VIEWPOINT

The Next Era of Idiopathic Normal Pressure Hydrocephalus

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In 1965, after publication of the first description of normal pressure hydrocephalus (NPH),[1] characterized as a treatable form of dementia, an era of enthusiasm and exuberance toward NPH began. Until then, no treatments for dementia were available or imaginable. Soon, many patients with dementia were diagnosed with NPH based on radionuclide cisternography or pneumo-encephalography and treated with shunt surgery. After an initial flurry of favorable articles, the research literature on NPH began showing worse outcomes. By 1992, an article titled, "Shunting Normal Pressure Hydrocephalus: Do the Benefits Outweigh the Risks?" found that nearly 70% of patients had no improvement and nearly 75% had complications.[2] An era of nihilism and retreat from NPH had settled in. Many neurologists and neurosurgeons became reluctant to evaluate patients for NPH, let alone proceed with shunt surgery.

However, centers for NPH were founded simultaneously in Europe, Japan, and the US in the 1980s and 1990s. They began publishing their research, focusing on idiopathic NPH (iNPH), a subacute, progressive syndrome in patients 60 years or older with no identifiable hydrocephalus risk factors that is difficult to diagnose. By the mid-2000s, the International and Japanese Guidelines for iNPH were published, setting diagnostic standards for clinical practice and for inclusion criteria in clinical research.[3,4]

Neurologists and neurosurgeons studying iNPH saw outcomes in their clinics and research that were better, safer, and more long-lasting than described in the earlier publications. However, patients often mentioned the difficulty and time it took to find physicians who would consider the possibility of iNPH, which suggested that skepticism toward iNPH based on the older literature was a barrier to care. Thus, rigorous, well-designed research to determine the effectiveness and safety of shunt surgery for iNPH was needed.

In fact, 4 randomized placebo trials, including 3 blinded "small-n" with ventriculoperitoneal shunts and 1 unblinded "large-n" with lumboperitoneal shunts, showed gait velocity improved by approximately 30%. However, a Cochrane review called for more studies with more participants "to increase our confidence in the evidence."[5] With work starting in 2007-2008, the Placebo-Controlled Efficacy in Idiopathic Normal Pressure Hydrocephalus Shunting (PENS) trial was designed to be a rigorous, sufficiently powered, randomized, blinded, placebo-controlled study of shunting. The key was a noninvasively adjustable shunt valve that has a setting with an opening pressure so high (>400 mm H_2O) that it is functionally "off" and can be used as a placebo vs the open shunt setting of 110 mm H_2O.[6]

The National Institute of Neurological Disorders and Stroke–funded PENS trial initial results were recently published.[7] Eligible patients selected for shunt surgery based on their gait response to cerebrospinal fluid (CSF) drainage[3] were randomized to receive either placebo or open shunt. The primary outcome measure was simple and robust: the change in gait velocity, a standard iNPH outcome and a recognized marker of health and functional capacity in older adults. At the primary end point 3 months after surgery, the placebo group (n = 50) had no change (0.03 m/s), while the open shunt group (n = 49) improved by 0.23 m/s, which is more than twice the minimum clinically important difference of 0.1 m/s in the older population. Importantly, the open shunt group had fewer falls and more improvement in quality of life and functional independence. However, no change was seen in screening measures of cognition or bladder symptoms.

These short-term results are not the final word. Twelve-month outcomes with an open shunt in all participants from 3 months onward are pending, including neuropsychological testing, and novel magnetic resonance imaging and CSF biomarker analyses, which will provide important data regarding the extent and durability of the benefits and risks of shunting, may yield insight into the neuronal and glial mechanisms responsible for iNPH symptom development and recovery. Nonetheless, the initial PENS trial results provide highly convincing evidence that iNPH is a distinct clinical entity and shunting can produce early, significant, clinically meaningful improvement in appropriately selected patients,[8] heralding the next era of iNPH, an era of evidence and engagement.

Relying on the response to temporary CSF removal to diagnose iNPH and identify shunt candidates has been correctly criticized as circular.[8] Unfortunately, no reliable biomarkers currently exist to allow iNPH identification without such testing, and none are likely to exist until the underlying mechanisms of symptom development and recovery are understood. Producing the evidence to solve this fundamental iNPH question will require innovative research. Further, if the underlying biological mechanisms of iNPH are discovered, then research to develop and test pharmacologic or biologic agents to treat iNPH either alone or in tandem with shunt surgery should soon follow. Additionally, discovery science for iNPH may identify overlapping mechanisms with neurodegenerative disorders.

The PENS trial results set the stage for engagement between iNPH specialty centers and community neurologists, geriatricians, physiatrists, primary care physicians, and neurosurgeons in complementary roles to identify and treat more patients with possible iNPH, a population that is larger than commonly believed. A Swedish longitudinal epidemiologic study found that the iNPH incidence is comparable with reported incidence rates for Alzheimer dementia, vascular dementia, and parkinsonism.[9]

In clinical practice, identifying the subset of patients with ventriculomegaly who have iNPH and would benefit from shunting is challenging. Because the cerebral ventricles enlarge with normal aging, imaging reports often raise the question of iNPH, whether it is present or not. The primary symptoms of iNPH (gait and balance impairment, urinary urgency and incontinence, and cognitive impair-

ment) are common in the older population, making the differential diagnostic process critical. Many patients initially suspected to have iNPH will not have it. Carefully following clinical guidelines[4,5] for diagnosis and treatment will help achieve a favorable benefit-risk ratio as more patients are evaluated and treated.

Community physicians and facilities have the vital role of first contact and evaluation of these patients. After a detailed history and neurological examination, practical steps may include evaluating for iNPH symptom mimics, such as spinal stenosis, musculoskeletal disorders, significant neuropathy, neurodegenerative disorders, urologic disorders, or medication adverse effects. If none are found, then referral to iNPH specialty centers can be considered.

Until research reveals reliable, less invasive methods of identifying iNPH, a potential bottleneck to expanding health care services for iNPH is the need to assess the gait response to CSF drainage, or to perform CSF infusion testing or intracranial pressure monitoring to identify patients who will respond to shunt surgery. These relatively invasive procedures require specialized protocols and interpretation and are best done at iNPH centers, but there are not enough to meet the expected increased patient demand.

The surgical aspects of iNPH treatment must also be addressed to improve outcomes. While a low rate of complications is observed in published reports from iNPH centers, significantly higher rates are seen in national hospital surveys.[10] Shunt surgery in older adults requires as much attention to surgical detail and complication prevention as complex cranial or spine procedures. Longitudinal care after surgery with adjustable shunts, optimally through interdisciplinary clinics, is needed to evaluate patients' response to shunting and monitor for complications to determine whether shunt setting adjustment is required.

Conclusions

Our hope is that the PENS trial is a catalyst for renewed scientific and clinical efforts in this emerging era of iNPH, an era of evidence and engagement that aims to understand disease mechanisms, develop predictive biomarkers, optimize and standardize diagnosis and treatment, and ultimately expand therapeutic options beyond neurosurgery. Through coordinated research, multidisciplinary care, and thoughtful translational work, we look forward to improved access to care and better outcomes for patients with idiopathic normal pressure hydrocephalus.

ARTICLE INFORMATION

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