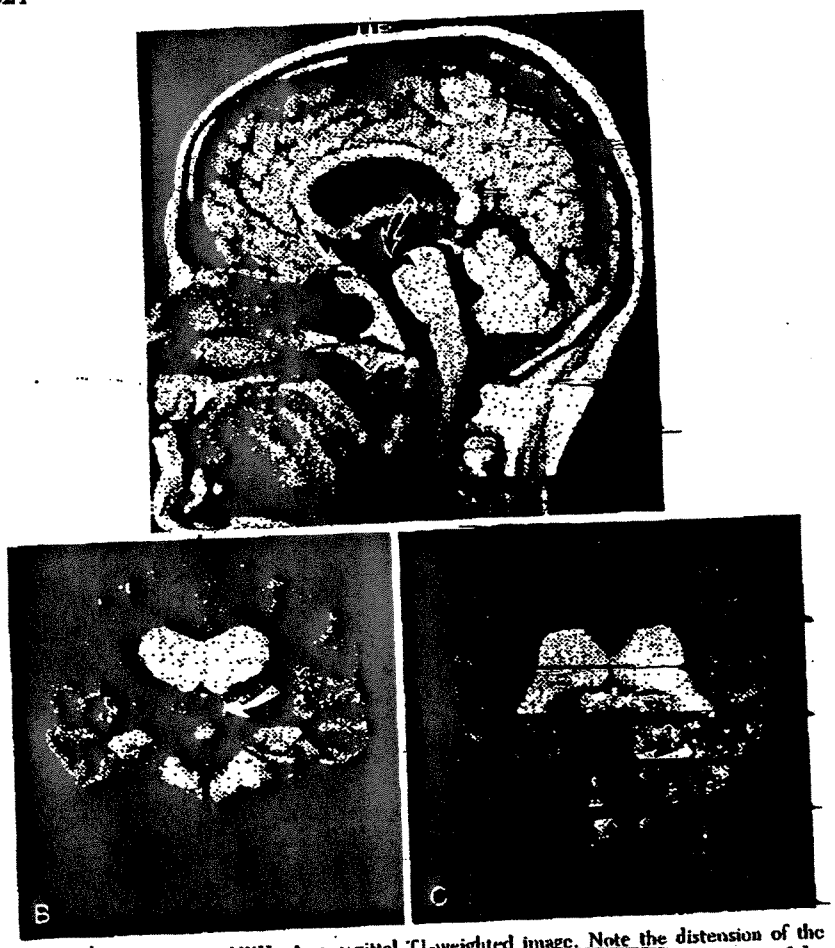

Figure 2. MRI in NPH. *A*, a sagittal T1-weighted image. Note the distension of the anterior inferior recesses of the third ventricle *(solid arrow)* and depression of the floor of the third ventricle *(open arrow)*. *B* and *C* are coronal T2-weighted images. There is enlargement of the ventricles (including the temporal horns) relative to the sulci. There is also pronounced loss of signal (CSF flow-void sign) due to turbulence in the posterior third ventricle, aqueduct, and fourth ventricle *(arrow)*.

MRI is unique in its ability to show phenomena related to CSF flow. Bulk flow of fluid either entering or leaving the image plane may have a noticeable effect on the image signal, in addition to turbulence and to and-fro or vortex motion. In standard imaging pulse sequences, decreased signal representing turbulence of CSF flow is the most common manifestation, thought to be mainly associated with the systolic/diastolic movement of CSF.[2] It has been suggested that decreased signal (cerebrospinal fluid flow void sign) is more prominent in patients with normal pressure hydro-

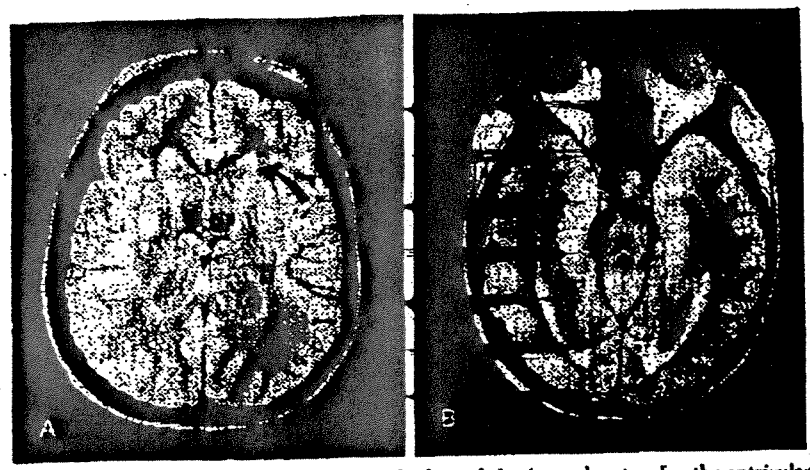

Figure 3. MRI in a case of obstructive hydrocephalus (secondary to a fourth ventricular tumor). Axial images (*A* and *B*) with mixed weighting show increased signal surrounding the intermediate signal CSF in the lateral ventricles *(arrow)*.

cephalus than in normal controls and in those with atrophy,[6, 25] which would be consistent with an increased pulse pressure in the same class of patients (Fig. 2).[15] However, a conflicting report suggests that prominent cerebrospinal fluid flow voids are merely more common in patients with enlarged ventricles, of whatever cause.[16] This is an area of active research, with investigations using a variety of specialized pulse sequences for the visualization and measurement of cerebrospinal fluid flow.[13, 16, 32]

CSF SHUNTING PROCEDURES

Selection of Shunting Sites

Once the decision has been reached regarding the need for a CSF shunting procedure, then the actual procedure is usually straightforward. The form of CSF diversion with the least overall risk and the highest long-term record of patency is from the lateral ventricles (Fig. 4) to either the right atrium (ventriculoatrial or V-A shunt) or the peritoneal cavity (ventriculoperitoneal or V-P shunt). Most neurosurgeons have extensive experience with both.[37, 45] If the hydrocephalus is clearly communicating (that is, an open connection between the lateral ventricles and the lumbar subarachnoid space) then a lumboperitoneal or L-P shunt may be considered. Most of the CSF shunts are placed under general anesthesia due to the relatively awkward position during the procedure and also the extensive subcutaneous tunneling. A variety of valve systems are in common use, but a medium (60 to 90 mm CSF) or high (90 to 150 mm CSF) pressure level is usually selected to decrease the subsequent risk of overdrainage of the CSF and formation of subdural hematomas. The postoperative recovery usually is rapid and patients can be discharged within a few days.

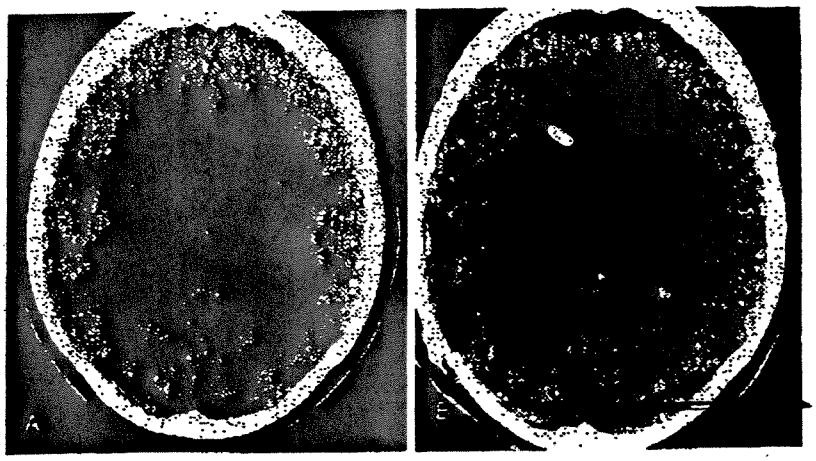

Figure 4. A case of chronic hydrocephalus. *A*, the distended lateral ventricles and small sulci before a CSF shunt was placed. *B*, the CSF shunt in the right frontal horn of the lateral ventricle (white cylinder). The ventricles show a more normal size and configuration, and sulci are visible.

Immediate and Late Risks of CSF Shunting

The immediate risks of the CSF shunting procedure usually are mainly related to anesthesia and subsequent cardiovascular and pulmonary problems. The longer-term risks, however, relate to the volume of CSF flow through the shunt catheter and the pressure within the ventricles. The ideal situation would be a variable shunt pressure, which would allow an immediate lowering of the intraventricular pressure for several days. This immediate lowering would allow the ventricular tension to decrease and give the patient the best chance for decreasing the ventricular size. If the pressure is kept low indefinitely, however, the risk of subsequent subdural hematoma formation is high. Thus, the second stage of an ideal shunt function would be a gradual increase in the ventricular pressure as the ventricles become smaller. Although such a shunt has been proposed,[44] it is not yet an available reality, and thus a compromise in a medium to high shunt pressure for the best combination of the short- and long-term risks is usually accepted.

Other long-term risks include, of course, shunt malfunction, which usually consists of either infection or blockage, or both. In either case a surgical revision of the shunt system may be necessary, or if there has been little improvement to that point, then removal of the shunt system completely may be the wisest course. Series of CSF shunting procedures for NPH have described complication rates in the range of 30 per cent overall for V-P shunts and even higher for V-A shunts, including the immediate and late problems.[3, 4, 20, 29, 31, 42, 43, 49] As alluded to above, more information on the etiology of the NPH may aid the treatment paradigms and also may help in the design of better CSF shunting systems. In summary, the place-

ment of a CSF shunting system does carry a substantial risk over the patient's lifetime, which emphasizes the importance of the decision underlying the original placement.

OUTCOME CHARACTERISTICS

In general, the percentage of selected patients improved following CSF shunting procedures with NPH (or variants) has been reported to be in the range of 25 to 80 per cent.[1, 3-5, 19, 20, 28, 29, 31, 40, 42, 43, 49] Unfortunately, there are many variables between series that prevent a direct comparison, but the main differences lie in patient selection and the nature of the improvement. A description of selection characteristics that are most likely to lead to patient improvement becomes a very helpful part of the evaluation, but as yet remains incomplete because of the high variability between patients in reported series. The most important prognostic factor at this time remains the clinical characteristics, which include the type of symptoms, the order of development, and the multiplicity. Thus, patients with only dementia and without gait abnormalities appear to do poorly after CSF shunting, while patients with mainly gait ataxia and significantly less dementia, memory loss or abulia do much better. The presence of the clinical triad does not appear absolutely important, as patients with mainly gait ataxia also improved.

The next most important factor appears to be the CT and MRI appearances of the brain. The most favorable abnormality on the CT was lack of significant cerebral atrophy in combination with large ventricles. On the CSF studies, intermittent pressure elevations within the ventricles were a better prognostic sign than low or consistently normal pressures on continuous monitoring. Clearly, the likelihood of an improved patient also increases with a raised resting CSF pressure. Likewise, a significantly higher CSF outflow resistance (or low outflow conductance) also increases the possibility of a good outcome. It is hoped that the early results with MRI and CSF pulse pressure studies will be substantiated as another potential set of helpful indicators.[6, 11, 13, 15, 32, 36, 46]

On the other hand, several diagnostic tests appear to have only a minor role in diagnosis at this time. These studies include EEG, blood flow patterns by PET, single photon emission tomography (SPECT), or Xenon-enhanced CT and radioisotope cisternography. Most series have in the end concluded that the onset of gait ataxia before dementia or without dementia has provided the indicator of a good outcome, irrespective of the diagnostic tests that were performed. Clearly, better studies are needed, in addition to improved validation of the currently available tests.

CONCLUSIONS

The standard initial format of evaluation for suspected NPH will usually consist of a detailed clinical examination, often in combination with

neuropsychologic testing for a significant dementia component. A brain CT or MRI is almost always obtained on patients that appear to have some recovery potential. The salient CT characteristic pointing to the likelihood of improvement after CSF shunting involves enlarged ventricles out of proportion to cerebral atrophy. The MRI diagnostic indicators include distended lateral ventricles and prominent CSF turbulence. The third test should be a lumbar puncture (unless the CT suggests a shift or mass), with pressure measurement and laboratory values. On the basis of these three tests, a number of patients may be selected for CSF shunting, particularly if the clinical description falls into the favorable outcome category of mainly gait ataxia, with mild or absent dementia. If a significant question remains, then continuous ventricular pressure measurement should be performed, searching for intermittent pressure elevations, which would place the patient in a favorable improvement category. As a final step, a lumboventricular infusion test for CSF outflow resistance may be performed, but this procedure would tax the resources of most nonacademic centers.

Several additional tests are probably not helpful, particularly the radioisotope cisternogram, and appear to have little if any role in the diagnosis of NPH. Once the patient is selected, then it is important to clearly indicate to the patient and the family that the procedure has a likelihood of helping, but that it certainly will not offer a cure of dementia. The importance of spelling out to the patient and family the limited goals of CSF shunt surgery cannot be overemphasized. Additionally, the immediate and long-term risks should be presented in a brief fashion, to enhance awareness that once the shunt is placed there remains the possibility of problems with the system. Thus, with a few standard clinical tests a reasonable decision may be made for the majority of patients.

The development of additional understanding regarding the NPH syndrome and in particular the etiology of the clinical symptomatology may be very helpful in deciding which tests are valuable overall. The ability of the MRI to visualize CSF pulsations appears to have considerable promise, if the pulse pressure changes can be substantiated and correlated to improvement in a series of patients with NPH. In addition, the development of more physiologic valve systems for CSF shunts may be very helpful in the prevention of late complications such as subdural hematomas, as well as promoting early low-pressure drainage to decrease the intraventricular pressure rapidly. However, the possibility of helping additional patients with moderate to severe dementia alone appears remote, as the ventricular enlargement is more likely to be due to brain loss in this instance rather than ventricular enlargement secondary to tension. Finally, the etiology of NPH and associated ventricular enlargement needs to be more thoroughly studied to see if other alternative therapies (besides CSF shunting) may be helpful.

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