Editorial

Cerebrospinal fluid production in patients with hydrocephalus

JAMES T. RUTKA, M.D., PH.D., F.R.C.S.(C)

Division of Neurosurgery, University of Toronto, Ontario, Canada

Since the first descriptions of patients with a clinical syndrome in which cognitive slowing, ataxia, and urinary incontinence were accompanied by ventricular enlargement in the face of normal cerebrospinal fluid (CSF) pressures, there has been hope that the pathophysiology of normal-pressure hydrocephalus (NPH) can be better understood and that such patients may harbor a treatable form of dementia. Thirty-five years later progress has surely been made regarding diagnostic tests for NPH; however, the failure and complication rates of treatment by CSF shunting remain high, indicating that we do not yet have a complete understanding of the pathophysiology of this disorder.

In the report by Silverberg, et al., the authors have used a modification of the Masserman method to study the CSF production rate in patients with acute and chronic hydrocephalus, and they have compared these values with the CSF production rate in a selected control population, patients with Parkinson disease. Quite unexpectedly, what the authors determined from their analysis was that a statistically significant decrease in the mean CSF production rate could be observed in patients with chronic hydrocephalus compared with patients with acute hydrocephalus and with control patients. Although these authors are unable to explain this result from the data they obtained and present, they postulate that a downregulation of CSF production by the choroid plexus may be involved in this process.

Who were the patients with chronic hydrocephalus in this study? They were patients in whom the clinical syndrome consisted of a gait disturbance (apraxia or ataxia), cognitive decline, and ventricular enlargement. Nocturnal incontinence was present in at least some of these patients. Therefore, the chronic hydrocephalus group was defined as one in which the entire clinical triad of NPH need not be present. From a practical standpoint, I think the authors were right to define this group of patients in this fashion; however, it would have been very interesting if they had been able to compare the CSF production rates between patients who exhibit the complete NPH clinical triad and those who do not. Obviously, a greater number of patients with chronic hydrocephalus would need to be studied.

One can quibble about the use of the Masserman method to measure CSF production rate in this study. To their credit, the authors have previously used this technique and recently reported their results on CSF production rate in patients with Alzheimer disease (AD). Still, it must be acknowledged that other methods of measuring CSF production could have been used, such as the one proposed by Pappenheimer and colleagues or the method of spinal recirculatory subarachnoid perfusion. These methods, which are based on the principle of indicator clearance, may have given slightly different results. The authors mention the potential use of magnetic resonance imaging–based methods of calculating CSF production rates. At the moment, because such imaging-based data on CSF production rates seem somewhat high (for example, 0.8 ml/minute), one cannot simply leave behind the normative data that have been accumulated using the Masserman or Pappenheimer methods.

One can also argue that the authors did not control for all variables that might influence CSF production in all patients. The primary variables include the following: anesthetic agents, PaCO2 levels throughout the procedure, drugs, mean arterial blood pressure, and patient age, position, and temperature. In their Discussion section, Silverberg, et al., have attempted to answer some of the limitations of their study in terms of these variables. What struck me as interesting, however, is just how little is known about CSF formation and absorption following drug or anesthesia administration in humans. Most of the primary data on factors that alter CSF production rates to which the authors refer have come from studies on rabbits or goats.

My only other comment relates to the measurement and reporting of the opening CSF pressures in each group. These were not statistically different among the three groups, but it must be acknowledged that the opening pressure for the acute hydrocephalus group was obtained only after patients had been receiving long-term drainage. As such, these results do not represent a true opening pressure.

I like the paper by Silverberg, et al., because it forces us to think outside conventional paradigms. Why would CSF production rates be downregulated in patients with chronic hydrocephalus? What would the CSF production rates be at early and intermediate time points of this disorder? If CSF production is downregulated late in the time course of chronic hydrocephalus, does it make sense to continue to use shunts in these patients? If so, what pressure valve should be used? These are just some of the questions that arise directly from a reading of this thoughtful paper by Silverberg, et al.
References


Response: The authors acknowledge all of the caveats and pitfalls noted by Dr. Rutka in his excellent review of our paper. We agree that there are errors inherent in all CSF production techniques. We chose the Masserman method because it was the least invasive and the safest, given that the patients required placement of a ventricular catheter for treatment of their underlying disease. Perfusion techniques are probably more accurate, but are time consuming and would add a great deal more anesthesia time and risk to the measurement. Of interest, we initially planned on including patients with chronic hydrocephalus in the control group for our study of CSF production in patients with AD. We were surprised to find that CSF production, at least that measured using the Masserman method, was diminished in this group as well. It is also of interest that a high incidence of the pathological characteristics of AD was observed in cortical biopsies of patients who received shunts for NPH—as many as 75% of patients suffering from severe dementia in one series. It may be that decreased CSF clearance of noxious metabolites, such as β-amyloid, due to CSF circulatory failure may underlie the dementia associated with both AD and NPH. If that were the case, a shunt designed to maintain a constant CSF pressure may not reliably provide sufficient flow to clear these metabolites. In our randomized, but unblinded, pilot study of long-term CSF drainage through a novel, constant, low-flow shunt as a treatment for AD, we found stable psychometric test scores in patients with AD who had been treated for longer than 1 year, whereas untreated patients with AD declined in the expected fashion. We also found a decrease in the biological markers for AD in the CSF of the treated patients. The key to treating the dementia associated with NPH may well be the augmentation of CSF turnover and clearance, rather than the maintenance of normal CSF pressure. Clearly more research needs to be done on CSF production, turnover, and clearance in association with normal aging and neurodegenerative diseases.

Gerald D. Silverberg, M.D.
Stanford University
Stanford, California

References