Comment: The trouble with "n" in normal-pressure hydrocephalus

Idiopathic normal-pressure hydrocephalus (iNPH) is a reversible syndrome of gait impairment, dementia, and incontinence that affects persons over 65 years of age.[1] Currently, the only effective treatment is surgical implantation of a shunt[2]; however, the need for pharmacologic adjunctive treatments was noted at the 2005 NIH workshop on hydrocephalus.[3]

This analysis of 8 patients with iNPH who were treated with low-dose acetazolamide (ACZ) found improvement in gait in 5 patients and periventricular white matter hyperintensities in 6 patients, which raises the hope that ACZ could be an adjunctive treatment for iNPH.[4] The investigators acknowledge multiple substantial limitations of the study (small "n," or number of subjects; convenience cohort; open-label treatment; and its retrospective nature), which is why the study should not be interpreted as evidence of efficacy. By the standards of *Neurology*®, this work is Class IV evidence.[5]

The trouble with small "n" studies is that of a type I error, which is to conclude that the treatment is effective when it may not be. A recent study of the natural history of iNPH in which shunt surgery was inadvertently delayed for at least 6 months for 33 patients in Gothenburg, Sweden, found that without treatment some patients improved while others worsened before surgery.[6] Thus, the outcomes in the small "n" ACZ study may simply reflect the natural history of iNPH. Further, the cohort in Sweden overall worsened before surgery and had less robust recovery, which implies that a delay in shunting by using ACZ off-label can potentially harm patients. Nonetheless, the ACZ study is promising, and evaluation of the potential benefit of ACZ in a carefully monitored, blinded, placebo-controlled large "n" multicenter trial of iNPH is well warranted.

1. Klinge P, Hellström P, Tans J, Wikkelsø C. One-year outcome in the European multicentre study on iNPH. Acta Neurol Scand 2012;126:145–153.
2. Bergsneider M, Black PM, Klinge P, Marmarou A, Relkin N. Surgical management of idiopathic normal-pressure hydrocephalus: iNPH guidelines, part IV. Neurosurgery 2005;57(3 suppl):S29–S39.
3. Williams MA, McAllister JP, Walker ML, et al. Priorities for hydrocephalus research: report from a National Institutes of Health–sponsored workshop. J Neurosurg 2007; 107(5 suppl):345–357.
4. Alperin N, Oliu CJ, Bagci AM, et al. Low-dose acetazolamide reverses periventricular white matter intensities in iNPH. Neurology 2014;82:xx–xx.
5. Gross RA, Johnston KC. Levels of evidence: taking *Neurology*® to the next level. Neurology 2009;72:8–10.
6. Andrén K, Wikkelsø C, Tisell M, Hellström P. Natural course of idiopathic normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry Epub 2013 Nov 29, doi: 10. 1136/jnnp-2013-306117.

Michael A. Williams, MD, FAAN

From The Sandra and Malcolm Berman Brain & Spine Institute, Adult Hydrocephalus Center, and Center for Gait and Mobility, Sinai Hospital of Baltimore, MD.

Study funding: No targeted funding reported.

Disclosure: M. Williams has been the Associate Editor for Ethics for *Continuum* since 2005. He holds the following patents: July 1, 2003: Shunt: United States Patent 6,585,677. August 17, 2004: Shunt: Canadian Patent 2,356,032. August 23, 2005: Shunt: United States Patent 6,932,787 B2. Continuation of US Patent 6,585,677. June 8, 2006: Self-sealing catheter for deformable tissue: International Patent WO 2006/060181 A1. M. Williams owns a 5% interest in Mensana Therapeutics, a start-up with intellectual property only that is related to CSF shunting for the treatment of Alzheimer dementia. M. Williams is the President in the International Society for Hydrocephalus and CSF Disorders for 2012–2014. Go to Neurology.org for full disclosures.