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 shunt2; 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.1 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.1

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.4 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.


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