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M S Huckman

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Special Article

Normal Pressure Hydrocephalus: Evaluation of Diagnostic and Prognostic Tests

Michael S. Huckman[1]

This paper reviews the clinical findings in the Hakim-Adams syndrome and distinguishes it from the more general term of normal pressure hydrocephalus. The radiographic tests to diagnose these entities are discussed in their historical context. Computed tomography has recently replaced the pneumoencephalogram for evaluating ventricular size and configuration and computed tomographic metrizamide cisternography is beginning to replace the more traditional radionuclide studies of cerebrospinal fluid dynamics. A protocol is suggested for the future study of Hakim-Adams syndrome which emphasizes strict adherence to clinical criteria for the diagnosis. Studies of the microanatomic and physiologic condition of the underlying brain seem to be emerging as more reliable predictors of the success of shunt procedures than those of cerebrospinal fluid dynamics which have heretofore dominated treatment planning.

The syndrome of dementia, gait apraxia, and urinary incontinence in conjunction with cerebral ventricular enlargement and normal cerebrospinal fluid pressure is referred to either as normal pressure hydrocephalus (NPH), the Hakim syndrome, or the Hakim-Adams syndrome. Initial reports of this syndrome [1, 2] claimed patients with this constellation of findings could benefit from ventricular shunt procedures, although it was subsequently demonstrated that not all patients responded well. This variable response spawned a number of radiographic studies designed to predict which of these patients would benefit from a shunt procedure. The early optimism generated by the hope of easily reversing a form of dementia has been replaced 15 years later by a sense of frustration on the part of physicians treating this illness. Great confusion still exists as to the pathology, etiology, and clinical symptoms that comprise this syndrome. The prognostic value of the various static and dynamic radiologic and other tests used to predict the outcome of shunting is still far from established. The following is a review of prevailing beliefs about the syndrome and the value of the symptoms and signs which allegedly define the disease and determine its prognosis.

Clinical Findings

The clinical picture described by Adams et al. [1] and Hakim and Adams [2] consisted of mild impairment of memory, slowness and paucity of thought and action, unsteady gait, and unconscious urinary and fecal incontinence. Impairment of consciousness ranged from mild inattentiveness to a state of coma, and the paucity of thought in its mildest form consisted of apathy but at times resembled akinetic mutism [1].

Gait abnormality was either a mild disorder or a total inability to stand or walk [1]. The gait problem was difficult to characterize but was clearly not due to a cerebellar deficit. Plantar reflexes were extensor and dependent reflexes in the legs were brisk. Headache was absent or negligible and papilledema did not occur. Cerebrospinal fluid pressure was less than 200 mm of water in all cases,

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[1]Department of Diagnostic Radiology, Rush-Presbyterian-St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, IL 60612.

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there were large lateral ventricles demonstrated by pneumoencephalography, and the patients benefited from ventricular shunting.

Since the initial reports, many patients with hydrocephalus and normal cerebrospinal fluid pressure have been labeled "normal pressure hydrocephalus" without applying the rigid clinical criteria outlined above. Often they have had little clinical resemblance to the original cases. As a result, the diagnosis of normal pressure hydrocephalus is often based on radiologic tests alone, which makes evaluation of the different treatments applied to these patients difficult.

Heinz et al. [3] reported 17 cases of normal pressure hydrocephalus. There was incontinence in only one case and only six had documented gait disturbance. Because of abnormal radiographic tests and dementia, these appear in the literature as 17 cases of normal pressure hydrocephalus. Only six of the 11 patients with this entity reported by Tator and Murray [4] had the clinical triad of dementia, gait disturbance, and incontinence. Belloni et al. [5] reported 22 patients with normal pressure hydrocephalus and psychic disturbance but only nine had incontinence and only 17 had gait disturbances. Their diagnoses rested heavily on the results of radiographic tests.

Botez et al. [6] described a syndrome for the early recognition of normal pressure hydrocephalus and atrophy before the classic signs appeared. This clinical and neuropsychological syndrome was useful as an early predictor of atrophy or normal pressure hydrocephalus, but the distinction between the two still required various radiographic tests. Sypert et al. [7] reported that a Parkinsonian movement disorder could occur with the usual clinical triad of symptoms.

Morariu [8] described progressive supranuclear palsy in two patients with the clinical triad reported by Hakim and Adams [2]. A third patient reported by Morariu had what was referred to as normal pressure hydrocephalus although incontinence was not present. All of the patients had hydrocephalus but this report again pointed out a major problem in the clinical definition of normal pressure hydrocephalus.

The electroencephalograms of 11 patients with normal pressure hydrocephalus were reported by Brown and Goldensohn [9] who reveiwed other articles on this subject. No specific electroencephalographic pattern could be determined. Diagnoses were mainly based on the radiographic demonstration of large ventricles, however, without strict adherence to the criteria of Hakim and Adams.

The distinction should be made between normal pressure hydrocephalus, a radiologic diagnosis, and the Hakim-Adams syndrome, a clinical entity which has associated normal pressure hydrocephalus demonstrated by radiographic tests. Benson et al. [10] emphasized the syndrome of dementia, gait disturbance, and incontinence in relation to the response to shunting, and suggested the term normal pressure hydrocephalus was descriptively misleading as it denoted any case of hydrocephalus where the cerebrospinal fluid pressure was not elevated. The above demonstrates the need to define terms properly. The Hakim-Adams syndrome is a clinical triad of dementia, incontinence, and gait apraxia associated with ventricular enlargement and normal cerebrospinal fluid pressure. The terms normal or low pressure hydrocephalus are synonyms for nonspecific cerebral ventricular enlargement and normal cerebrospinal fluid pressure without the radiologic finding of large cortical sulci. These signs may be associated with Hakim-Adams syndrome but they may also have other associated clinical presentations which have yet to be classified. In this report, both terms are used but Hakim-Adams syndrome is used only where reported cases specifically fulfill the clinical criteria of Hakim-Adams [2].

Etiology

Adams and Hakim suspected arachnoiditis, due to meningitis or trauma, as the etiology of Hakim-Adams syndrome, although one of the first cases was due to a third ventricular cyst [1]. Arachnoiditis in patients with the syndrome was demonstrated at autopsy by DeLand et al. [11]. The combination of large ventricles and normal cerebrospinal fluid pressure was induced in dogs [12], by the injection of silastic into the subarachnoid space, producing a chemical arachnoiditis. Clinical changes in the dogs were not described.

Bannister et al. [13], using radionuclide cisternography [14–17], demonstrated obstruction of cerebrospinal fluid flow in eight of 14 patients with the Hakim-Adams syndrome. They proposed that the cause of the syndrome was the obstruction of cerebrospinal fluid flow over the brain convexity and around the incisura, probably secondary to trauma, subarachnoid hemorrhage, or meningitis.

Greitz et al. [18] advanced the theory that an ectatic basilar artery could cause this syndrome. In their cases, there was dementia and gait disturbance but no incontinence. Their patients did have hydrocephalus, ectatic arteries, and did improve clinically after shunting. They proposed that ectatic arteries produced hydrocephalus by (1) direct compression of the cerebrospinal fluid pathways; (2) deforming the third ventricle; or (3) bleeding. They showed that in one case where the shunt produced clinical improvement, it also increased the regional cerebral blood flow.

Earnest et al. [19] proposed that hypertensive cerebrovascular disease, with multiple small infarcts of the deep cerebral and cerebellar gray matter, might be the initial pathologic process in some cases of normal pressure hydrocephalus and demonstrated such pathologic changes in patients with Hakim-Adams syndrome at autopsy. Neither of the brains in their two patients showed thickened pia arachnoid at the base or over the convexities. Haidri and Modi [20] showed that, in a well documented case of Hakim-Adams syndrome, there was autopsy evidence of hypertensive changes in the large and small vessels of the brain, slight ventricular dilation, multiple infarcts in the deep gray and white matter of both hemispheres, and the absence of degenerative changes characteristic of Alzheimer disease. Kitching et al. [21] showed microinfarcts in normal pressure hydrocephalus accompanying lupus phlebitis and Koto et al. [22] also demonstrated the pathologic changes of hypertensive cerebrovascular disease in Hakim-Adams syndrome.

Botez et al. [6] added long periods of hypoglycemia, and vitamin B_{12} and folic deficiency to the list of etiologies of normal pressure hydrocephalus (but not necessarily Hakim-Adams syndrome). Morariu's [8] report of normal pressure hydrocephalus in progressive supranuclear palsy suggested the histopathologic changes of this disease could alter the resilience of cerebral tissue to pressure changes and explained why progressive supranuclear palsy and even Alzheimer disease could be the underlying cause of normal pressure hydrocephalus.

DiRocco et al. [23] studied the brains of three adults with Hakim-Adams syndrome, all of which showed leptomeningeal, nonobstructive fibrosis, ependymal disruption, subependymal glial reaction, periventricular demyelination, and spongiosis. Unique to some patients were meningeal signs of previous subarachnoid hemorrhage, arteriosclerosis, multiple infarcts, and Alzheimer plaques in gray matter. They concluded there was no single cause for the Hakim-Adams syndrome.

In summary, various etiologies for Hakim-Adams syndrome and normal pressure hydrocelphalus have been put forth. They include parenchymal disease, such as hypertensive encephalopathy and Alzheimer disease, resorptive disorders, such as arachnoid fibrosis of multiple etiologies, and defective resorption due to abnormal development of arachnoidal granulations [24, 25].

Pathogenetic Mechanisms

Early descriptions of Hakim-Adams syndrome [1, 2] included an explanation for the paradox of symptomatic hydrocephalus and normal cerebrospinal fluid pressure. Authors referred to Pascal's Law [26] which stated "the pressure applied to an enclosed fluid is transmitted undiminished through every portion of the fluid and to the walls of the containing vessel." In other words, the force (F) applied to the surface of the enclosed container is the product of the area (A) of the interior of the container and the pressure (P) in the fluid, or $F = A \times P$. Applying this to the brain, the ventricular surface is the area of the container, cerebrospinal fluid pressure is the fluid pressure in the system, and the product is the force exerted on the brain by the obstructed cerebrospinal fluid space. From Pascal's equation it can be seen that, as the ventricles enlarge, their surface area increases and if cerebrospinal fluid pressure remains constant, the force exerted will increase. By the same reasoning, low pressure in a large ventricle may exert more force on the brain than high pressure in a normal or small ventricle. Application of Pascal's Law to the central nervous system assumes the elasticity of the brain is altered, allowing ventricular expansion without an increase in the cerebrospinal fluid pressure.

Hakim et al. [27] view the brain as a viscoelastic sponge. The cells of the sponge are the venous capillaries and extracellular spaces and the liquids and proteins within white matter. The compressibility of the sponge is controlled by shifts of fluid into the venous system which then control the general pressure level within the cells of the sponge. The effective cerebrospinal fluid pressure which squeezes liquid out of the parenchymal sponge is the gradient between the intraventricular cerebrospinal fluid pressure and the venous blood pressure. Changes in ventricular size are triggered by the effective cerebrospinal fluid pressure and not by the intracranial pressure measured in relation to atmospheric pressure. Hakim et al. stated that very high ventricular pressure could be compatible with normal or even small ventricular size, and large ventricles could develop with slightly increased intracranial pressure.

Bannister et al. [13] suggested low pressure hydrocephalus was probably a misnomer because it is likely cerebrospinal fluid pressure increases at some time during the disease. However, regardless of the theory involved, patients with normal pressure hydrocephalus improved if the pressure were lowered.

Greitz and Grepe [28] believed dilation of the ventricular system depended on two factors: (1) the intraventricular pressure or ventricular-subarachnoid pressure gradient, and (2) the tensile strength of the ventricular walls (i.e., brain tissue). They assumed that decreased tensile strength was the precipitating factor in normal pressure hydrocephalus due to degenerative diseases but was not a factor in hydrocephalus where pressure changes are the initial cause of ventricular enlargement. They concluded that these different etiologies formed the basis for different appearances in these two conditions and explained why some shunting procedures were unsuccessful.

The development of an animal model of normal pressure hydrocephalus [29] prompted a series of experiments [30–33] which demonstrated transependymal resorption of intrathecally injected radiopharmaceutical and cerebrospinal fluid occurred when the usual pathways were obstructed. This mechanism partly explained how ventricular pressure remained low despite obstruction of normal cerebrospinal fluid flow.

The mechanism of transependymal resorption was also postulated by Cutler et al. [34] when studying a child with normal pressure hydrocephalus and a documented overproduction of cerebrospinal fluid. Lorenzo et al. [35] described complicating intrinsic brain disease in two patients with normal pressure hydrocephalus who failed to respond to shunting, suggesting that the poor response stemmed from failure of transependymal resorption of CSF due to the underlying, intrinsic brain disease.

Other compensating mechanisms suggested by animal models included diminished cerebrospinal fluid production when its resorption was altered [36, 37]. It was also proposed from this animal model that spontaneous cerebrospinal fluid rhinorrhea might also serve as a compensatory mechanism, especially in the early development of normal pressure hydrocephalus [38].

Hoff and Barber [39], using constant infusion manometry, monitored ventricular and subdural pressure simultaneously. In patients with normal pressure hydrocephalus, they showed a pressure gradient between the ventricle and the subdural space which increased as the ventricular pressure increased. In patients without ventricular dilation, no gradient was measured across the cerebral mantle. They concluded this supported the theory of Fishman [40] which

stated that ventricular pressure exceeding cortical surface pressure may simulate an intraventricular water hammer, which in turn eventually produces dilated ventricles.

In light of these speculations on pathogenesis, DiRocco et al. [23] concluded there were two pathogenetic mechanisms in normal pressure hydrocephalus which may operate independently or together, either simultaneously or in sequence. The first is defective cerebrospinal fluid circulation or absorption with subsequent increase in intraventricular cerebrospinal fluid pressure. The second factor is changing tensile properties of periventricular white matter due to edema, spongiosis, ependymal disruption, or parenchymal damage due to vascular insufficiency [22], Alzheimer disease, or other degenerative diseases.

Evaluation of Ventricular Size and Configuration

Pneumoencephalography

The earliest reports of Hakim-Adams syndrome [1, 2] verified ventricular enlargement by pneumoencephalography. The reports described pneumoencephalography in Alzheimer disease as showing ventricles which were smaller than those seen in normal pressure hydrocephalus. Air entered the subarachnoid space easily in Alzheimer disease and outlined enlarged sulci but did not do so in Hakim-Adams syndrome.

Bannister et al. [13] stated that pneumoencephalography was required to demonstrate focal blockage in the basal cisterns and dilation of cisterns caudal to the obstruction. However, Heinz et al. [3] reported partial blockage to the flow of subarachnoid gas was difficult to evaluate by this method, often making a definitive diagnosis of normal pressure hydrocephalus impossible.

LeMay and New [41] evaluated 41 patients with normal pressure hydrocephalus and found the pneumoencephalographic findings were identical to those associated with obstructive or internal hydrocephalus. None of their patients with the pneumoencephalographic picture of atrophy and normal cerebrospinal fluid pressure responded clinically to a shunt procedure. All patients with normal pressure hydrocephalus whose ventricular size responded to shunting had a corpus callosum angle on pneumoencephalogram greater than 120°.

Greitz and Grepe [28] found pneumoencephalography useful for evaluation of patients with normal pressure hydrocephalus. They reported marked dilation of the Sylvian and interhemispheric fissures with compression of the cerebral hemispheres against the calvarium was their most frequent finding, and cautioned that it not be confused with the picture seen in cerebral atrophy. They also observed that dilation of the temporal horns of the lateral ventricles indicated the patient would probably benefit from a shunt procedure. The importance of temporal horn enlargement on pneumoencephalography was later confirmed by Forslo et al. [42].

Tator and Murray [4] reiterated the difficulties in evaluating patency of the subarachnoid pathways by pneumoencephalography. They pointed out that the image of the subarachnoid pathways was influenced by the amount of air injected, the position of the head during injection, and subsequent movement of the head.

Rovit et al. [43] reported progressive ventricular dilation after pneumoencephalography as a sign of normal pressure hydrocephalus. They hypothesized that this phenomenon occurred because air replacing ventricular fluid caused a decreased resorption of cerebrospinal fluid via the ventricular ependyma. Sjaastad et al. [44] showed atrophy on pneumoencephalogram usually involved the upper part of the lateral ventricles with relative sparing of the temporal horns whereas generalized dilation of the ventricular system, including the temporal horns, indicated a high pressure hydrocephalus. A later study [45] showed patients with normal intracranial pressure and ventricular dilation could be divided into two groups, those with or without enlargement of the temporal horns. The two groups showed markedly different patterns of cerebrospinal fluid flow. The authors concluded that dilation of the ventricles in NPH was due to a pressure factor despite recorded normal pressure.

Measurement of the callosal angle on pneumoencephalogram was thought to distinguish normal pressure hydrocephalus from atrophy [46, 47]. A callosal angle of less than 120° was considered indicative of either high pressure or normal pressure hydrocephalus.

Belloni et al. [5] described four pneumoencephalographic patterns applied to the diagnosis of normal pressure hydrocephalus: (1) *Complete*—no air over the cerebral convexity and dilation of the temporal horns; (2) *Incomplete*—partial or local demonstration of the subarachnoid space not always associated with temporal horn enlargement; (3) *Atypical*—diffuse but poor filling of the subarachnoid space over the convexities with normal sized temporal horns; (4) *Atrophy*—diffuse and abundant air in the subarachnoid space. All patients in category 1 responded well to shunting and none in category 4 showed any improvement after shunting. Most in category 2 improved but very few in category 3 showed any response.

In summary, this technique seems to distinguish normal pressure hydrocephalus (not Hakim-Adams syndrome) from atrophy by several criteria although it is still a questionable predictor of the response to shunting. Normal pressure hydrocephalus is the most likely diagnosis if the callosal angle is less than 120°, the temporal horns are large, the sulci fill partly or not at all, and the patient's condition deteriorates after pneumoencephalography.

CT Scanning

Because of the ease with which the ventricles and sulci can be demonstrated, CT scanning quickly replaced pneumoencephalography in the workup of normal pressure hydrocephalus. New et al. [48] and Adapon et al. [49] stated that large ventricles on CT without large sulci could be due to normal pressure hydrocephalus. Jacobs and Kinkel [50] reported CT often demonstrated atrophy in cases where pneumoencephalography showed no air over the convexity. In fact, one-third of the patients who showed absence of air over the convexity on pneumoencephalography had atrophy on CT scan and at autopsy.

Gado et al. [5] described a spectrum of CT appearances

in patients with normal pressure hydrocephalus. At one end of the spectrum was dilation of the fourth and lateral ventricles with normal cortical sulci typical of normal pressure hydrcephalus. At the other end was dilation of the cerebral sulci, slight enlargement of the lateral ventricles, and a normal appearing fourth ventricle. The latter pattern was considered typical of atrophy.

Yamada et al. [52] described a fan-shaped irregular area of low density surrounding the frontal horns and extending to the frontal poles of the brain in normal pressure hydrocephalus. This area disappeared after shunt procedures and clinical symptoms improved in proportion to the degree of disappearance of the low density area.

LeMay and Hochberg [53] used CT to differentiate hydrostatic hydrocephalus (obstructive or normal pressure hydrocephalus) from hydrocephalus ex vacuo (atrophy). According to their report, the diagnosis of hydrostatic hydrocephalus was probable when (1) tips of both temporal horns were 2 mm or more wide and the interhemispheric fissures and cerebral sulci were not visible or, (2) the tips of the temporal horns were 2 mm or more or the bifrontal index of the lateral ventricles was 0.5 or more. Tans [54] confirmed these findings and showed that the mean width of all ventricles was significantly greater in normal pressure hydrocephalus than in atrophy. The third and fourth ventricles and temporal horns were markedly enlarged in normal pressure hydrocephalus and slightly larger than normal atrophy. The temporal horns were identified in 91% of patients with hydrocephalus and 26% of those with atrophy. All patients with normal pressure hydrocephalus showed a widened third ventricle but this was also shown in 80% of atrophy patients. Tans believed frontal periventricular lucency favored an obstructive hydrocephalus but this finding was also encountered in two patients with Alzheimer disease.

Heinz et al. [55] not only showed ventricular size was larger in obstructive than in atrophic dilation of the ventricles, but also that the temporal horn diameter and frontal horn radius were larger and the frontal horn angle was smaller in obstructive than in atrophic ventricular dilation.

In summary, the sizes of the third and fourth ventricles and temporal horns, and particularly, the shape of the frontal horns are useful CT measures in separating obstructive from atrophic ventricular dilatation. While periventricular frontal lucency usually suggests obstructive hydrocephalus, it may also be seen in Alzheimer disease. All of the authors cited in this section believe CT has replaced pneumoencephalography as the ideal method to show ventricular size in patients with normal pressure hydrocephalus.

CSF Dynamics

Radionuclide Cisternography

DiChiro et al. [14, 15] described intrathecally injected radioactive iodinated serum albumin (RISA) to study the anatomy and physiology of the cerebrospinal fluid-containing spaces of the brain by external scintillation scanning. DiChiro [16, 17] described the normal flow of intraventricular injected RISA. Within minutes it was detected in the basal cisterns and by 12–24 hr, most activity was detected along the superior sagittal sinus. When injected in the lumbar area, it was detected in the basal cisterns in about 1 hr and then followed the same pattern. DiChiro observed that positioning and physical activity did not influence the flow of RISA and that pathologic blocks to cerebrospinal fluid flow were characterized by high concentration of the material in the cerebrospinal fluid pathway immediately proximal to the site of the block.

Bannister et al. [13] applied this technique to the evaluation of adults with unexplained progressive dementia. In normal individuals they showed that RISA, injected via lumbar puncture, was at no time detected in the lateral ventricles.

They graded abnormalities as follows: (A) Appearance of radionuclide in the lateral ventricles at 24 hr (intensity graded 0–4); (B) Delay in clearing radionuclide activity from the lateral ventricle. Grade I: less than 24 hr; Grade II: 24–48 hr; Grade III: 48–72 hr; Grade IV: greater than 72 hr; (C) Cortical subarachnoid radionuclide activity at 24 hr (present or absent). They proposed that the appearance and persistence of RISA in the ventricles distinguished atrophy from normal pressure hydrocephalus. Subsequent studies [56, 57], using radionuclide cisternography suggested the retention of radioactivity in the basal cisterns and absence over the convexity at 24 and 48 hr established incisural block to cerebrospinal fluid flow as the cause of hydrocephalus.

Ojemann et al. [58] proposed this method to select patients for shunt procedures. They showed that shunt procedures induced striking improvements in patients with Hakim-Adams syndrome with complete obstruction to cerebrospinal fluid flow in the basal cisterns demonstrated by cisternography. Five patients with Alzheimer disease showed no obstruction on cisternography and did not improve with shunting.

Heinz et al. [3] confirmed the usefulness of the radionuclide cisternogram as a predictor of shunt response but were guarded as to its accuracy. They considered a delay of 72 hr or longer in the passage of RISA from base to convexity of the brain as signifying incisural block. Ventricular activity at 24 hr was considered abnormal. The authors described the normal flow of intrathecal radionuclide from the lumbar area to the convexity and considered variation in the chronologic pattern of this migration as representing an abnormal cisternogram.

By 1970 several investigators [10, 41] observed that the clinical definition of normal pressure hydrocephalus included entities which had the radiographic findings of normal pressure hydrocephalus but lacked the clinical picture of Hakim-Adams syndrome. In normal cisternograms they noted no radionuclide in the ventricles at any time; in atrophy, it was seen in the ventricles from 6 to 48 hr. Patients with hydrocephalus showed early (4 hr) and persistent (48–72 hr) concentration of the radionuclide in the lateral ventricles. In normal patients and those with atrophy there was immediate activity in the subarachnoid space and eventual concentration in the parasagittal area. Little or no activity was present in the sagittal area in normal pressure hydrocephalus. Intermittent or partial obstruction such as that due to an ectatic basilar artery showed marked early ventricular concentration which cleared late but completely so at 72 hr,

only sagittal activity remained. They also reported that cortical atrophy might demonstrate increased activity pooled over the cortical surface.

James et al. [59] classified hydrocephalus into three groupings: obstructive noncommunicating, obstructive communicating, and primary atrophic hydrocephalus. They further divided the obstructive communicating group into overt and occult subgroups by their cisternographic appearance. Obstructive communicating hydrocephalus (OCH) was defined as an increase of cerebrospinal fluid volume due to obstruction of the subarachnoid pathway in the presence of normal communication between the ventricles and subarachnoid space. In the *overt* obstructive variety of this entity, the point of obstruction of cerebrospinal fluid flow was seen on the cisternogram as an abnormal concentration of radioactivity and failure of movement past that point. Such a well defined area of blockage usually occurred at the tentorial hiatus, over the cerebral convexity, or at the level of the brain stem. If no sharply defined site of blockage was seen, obstructive communicating hydrocephalus might be suspected by the increased radioactivity in secondary or collateral pathways of cerebrospinal fluid flow. Ventricular activity appeared early and often persisted in this abnormality.

The *occult* form was normal pressure hydrocephalus which had no increase of intracranial pressure, no definite point of cisternal blockage, and showed early and persistent ventricular radioactivity. This was associated with failure of the radionuclide to concentrate in the usual parasagittal resorptive sites, even on delayed studies.

Lumbar Infusion Testing

Katzman and Hussey [60] developed the intrathecal lumbar spinal infusion test to detect normal pressure hydrocephalus. Normal saline was infused into the lumbar subarachnoid space at a rate of 0.76 ml/min. The test was considered abnormal if the cerebrospinal fluid pressure exceeded 300 ml of water during the 60 min infusion, the rationale being that an abnormal test indicated a compromised resorptive capacity. Subsequent studies [5, 46, 61] showed the test had poor prognostic value, probably due to artifacts such as leaks at the puncture site or extradural needle placement.

Trotter et al. [62] showed poor correlation between abnormal spinal infusion testing and pneumoencephalographic criteria for normal pressure hydrocephalus. However, they showed excellent correlation between spinal infusion testing and ventricular radioactivity beyond 48 hr on radionuclide cisternography. Hartmann and Alberti [63] could not distinguish normal from normal pressure hydrocephalic patients by spinal infusion testing using the infusion rate of 0.76 ml/min suggested by Katzman and Hussey [60]. However, when the infusion rate was doubled (1.47 ml/min) cerebrospinal fluid pressure increased faster in hydrocephalic than in control patients. Tans [54] found that together, CT and the spinal infusion test correctly distinguished atrophy from normal pressure hydrocephalus in 71% of their patients.

James et al. [31] studied the behavior of I^{131} in the ventricles of an animal with normal pressure hydrocephalus. By autoradiography they showed transependymal migration of the radionuclide. On this basis, they suggested [33] that in patients with ventricular "stasis" on delayed cisternography, apparent ventricular enlargement probably reflected transependymal migration of the radiopharmaceutical, which in turn was caused by mechanically altered morphology of ependymal cells. By comparing pneumoencephalograms with cisternograms, Bartelt et al. [64] showed that patients with ventricular entry of radionuclides and no stasis had larger ventricles than normal individuals but not as large as ventricles in patients with both entry and stasis on the cisternogram.

Henriksson and Voigt [65] related cisternographic patterns to age and concluded that total cerebrospinal fluid flow was highest in patients under age 25 yr and decreased constantly with increasing age. The rate of clearance of radionuclide from the basal cisterns and convexities also decreased with age. The authors cautioned against diagnosing normal pressure hydrocephalus in older persons since the cisternographic changes might in part be age related.

Metrizamide Cisternography

The study of dynamics of cerebrospinal fluid using CT and intrathecal metrizamide was introduced by Greitz and Hindmarsh [66]. Drayer et al. [67] later studied hydrocephalic patients by the injection of 6–7 ml of metrizamide (190 mg/ml iodine) into the lumbar subarachnoid space. After 30 sec in the Trendelenburg position, cranial CT scans were performed immediately, at 6 hr, 12 hr, and 24 hr. In normal individuals, the scan showed metrizamide appeared in the basal cisterns immediately. By 6 hr, there was a marked decrease in the cisternal metrizamide, and by 24 hr, it was no longer visible. The cortical sulci and interhemispheric fissure were filled with metrizamide at 6 hr. The fourth ventricle contained metrizamide in the immediate scan but not on later scans. If third and lateral ventricular filling occurred on the immediate scan, low concentrations of metrizamide in these ventricles at 6 and 12 hr was not considered abnormal. At 12 hr and 24 hr, normal scans showed metrizamide in the cerebral and cerebellar substance contiguous with the subarachnoid space. This "blush" was most distinct in the cerebellum, lateral cerebral convexity, and parasagittal area.

Drayer et al. [67] also described the abnormal patterns seen in metrizamide cisternography. The pattern in hydrocephalus showed ventricular stasis on 24 hr and occasionally at 48 hr, asymmetrical filling of the Sylvian fissures, a diminished parasagittal blush, and periventricular edema highlighted between metrizamide in the lateral ventricle and normal cerebral white matter. The "diffuse" pattern was seen in diffuse degenerative abnormalities such as Alzheimer disease. This showed ventricular stasis at 6 hr and 12 hr but not at 24 hr. Periventricular edema was not seen and the parasagittal blush was normal. In some cases, metrizamide filled markedly enlarged sulci.

Hindmarsh and Greitz [68] compared radionuclide cis-

ternography with metrizamide CT cisternography in 51 patients and found no single symptom, sign, or combination of signs to reliably distinguish between atrophy and normal pressure hydrocephalus. Patients with widened sulci and dilated ventricles showed normal cerebrospinal fluid circulation and patients with dilated ventricles and few dilated pathways such as the Sylvian and interhemispheric fissures tended to have abnormal cerebrospinal fluid circulation and ventricular stasis. Ostertag and Mundinger [69] also showed metrizamide CT cisternography and radionuclide cisternography yielded comparable results. Enzmann et al. [70] also confirmed this fact but disagreed with the contention of Hindmarsh and Greitz [68] that the plain CT appearance of the ventricles and sulci could predict whether the CT cisternogram would be normal or abnormal.

Partain et al. [71] developed time density curves for quantitating metrizamide in the cisterns of experimental animals. Normal curves were established in the cisterna magna, suprasellar and quadrigeminal cisterns, and Sylvian fissures of the rhesus monkey. The authors suggested that time density curves using metrizamide CT would have application in the human, but this has not yet been proved.

In summary, metrizamide CT cisternography can demonstrate the same cerebrospinal fluid dynamics shown previously by radionuclide cisternography and may be used to study transependymal migration of cerebrospinal fluid. Whether cerebrospinal fluid dynamics demonstrated by metrizamide CT cisternography are better predictors of response to shunt therapy than those determined by radionuclide cisternography remains to be proved.

Cerebral Blood Flow

Greitz et al. [18] reported that one of their patients with occult hydrocephalus due to basilar artery ectasia showed a good clinical response to shunting and a mild increase in cerebral blood flow after the procedure. They proposed that the two phenomena might be related and demonstrated [72] a measurable relationship between the decrease in ventricular size after shunting and increased cerebral blood flow. However, decreased cerebral blood flow was also demonstrated in Alzheimer disease [61, 73] and so it could not be distinguished from normal pressure hydrocephalus on the basis of regional cerebral blood flow.

Mathew et al. [74] measured regional cerebral blood flow, and regional cerebral blood volume before and after shunting in 15 patients with hydrocephalus and in 10 patients with atrophy and found the most marked reduction in flow and volume occurred in the anterior cerebral artery territory in hydrocephalus but not in atrophy. Both values increased after decreasing cerebrospinal fluid pressure by lumbar puncture. The highest preshunt blood flow and the maximum increase in blood volume and flow after shunting correlated with the best clinical improvements. Regional cerebral blood flow normally remains constant over a wide range of intracranial pressures. Increased blood flow after lumbar puncture in individuals with normal pressure hydrocephalus suggested that hydrocephalus responsive to shunting indicated underlying impairment of autoregulation of the cerebral circulation. Koto et al. [22] proposed that the increase in cerebral blood flow after shunting accelerated the resorption of cerebrospinal fluid and removal of metabolic products from the brain.

Lying-Tunell et al. [75] demonstrated that normal pressure hydrocephalus patients showed a decrease in cerebral metabolism which approached normal values after shunting. Hartmann et al. [76] proposed using cerebral blood flow monitoring to detect decreased regional cerebral blood flow in acute subarachnoid hemorrhage and normal pressure hydrocephalus and thereby determine the optimal time to shunt.

In summary, investigations concerning regional cerebral blood flow in the demented patient, while limited, seem to indicate that hydrocephalic patients, in whom a low regional cerebral blood flow can be demonstrated, may be good candidates for shunting. It also suggests that physiologic changes in the underlying brain may be a more important determinant of response to therapy than the demonstration of abnormal cerebrospinal fluid dynamics.

Why Do Shunts Fail To Relieve Symptoms?

Why do ventricular shunts fail to improve all patients with the clinical and radiographic signs of normal pressure hydrocephalus? Numerous authors [4, 35, 41, 49] have hypothesized that such failures are due to concomitant parenchymal damage or preexisting primary degenerative brain disease. Tator and Murray [4] suggested failure may occasionally result from attempting treatment too late in the course of the disease. Samuelson et al. [77] reported subdural hematoma occurred after shunting in five of 24 patients. Hoff and Barber [39] suggested patients who did not respond might already be adequately compensated at the time of shunting.

Shenkin et al. [78] reported no consistent relationship between clinical improvement after shunting and reduction in ventricular size. In their 19 patients the positive effect of shunting in some instances appeared due to some factor other than decreased ventricular size.

Mathew et al. [74] related shunt failure to regional cerebral blood flow and showed that patients with successful response to shunting had higher blood flow before shunting and a higher percentage increase after shunting compared to the measurements in patients who responded poorly to therapy.

Udvarhelyi et al. [79] reported a 44% rate of shunt complications; 9% of these were fatal. Complications included infection, subdural hematoma, and pulmonary embolism. Black et al. [80] reported a 35.5% complication rate after shunts. Subdural hematoma, shunt malfunction, and seizures were the most frequent complications.

Hakim [81] introduced the concept of subdural stress, that being the compressive stress which reaches the surface of the brain. This was thought to be a function of both cerebrospinal fluid pressure and the "biotrophic yield" (compressibility) of the brain parenchyma. With small ventricles, large changes in cerebrospinal fluid pressure produce little change in subdural stress, but with large ventri-

cles, any increase in pressure causes an immediate and almost equal increase in subdural stress. Therefore, the aim of treating hydrocephalus by shunting is to restore the ventricles to normal size. Hakim, however, states it is important not to allow subdural stress to diminish below its normal value or new symptoms may appear. He believes the maintenance of normal subdural stress should be the measure of the success of shunt therapy since it indicates the state of compression of the brain. A successful shunt should maintain ventricular pressure at a value inversely proportional to ventricular size. To this end, Hakim designed a prototype valve with a pressure sensor in the subdural space. If subdural stress is high, the sensor reduces the popping pressure in the ventricular shunt valve, allowing it to open and drain the ventricle and vice-versa if the subdural stress is too low.

Prognostic Value of Current Diagnostic Tests

Up to this point, we have defined normal pressure hydrocephalus, and discussed its pathology, physiology, and how to recognize it. This information is of little importance, however, unless predicting and guiding treatment. To evaluate the effectiveness of treatment it is necessary to establish criteria of improvement. Certainly one cannot say that a decrease in ventricular size without improvement in the dementia, incontinence and gait apraxia represents a cure. If these three clinical findings did not exist before treatment, what has been treated cannot be called what is defined as HAS.

Initial reports of Hakim-Adams syndrome [1, 2] reported the reversal of symptoms after the shunt operation. This occurred several years before sufficient cases were accumulated to permit an evaluation of predictive factors. Ojemann et al. [58] analyzed 28 patients with this syndrome and showed improvement after shunting was most striking in patients with the typical clinical syndrome and complete obstruction of the cerebrospinal fluid flow in the basal cisterns on radionuclide cisternography. Patients with only partial obstruction of cerebrospinal fluid flow showed less improvement, and five cases of Alzheimer disease without flow obstruction showed no improvement. Greitz et al. [72] showed that clinical improvement was accompanied by an increase in cerebral blood flow after shunting. They did not specify, however, how a measure of cerebral blood flow could preoperatively predict the outcome of shunting.

Heinz et al. [3] did not adhere to the strict clinical criteria in their series of 130 dementia patients, nor did they describe what was considered criteria for improvement after shunting. However, they indicated that a positive radionuclide cisternogram showing subarachnoid block and a dilated 4th ventricle suggested a good prognosis. They believed the longer a block was present, the less favorable were chances for improvement by shunting. These findings were confirmed by several other investigators [5, 82]. McCullough et al. [83] analyzed cisternography in 38 patients with normal pressure hydrocephalus, only two of whom showed Hakim-Adams syndrome clinically. They reported that late stasis of the radionuclide in the ventricles was a good predictor of clinical improvement after shunting. However, clinical improvement was defined merely as "a regression of neurologic findings".

Greitz and Grepe [28] evaluated 23 patients undergoing shunt for normal pressure hydrocephalus and found radionuclide cisternography alone could not predict which patients were suitable for operation. They concluded that the demonstration of dilated temporal horns was as good as any other test in predicting which patients would respond to shunting. These findings were confirmed by Forslo et al. [42].

The initial enthusiasm of investigators was put into perspective by Bannister [84] who followed eight patients with Hakim-Adams syndrome by clinical examination, cisternography, and pneumoencephalography. In none of these cases did operation lead to improvement and while a diagnosis could be made, no criteria was found which predicted the response to shunting. Halpern et al. [85] seriously questioned the use of cisternography to deny or suggest surgery and recommended a prospective study of its value.

Guidetti and Gagliardi [86] found that etiology of the disease was a good predictor of shunt success. Patients with antecedent history of head trauma, subarachnoid hemorrhage, or intracranial surgery had a better prognosis than patients without these etiologies. Coblentz et al. [61] confirmed that shunting was particularly effective in Hakim-Adams syndrome due to postmeningeal irritation. Haidri and Modi [20] found shunting of little value in patients with systemic hypertension and focal neurologic findings in association with Hakim-Adams syndrome. Wolinsky et al. [46] reported that a callosal angle less than 120° on pneumoencephalogram was a better predictor of shunt success than were tests of cerebrospinal fluid dynamics.

Shenkin et al. [87] found radionuclide cisternography was not an accurate predictor of shunt success. However, of their 28 patients with Hakim-Adams syndrome, those with gait disturbance as a prominent feature responded to shunting more often but not necessarily better than patients with dementia as the most marked feature. These findings were corroborated by Hughes et al. [88]. Since there was little response to shunting in those without gait disturbance, Shenkin et al. [87] suggested that gait disturbance was due to the hydraulic effect of the hydrocephalus and that dementia was more closely related to brain degeneration.

Chawla et al. [89] continuously monitored intracranial pressure [90] for 48–72 hr in 12 patients and concluded that patients with variable intracranial pressure improved after shunting but those with flat tracings over the 72 hours did not improve. This was confirmed by other investigators [63, 91].

By 1974, the frustration of investigators in trying to establish criteria for predicting shunt response became acute. Messert and Wannamaker [92] attributed the unpredictable results of treatment to a relaxation of criteria for the diagnosis of the syndrome. They proposed the following criteria for selecting patients for shunt: (1) The clinical findings of dementia, gait apraxia, and incontinence; (2) Evidence of progression of the disease; (3) A diagnostic pneumoencephalogram; (4) Strict cisternographic evidence of block;

(5) Electroencephalographic evidence of decompensation. Several other studies also stressed the importance of strict adherence to clinical criteria as the best predictor of shunt success [50, 88, 93, 94].

The unrealiability of radiologic features alone has led others to propose prospective studies with strict criteria [85, 95] to select patients for shunting. These reports emphasize the unreliability of cerebrospinal fluid dynamics by cisternography. In a recent report [80], a combination of clinical and CT patterns has been a fairly successful predictor.

Having carefully reviewed this extensive literature it appears a prospective study of this disease with adherence to a strict set of criteria is needed. Patients admitted to the study should satisfy the following criteria: (1) Well documented dementia, gait apraxia, and incontinence with known time of onset; (2) Absence of other focal neurologic signs and systemic hypertension. (3) CT demonstration of symmetrical large lateral ventricles with or without a large fourth ventricle, Sylvian fissures, suprasellar cistern or cisterna magna. The tips of the temporal horns should be large enough to be seen and should be symmetrical. Cortical sulci should not be prominent and there should be no focal lesions; (3) Decrease in regional cerebral blood flow compared to a group of normal individuals; (4) Variable rather than unchanging cerebrospinal fluid pressure with the mean pressure being normal; (5) Random selection for shunting, the unshunted patients serving as controls; (6) The effectiveness of shunting should be judged by length of life, objective cognitive testing, gait apraxia, and changes in incontinence.

Bachman [95] reported a patient with "classical" clinical and radiographic findings of Hakim-Adams syndrome who showed spontaneous improvement over 3 years without shunting. Bachman suggested that, had the patient been shunted at the time of diagnosis, the procedure would have been considered an impressive success. Stein and Langfitt [96] believe shunting is the only treatment to offer despite their study which showed that only two of 33 patients showed a "truly dramatic" response to shunting. They suggested the criteria to select shunt patients should depend less on preoperative tests and more on severity of the dementia, the patient's age, the expected cost and length of hospitalization, and the wishes and expectations of the patient and family.

While experience indicates this is a reasonable approach, the fact that Hakim-Adams syndrome, with or without treatment, is occasionally reversible, makes it premature to abandon hope of making some sense of this problem.

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