Revisiting secondary normal pressure hydrocephalus: does it exist? A review

Badih Daou, MD,¹ Petra Klinge, MD,² Stavropoula Tjoumakaris, MD,¹ Robert H. Rosenwasser, MD,¹ and Pascal Jabbour, MD¹

¹Department of Neurological Surgery, Thomas Jefferson University and Jefferson Hospital for Neuroscience, Philadelphia, Pennsylvania; and ²Department of Neurosurgery, The Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, Rhode Island

OBJECTIVE There are several etiologies that can lead to the development of secondary normal pressure hydrocephalus (sNPH). The aim of this study was to evaluate the etiology, diagnosis, treatment, and outcome in patients with sNPH and to highlight important differences between the separate etiologies.

METHODS A comprehensive review of the literature was performed to identify studies conducted between 1965 and 2015 that included data regarding the etiology, treatment, diagnosis, and outcome in patients with sNPH. Sixty-four studies with a total of 1309 patients were included. The inclusion criteria of this study were articles that were written in English, included more than 2 patients with the diagnosis of sNPH, and contained data regarding the etiology, diagnosis, treatment, or outcome of NPH. The most common assessment of clinical improvement was based on the Stein and Langfitt grading scale or equivalent improvement on other alternative ordinal grading scales.

RESULTS The main etiologies of sNPH were subarachnoid hemorrhage (SAH) in 46.5%, head trauma in 29%, intracranial malignancies in 6.2%, meningoencephalitis in 5%, and cerebrovascular disease in 4.5% of patients. In 71.9% of patients the sNPH was treated with ventriculoperitoneal shunt placement, and 24.4% had placement of a ventriculoatrial shunt. Clinical improvement after shunt placement was reported in 74.4% and excellent clinical improvement in 58% of patients with sNPH. The mean follow-up period after shunt placement was 13 months. Improvement was seen in 84.2% of patients with SAH, 83% of patients with head trauma, 86.4% of patients with brain tumors, 75% of patients with meningoencephalitis, and 64.7% of patients with NPH secondary to stroke.

CONCLUSIONS Secondary NPH encompasses a diverse group of clinical manifestations associated with a subset of patients with acquired hydrocephalus. The most common etiologies of sNPH include SAH and traumatic brain injury. Secondary NPH does indeed exist, and should be differentiated from idiopathic NPH based on outcome and on clinical, pathophysiological, and epidemiological characteristics, but should not be considered as a separate entity.

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KEY WORDS normal pressure hydrocephalus; NPH; secondary

IN 1965, Hakim and Adams described a syndrome of symptomatic hydrocephalus with a normal CSF pressure that presents with gait disturbance, dementia, and incontinence without overt signs and symptoms of elevated intracranial pressure (ICP).¹⁷ They called it nor-

mal pressure hydrocephalus (NPH) and found that it was a “treatable syndrome” with the performance of neurosurgical shunting procedures.¹ Further studies have confirmed these findings and have shown that in spite of a normal CSF pressure approximately 50% of patients with NPH

ABBREVIATIONS CVD = cerebrovascular disease; ICH = intracerebral hemorrhage; ICP = intracranial pressure; LP = lumboperitoneal; NPH, iNPH, sNPH = normal pressure hydrocephalus, idiopathic NPH, secondary NPH; SAH = subarachnoid hemorrhage; VA = ventriculoatrial; VP = ventriculoperitoneal.

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improve after shunt surgery.⁷² In 50% of patients with NPH, no known cause can be identified.⁶ These cases are referred to as idiopathic NPH (iNPH). The other 50% of NPH cases occur in association with prior events that lead to the development of this syndrome. These are termed secondary NPH (sNPH). The causes of sNPH are multiple and include mainly subarachnoid hemorrhage (SAH), trauma, malignancy, meningitis, stroke, and intracerebral hemorrhage (ICH).⁴ Idiopathic NPH generally occurs in adults during the 6th and 7th decades of life, whereas sNPH can occur at any age.²⁰ Differences in outcome between iNPH and sNPH have been observed, with substantial improvement after shunt placement occurring in approximately 30%–50% of patients with iNPH and in approximately 50%–70% of patients with sNPH.⁷²

Many articles have described the diagnosis and management of NPH and the predictive tests used for selecting the most appropriate candidates for shunt placement. In 2005, Marmarou and colleagues published guidelines for the diagnosis and management of iNPH and emphasized the importance of distinguishing between iNPH and sNPH.^{3,28,34,35,55} Because sNPH is so heterogeneous with regard to pathology, diagnosis, treatment, and outcome, it is not clear if the term “secondary normal pressure hydrocephalus” should be used to encompass such a wide array of entities and whether unifying guidelines should be made for the diagnosis and management of sNPH. The aim of this review study was to evaluate the etiology, diagnosis, treatment, and outcome in patients with sNPH and to highlight important differences among the separate etiologies. We also sought to answer the following questions: What are the most common etiologies of sNPH? What are the treatments used to manage it? How successful are the treatments?

Methods

A comprehensive review of the literature was performed using the key words “secondary normal pressure hydrocephalus,” “normal pressure hydrocephalus,” “NPH,” “hemorrhage and normal pressure hydrocephalus,” “trauma and normal pressure hydrocephalus,” “meningitis and normal pressure hydrocephalus,” “tumor and normal pressure hydrocephalus,” and “stroke and normal pressure hydrocephalus.” These terms were used to conduct searches in the following databases: PubMed, Ovid, and Scopus. The databases were last queried on July 1, 2015. The inclusion criteria of this study were articles published between 1965 and 2015, written in English, including more than 2 patients with the diagnosis of sNPH, and containing data regarding the etiology, diagnosis, treatment, or outcome of NPH. The exclusion criteria were the following: case reports, technical notes, review articles, and articles not written in English. Studies that included sNPH cases but did not elaborate on etiology, treatment, or outcome were excluded. Despite the methodological limitations, all publications meeting these criteria were included due to the paucity of research papers dealing with the topic of sNPH. Data regarding etiology, treatment, and outcome in patients with sNPH were extracted independently after a thorough review of the results of each published article.

Summary measures included assessment of the frequency of patients with certain etiologies and the mean number of patients who improved after shunt placement.

Most identified publications combined both iNPH and sNPH, or excluded sNPH cases. Many of these studies did not differentiate among diagnostic, treatment, and outcome differences between these 2 entities. The design, patient selection criteria, outcome criteria, and conclusions of each study were analyzed. Outcome definitions and post-operative follow-up periods varied widely across studies. Several scales and scores were used to assess clinical improvement following shunt placement. The most common assessment of clinical improvement was defined as a decrease of at least 1 grade on the Stein and Langfitt grading scale, or equivalent improvement on other ordinal grading scales.⁶¹ Marked improvement was defined as a decrease of at least 2 grades on the Stein and Langfitt grading scale, or equivalent improvement on other ordinal grading scales.

Results

Study Selection

The search generated approximately 3000 articles, of which 64 met our inclusion criteria (Table 1).^{2,5,7–11,14,16,18,19,21–24,26,27,29–33,36,38–50,52,54,56–63,65–71,73–83} A total of 1309 patients with sNPH were included. The mean number of patients per study was 21. Of the articles that mentioned the study design, 21 were prospective and 27 were retrospective. Fifty-nine studies reported the etiology of sNPH, 61 studies reported the diagnostic tests used to identify patients with NPH and the prognostic tests used to predict the outcomes of shunt placement, 46 studies reported the type of shunt used for management of NPH cases, and 38 studies mentioned the valve system used. The outcome specific to patients with sNPH after shunt surgery was reported in 35 studies.

Etiology of sNPH

The etiology of sNPH was reported in 1208 patients (Table 2). The most common cause of sNPH was SAH ($n = 562$, 46.5%). The second most common etiology resulting in sNPH was head trauma ($n = 349$, 29%). Other important etiologies included brain tumors and surgery for resection of intracranial malignancies in 75 patients (6.2%), meningococcalitis in 61 patients (5%), cerebrovascular disease (CVD) in 55 patients (4.5%), and ICH in 49 patients (4%). Other etiologies made up for 5% of the causes of sNPH. These included mainly intracranial operations, radiosurgery, aqueductal stenosis, and Paget’s disease.

Diagnosis of sNPH

The diagnosis of sNPH was based on a combination of clinical history, physical examination, and imaging studies. The NPH was considered to be secondary when an identifiable event occurred prior to the onset of symptoms and was judged to be directly related to the development of NPH. In most studies the diagnosis of NPH was established when patients presented with the classic symptoms of dementia, gait disturbance, and urinary incontinence accompanied by enlarged ventricles on brain imaging, with an Evans index of ≥ 0.3 (maximum width of the

TABLE 1. Evaluation of studies included in the literature review of patients with NPH

Authors & Year	Study Design	No. of Pts w/ sNPH	Etiology	Follow-Up Period	Shunt Treatment	Outcome
McQuarrie et al., 1984	Retrospective	25	SAH & trauma: 25	3 mos	21 VP & 4 VA shunts	53% w/ early disease improved, whereas 27% w/ advanced disease improved.
Reinprecht et al., 1995	Retrospective	20	SAH: 12; trauma: 3; tumor: 5	7–29 mos	VP & VA shunts	71.1% had complete reversal of symptoms & 21.1% of pts had improvement w/ residual symptoms (mixed iNPH & sNPH cases).
Salmon, 1972	Retrospective	44	SAH: 3; trauma: 26; meningoencephalitis: 2; other: 13	6 mos	VP shunts	9 pts had moderate or marked improvement (20%), 8 pts showed minimal improvement (17.8%), 24 had no change (53.3%), & 4 deteriorated (8.9%).
Stein & Langfitt, 1974	Prospective	10	SAH: 3; trauma: 3; tumor: 3; meningoencephalitis: 1	18 mos (mean)	Not specified	80% w/ known etiology significantly improved. In pts w/ iNPH, 64% showed some improvement; this was substantial & sustained in 24%.
Vanneste et al., 1993	Retrospective	23	Not specified	12 mos	Not specified	56.5% of sNPH cases had substantial improvement & 8.7% had some improvement. 14.6% of iNPH cases had substantial improvement & 15.9% had some improvement.
Vanneste et al., 1992	Retrospective	25	Not specified	3.1 yrs (median)	VP & VA shunts	52% of pts w/ sNPH had marked improvement & 8% had slight improvement. 14.9% w/ iNPH had marked improvement & 16.5% had slight improvement.
Walchenbach et al., 2002	Prospective	6	Not specified	2, 6, & 12 mos	VP shunts	Clinically meaningful improvement after 2 mos was seen in 73% of pts.
Yamashita et al., 1999	Retrospective	65	SAH: 65	13.3 mos (mean)	VP shunt	Shunt reprogramming was frequently performed in pts w/ subdural effusion, meningitis, & iNPH, but infrequently in pts w/ sNPH after SAH.
Zemack & Romner, 2002	Retrospective	71	SAH: 37; trauma: 21; tumor: 4; meningoencephalitis: 2; other: 7	26.7 mos (mean)	VP (89.5%) & VA (10.5%) shunts	Outcomes were excellent or good in 69.8% of pts w/ sNPH & in 78.9% of pts w/ iNPH.
Kahlon et al., 2002	Prospective	17	SAH: 1; trauma: 5; tumor: 2; meningoencephalitis: 2; ICH: 7	6 mos (mean)	VP or ventriculovenous shunt	Postop assessments verified improvements in 81% of pts.
Larsson et al., 1991	Retrospective	48	SAH: 19; trauma: 15; tumor: 3; CVD: 11	2.1 yrs (mean)	VP shunts	Improvement occurred in 78%, & 22% deteriorated. Improvement in clinical function was seen in 94% of SAH pts, 79% of posttrauma pts, 77% of iNPH pts, & 70% of pts w/ CVD.
Magnaes, 1978	Retrospective	34	SAH: 14; trauma: 8; tumor: 7; ICH: 5	3 & 12 mos	VA shunts	59.2% of sNPH & 33.3% of iNPH cases improved.
Gustafson & Hagberg, 1978	Prospective	18	SAH: 5; trauma: 7; tumor: 2; meningoencephalitis: 1; other: 3	3–6 mos	VA shunts	50% of pts improved.
Thomsen et al., 1986	Prospective	21	SAH: 9; trauma: 9; other: 3	3 & 12 mos	VA shunts	14/21 pts w/ sNPH improved vs 2/19 pts w/ iNPH.
Mathew et al., 1975	Prospective	10	SAH: 7; trauma: 1; meningoencephalitis: 1; CVD: 1	6 mos	VA & VP shunts	Excellent outcome: 3 sNPH cases (1 trauma, 1 SAH, 1 meningitis) & 1 iNPH case. Good outcome: 2 sNPH (after SAH) & 0 iNPH cases. Fair outcome: 3 sNPH & 2 iNPH cases. Poor outcome: 2 sNPH & 2 iNPH cases.
Wood et al., 1974	Retrospective	46	SAH: 16; trauma: 14; meningoencephalitis: 4; CVD: 8; other: 4	1–7 yrs	VA, VP, or theco-peritoneal shunts	60% improved.

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» CONTINUED FROM PAGE 3

TABLE 1. Evaluation of studies included in the literature review of patients with NPH

Authors & Year	Study Design	No. of Pts w/ sNPH	Etiology	Follow-Up Period	Shunt Treatment	Outcome
Ishikawa et al., 1989	Retrospective	6	SAH: 6	Not specified	Not specified	Excellent outcome in all 6 pts (100%) w/ sNPH.
Chen et al., 1994	Retrospective	31	SAH: 4; trauma: 20; ICH: 7	6 mos	VP shunts	71% of pts had improvement.
Chen et al., 2009	Retrospective	39	SAH: 39	1 & 6 mos	VP shunts in 61.5% & no shunt in 38.5%	There was a significant improvement in pts who had CSF shunting as compared to pts w/o shunt treatment.
Wen et al., 2009	Retrospective	31	Trauma: 31	12 mos	Not specified	64.5% showed clear improvement, & the other pts remained unchanged or deteriorated.
Eide & Sorteberg, 2008	Retrospective	4	SAH: 4; trauma: 1	3 mos	VP shunts	All sNPH pts had improvement in NPH score.
Pfisterer et al., 2007	Prospective	18	SAH: 5; trauma: 8; meningoencephalitis: 5	6.5 yrs (median)	VA shunts	96.1% improved in gait disturbance, 77.1% in cognitive impairment, & 75.7% in urinary dysfunction.
Kilic et al., 2007	Retrospective	49	Trauma: 26; meningoencephalitis: 8; ICH: 15	25 mos (mean)	VP & VA shunts	Improvement observed in 88% of pts who had CSF tap test, 91% of pts who had external lumbar drainage, & 66% of pts who had cisternography.
Chang et al., 1999	Retrospective	26	SAH: 18; trauma: 7; ICH: 1	Not specified	LP shunts	30/32 pts improved after surgery (93.75%).
Panagiotopoulos et al., 2005	Prospective	3	Not specified	3 mos	VP shunts	NA
Poca et al., 2005	Retrospective	13	SAH: 2; tumor: 3; meningoencephalitis: 2; ICH: 1; other: 5	3 mos	Not specified	NA
Owler et al., 2004	Not specified	5	Tumor: 1; meningoencephalitis: 2; ICH: 1	Not specified	VP shunts	NA
Chang et al., 1999	Prospective	28	SAH: 14; trauma: 10; tumor: 1; ICH: 3	3 mos	VP & LP shunts	Excellent & good outcomes were seen in 64.3% of pts w/ sNPH & 22.2% of pts w/ iNPH.
Lee et al., 2012	Prospective	9	SAH: 7; trauma: 1; aqueductal stenosis: 1	3 mos	Not specified	7 pts responded, 4 pts had shunt failure.
Shiino et al., 2004	Prospective	21	SAH: 17; tumor: 1; meningoencephalitis: 2; ICH: 1	1 & 12 mos	VP shunts	Outcome was excellent in 10 pts, fair in 5, & poor in 4.
Kosteljanetz et al., 1990	Prospective	8	SAH: 5; trauma: 1; meningoencephalitis: 1; CVD: 1	3 mos	VP shunt	2/4 pts w/ SAH who underwent CSF shunting improved. 3/9 pts w/ iNPH who underwent CSF shunting improved.
Chen et al., 1994	Retrospective	8	Trauma: 5; CVD: 3	12 mos	VP & LP shunts	8 pts had improvement.
Hashimoto et al., 1990	Prospective	15	SAH: 13; trauma: 1; ICH: 1	2 mos	VP shunts	Shunt was ineffective in 7 pts & was effective in 8.
Wikkelsö et al., 1986	Prospective	21	SAH: 9; trauma: 8; CVD: 4	3–6 mos	VP shunts	9/9 pts w/ NPH after SAH had excellent improvement. 3/8 w/ head trauma did not improve, 4 improved, & only 1 showed excellent improvement. 3 pts w/ iNPH improved, & 2 were unchanged. 2/2 pts w/ CVA who received follow-up improved.
Vorstrup et al., 1987	Not specified	3	Trauma: 1; meningoencephalitis: 2	4 mos	VP & VA shunts	47% of pts showed clinical improvement postop, w/ 4 pts having a good or very good improvement & 4 pts having a moderate improvement.

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TABLE 1. Evaluation of studies included in the literature review of patients with NPH

Authors & Year	Study Design	No. of Pts w/ sNPH	Etiology	Follow-Up Period	Shunt Treatment	Outcome
Shimoda et al., 1994	Retrospective	22	SAH: 14; trauma: 3; tumor: 1; meningoencephalitis: 1; ICH: 3	Not specified	Not specified	14 shunt-responsive & 8 shunt-unresponsive cases.
Tsunoda et al., 2002	Retrospective	17	SAH: 7; trauma: 3; tumor: 4; ICH: 3	Not specified	Not specified	Improvement was seen in 17/17 sNPH pts. Some improvement occurred in 11/15 iNPH pts who had CSF shunting.
Yamada et al., 1978	Not specified	12	SAH: 12	Not specified	Not specified	NA
Hirai et al., 1993	Retrospective	24	SAH: 24	99 wks (mean)	Not specified	18/24 pts w/ sNPH after SAH had excellent & good outcomes, whereas 6 pts had fair or poor outcomes. 7/20 pts w/ iNPH had excellent & good outcomes, whereas 13/20 had fair or poor outcomes.
Belloni et al., 1976	Retrospective	19	SAH: 3; trauma: 14; meningitis: 2	12 mos	VA shunts	All pts w/ sNPH improved after shunt insertion. The 3 pts w/ iNPH did not improve.
Gjerris et al., 1987	Prospective	22	SAH: 22	12 mos	VP & VA shunts	17/18 pts w/ sNPH after SAH improved after shunt placement.
McGovern et al., 2014	Retrospective	19	Trauma: 1; tumor: 15; other: 3	Median: 42 mos	VP & VA shunts	NA
Børgesen & Gjerris, 1982	Prospective	40	SAH: 16; trauma: 10; meningoencephalitis: 8; other: 6	3 mos & 1 yr	VA shunts (16 pts did not receive shunts)	70% of pts w/ sNPH experienced an effect from CSF shunting, compared w/ 52% of pts w/ iNPH.
Tisell et al., 2006	Prospective	49	SAH: 18; trauma: 12; meningoencephalitis: 2; CVD: 7; other: 10	4.2 yrs (mean)	VP shunts	Improvement was seen in 65% of pts w/ sNPH & in 55% of pts w/ iNPH.
Waldemar et al., 1993	Not specified	5	SAH: 2; trauma: 2; CVD: 1	3 & 6 mos	VP shunts	11/13 pts (85%) improved after CSF shunting.
Moretti et al., 1988	Not specified	6	SAH: 1; trauma: 4; meningoencephalitis: 1	4 mos	Not specified	3/6 pts w/ sNPH had clinical improvement after CSF shunting.
Tamaki et al., 1984	Not specified	15	SAH: 5; trauma: 7; tumor: 1; meningoencephalitis: 2	Not specified	Not specified	6 pts had an excellent outcome, 12 pts had a good outcome, & 13 pts had a poor result after CSF shunting.
Mori et al., 2002	Retrospective	13	SAH: 13	1 mo	VP shunts	15 pts had excellent & good outcomes & 7 did not. 6/7 pts w/ sNPH after SAH improved vs 3/15 pts w/ iNPH.
Matsuda et al., 1990	Not specified	12	SAH: 8; tumor: 3; CVD: 1	Not specified	VP shunts	All pts showed improvement.
Kamiya et al., 1991	Not specified	4	SAH: 4	Not specified	Not specified	All pts w/ sNPH after SAH improved.
Mamo et al., 1987	Not specified	7	SAH: 2; tumor: 3; meningoencephalitis: 2	4 mos	VP & VA shunts	Excellent outcome in 6 pts, good outcome in 9 pts, fair in 7 pts, & poor in 3 pts. Overall, 88% of cases were improved.
Tullberg et al., 2002	Not specified	13	SAH: 5; trauma: 3; tumor: 1; CVD: 3; aqueductal stenosis: 1	3 mos	VP or ETV (2 pts)	27 of the NPH pts improved after shunt surgery (93%).

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TABLE 1. Evaluation of studies included in the literature review of patients with NPH

Authors & Year	Study Design	No. of Pts w/ sNPH	Etiology	Follow-Up Period	Shunt Treatment	Outcome
Tullberg et al., 2004	Not specified	19	SAH: 6; trauma: 1; tumor: 2; meningoencephalitis: 1; CVD: 9	3 mos	VP or ETV (2 pts)	21/28 pts improved after shunt surgery in motor & neuro-psychological performance (75%), 5 were unchanged, & 2 pts deteriorated.
Tanaka et al., 1997	Not specified	15	SAH: 11; trauma: 2; CVD: 2	Not specified	VP shunts	9 pts improved clinically after CSF shunting, 12 pts did not improve.
Mase et al., 1998	Not specified	17	SAH: 17	Not specified	Not specified	Not specified.
Kiefer et al., 2006	Prospective	19	Not specified	1 & 12 mos	Not specified	NPH pts responded to shunt surgery in 71% of cases (66% of iNPH pts & 82% of sNPH pts).
Ojemann et al., 1969	Retrospective	10	SAH: 4; trauma: 4; tumor: 2	6–12 mos	Ventriculovenous shunt	All pts w/ sNPH had improvement.
Marmarou et al., 1996	Not specified	7	Trauma: 7	3, 6, & 12 mos	Not specified	Favorable outcome was recorded in 33.3% of pts w/ post-traumatic hydrocephalus.
Hartmann & Alberti, 1977	Not specified	15	SAH: 9; trauma: 2; tumor: 2; meningoencephalitis: 2; other: 1	Not specified	VA shunts	Not specified.
Meyer et al., 1985	Prospective	4	SAH: 2; tumor: 1; aqueductal stenosis: 1	4–12 mos	VP shunts	Marked improvement was found in 85% of cases.
Sahuquillo et al., 1991	Prospective	38	SAH: 12; trauma: 8; tumor: 2; meningoencephalitis: 1; aqueductal stenosis: 12; postcraniotomy: 3	6, 9, 12, & 24 mos	Not specified	54/65 pts (83%) improved.
Soelberg Sørensen et al., 1986	Prospective	5	SAH: 2; trauma: 1; meningoencephalitis: 1; CVD: 1	3–6 mos	VP or VA shunts	Improvement in 12/16 pts.
Vassilouthis, 1984	Retrospective	24	SAH: 10; trauma: 5; tumor: 6; meningoencephalitis: 3	3 mos–4 yrs	VP shunts	Of 10 pts w/ SAH, 9 had excellent improvement & 1 had fair improvement. Of 6 pts w/ craniotomy for tumor resection, 5 had an excellent outcome & 1 had a good outcome. All 3 pts w/ CSF infection had an excellent outcome. Of 5 pts w/ head trauma, 3 had excellent outcome, 1 had a good outcome, & 1 had a fair outcome.
Piechnik & Hultin, 2005	Not specified	6	Trauma: 3; CVD: 2; other: 1	3 mos	Not specified	1 pt worsened, 7 remained the same, & 5 improved after surgery.

CVA = cerebrovascular accident; ETV = endoscopic third ventriculostomy; NA = not available; pts = patients.

frontal horns divided by the transverse inner diameter of the cranium) and a “normal” CSF opening pressure measured by lumbar puncture in the lateral recumbent position (normal indicated a CSF pressure as low as < 150 mm H₂O or as high as < 240 mm H₂O). Additional diagnostic studies that were used to identify patients with sNPH included MRI in 14 studies and pneumoencephalography in 9 studies. In an attempt to differentiate patients who would benefit the most from shunting (patients with shunt-responsive NPH) from patients who would have

less favorable outcomes (shunt-unresponsive patients), a multitude of prognostic tests were performed. The CSF tap test was used in 12 studies, cisternography was performed in 19 studies, cerebral blood flow determination was used in 20 studies, external lumbar drainage was performed in 4 studies, continuous ICP monitoring prior to shunt placement was used in 10 studies, and CSF dynamic studies with determination of conductance and resistance to CSF outflow using a lumbar infusion test were used in 24 studies.

TABLE 2. Etiologies of sNPH in 1208 patients

Etiology	No. (%)
SAH	562 (46.5)
Head trauma	349 (29)
Brain tumors & surgery for resection	75 (6.2)
Meningoencephalitis	61 (5)
CVD	55 (4.5)
ICH	49 (4)
Other (intracranial ops, radiosurgery, aqueductal stenosis, & Paget's disease)	57 (5)

TABLE 3. Outcome of sNPH in 708 patients after shunt treatment

Etiology	% Clinical Improvement After CSF Shunting
SAH	84.2
Head trauma	83
Brain tumors	86.4
Meningoencephalitis	75
CVD	64.7
ICH	71.4
All sNPH cases	74.4

Treatment of sNPH

Ventriculoperitoneal (VP) shunting was used to treat patients with sNPH in 25 studies. Seven studies reported treatment with ventriculoatrial (VA) shunting, 10 studies reported that either VA or VP shunting was performed, and 2 studies reported that either VP or lumboperitoneal (LP) shunting was performed to manage sNPH cases. One study used LP shunting and another study used ventriculovenous shunting as the only treatment strategies. The treatment that was used to specifically manage sNPH was reported in 711 patients; 71.9% had insertion of a VP shunt, 24.4% had placement of a VA shunt, and 3.7% were treated with an LP shunt.

Three studies reported the use of a low-pressure valve system, 13 studies reported the use of a medium-pressure valve system, 11 studies used either a low- or a medium-pressure valve system, and 11 studies reported the use of programmable valves. The valve system specifically used in the management of sNPH was reported in 692 patients. Programmable valves were used in 47.8%, medium-pressure valves were used in 39.6%, and a low-pressure valve system was used in 12.6%.

Outcome of NPH

Several studies combined the outcomes of patients with iNPH and those with sNPH after shunt placement, and could not be included in the outcome analysis. Outcomes were available in 708 patients with sNPH who underwent shunt placement (Table 3). Of these patients, 527 showed clinical improvement (74.4%); excellent clinical improvement was reported in 58% of patients. The mean follow-up period after shunt placement was 13 months. In studies that further reported the outcome for the different etiologies of sNPH, 84.2% of patients with NPH secondary to SAH and 83% of patients with NPH secondary to head trauma had clinical improvement after shunting. A positive outcome after shunting was reported in 86.4% of patients with NPH secondary to brain tumors, in 75% of patients with NPH following meningoencephalitis, in 71.4% with NPH secondary to ICH, and in 64.7% of patients with NPH secondary to stroke and CVD. It is important to note that some of the studies that reported the lowest rates of improvement after shunting did not differentiate outcome based on etiology. The overall complication rate after shunt placement was 22%.

Discussion

In the 5 decades since the description of the syndrome of NPH, the understanding of the pathophysiological mechanism is still not fully elucidated, but our knowledge regarding the etiologies, diagnosis, prognosis, treatment, and assessment of patients who will benefit from shunt placement has evolved. Marmarou et al. reported that the “mixing” of cases of iNPH with cases of sNPH has led to considerable controversy regarding diagnostic and therapeutic strategies.³⁵ The differentiation between iNPH and sNPH has been highlighted by several authors as well, at least with regard to outcome after shunting.^{4,30,71} Most of the recent work has focused on iNPH, whereas most of what we know regarding sNPH stems from studies originating from the 1960s to the 1990s. Differences in outcomes of iNPH and sNPH have been observed, with substantial improvement after shunting occurring in approximately 30%–50% of patients with no identifiable cause and in about 50%–70% of patients with sNPH.⁷²

The leading cause of sNPH (46.5%) was SAH. Chronic hydrocephalus develops in approximately 7%–37% of patients with SAH.¹⁰ Fibrosis and adhesion at the level of the basal cisterns and the subarachnoid and arachnoid villi in patients with SAH can lead to the development of NPH.²⁵ Intracranial malignancies (6.2%) release proteinaceous products and cellular components into the CSF, which increases CSF viscosity and impairs its reabsorption at the level of the arachnoid granulations, leading to NPH.⁵¹ There has been a wide variation in the incidence of posttraumatic hydrocephalus, mainly because of the different definitions used to identify this entity. The rate has been reported to be as low as 1% and as high as 29%.³⁶ Posttraumatic NPH accounted for 29% of sNPH cases. Similarly, posttraumatic NPH develops when there is impairment in the flow and absorption of CSF. Most etiologies lead to the development of sNPH as a result of 2 mechanisms. The first results from increased content of cells or proteins in the CSF (from SAH, meningitis, tumors, and so on), which causes clogging of CSF outflow and leads to obstruction from reduced absorption through the arachnoid granulations. This results in a decrease in conductance and an increase in resistance to CSF outflow. The second mechanism is due to leptomenigeal fibrosis, arachnoid adhesions, and scarring in the basal cisterns, leading to disturbances in CSF dynamics.^{5,53} There is an initial increase in CSF pressure that results in enlargement of the ventricles. The pressure normalizes afterward

but the ventricular enlargement is maintained because of Laplace's law.¹⁷

For NPH to be considered secondary, patients should have a well-established event preceding the occurrence of symptoms that is directly correlated with the development of the characteristic NPH symptoms and imaging findings. The time required for the development of NPH after SAH, trauma, meningitis, stroke, tumors, or intracranial surgery has not been established, but studies have suggested that symptoms may begin immediately after the inciting event, or there may be a delayed onset of a few months' duration.⁸⁰ As described in Wood et al., Hammes et al. reported that obliteration of subarachnoid spaces secondary to fibrosis begins as early as the 10th day after SAH. Ojemann et al. reported that 3 weeks may be sufficient for the development of NPH.⁴⁶ Marmarou et al. reported that hydrocephalus occurred within 2 weeks posttrauma in most patients, and within 1 month in all patients.³⁶ Wood et al. reported on 46 cases of sNPH and found that symptoms began either immediately or as late as 4 months after the event, with the majority of patients experiencing onset of disease within 1 month.⁸⁰ Hirai et al. reported that the mean preoperative period was significantly longer in iNPH (10 months vs 1 month).²¹ Other studies have reported that NPH can still develop years after the initial event.^{2,30} In general, most patients develop NPH soon after the primary diseases. Onset of iNPH is usually gradual, with progressive worsening over time. Onset of sNPH may actually be acute or subacute. It is important to determine the time of onset because symptom duration affects the outcome of intervention.¹²

Patients with sNPH do not always show the typical symptoms of dementia, gait abnormalities, and urinary incontinence as in the idiopathic counterpart, and may manifest other atypical symptoms, including seizures, altered consciousness, and motor and sensory deficits. This is because the primary diseases (SAH, traumatic brain injury, intracranial tumors, meningitis, stroke, and so on) often cause severe neurological deficits that might mask the typical NPH symptoms and make it more difficult to establish a diagnosis.⁷⁷ In certain cases, NPH might be suspected only when preexisting neurological deficits begin to deteriorate or when patients fail to have a satisfactory recovery following the initial event. Early diagnosis and shunt placement is essential because it may improve functional outcome and prevent further functional deterioration. Otherwise, functional recovery may be suboptimal.¹⁰

Several tests have been proposed to accurately identify patients with NPH who will have the best outcome after shunting. These investigations include CT, MRI, isotope cisternography, pneumoencephalography, CSF withdrawal tests, cerebral blood flow measurements, continuous ICP monitoring, and infusion studies with evaluation of CSF dynamics. Whereas the importance of these preoperative evaluations has been widely established in the diagnosis of iNPH, the value of some of these tests remains questionable for sNPH. Stein and Langfitt reported that 80% of patients with sNPH had significant improvement, whereas significant improvement was only seen in 24% of iNPH cases. They reported that shunting should be performed directly in patients with sNPH and that preoperative tests

are of little help in selecting this group of patients for surgery.⁶¹ Børgesen and Gjerris identified a subset of patients with NPH who have a known etiology, short duration of symptoms, severe dementia and gait disturbances, and urinary incontinence who would benefit the most from shunt placement. They reported that these patients are most likely to improve without the need for excessive preoperative testing.^{4,5}

On the other hand, patients not fulfilling these criteria should be investigated using other preoperative tests. Wikkelsö et al. reported that NPH after SAH has a good prognosis, and that these patients present typical changes on CT and radionuclide cisternography and represent a minor diagnostic problem as compared with patients with iNPH.⁷⁹ Gjerris et al. reported that CSF dynamic studies can be used to predict outcomes in patients with sNPH after SAH, especially in patients with high resistance to CSF outflow.¹⁴ Similarly, Marmarou et al. suggested that CSF dynamic studies can help in establishing the diagnosis and prognosis of patients with sNPH that results from head trauma.³⁶ When patients display atypical symptoms of NPH, CSF dynamic studies can help in deciding whether to perform shunt placement for those with suspected sNPH.⁷⁸

Responsiveness to shunting procedures constitutes the most important difference between idiopathic and secondary forms of NPH. Of the patients with sNPH, 74.4% were found to have improvement in clinical status after shunting. Børgesen reported that of 31 patients without a known etiology, only 42% improved 1 year after shunting, whereas 72% of patients with a known etiology had improved. The trend toward better results in patients with a known etiology was significant ($p < 0.01$).⁴ In the same study it was reported that both patients with iNPH and those with sNPH had similar pretreatment clinical status, and that the observed difference in outcome cannot be attributed to differences in the initial clinical status. Vanneste et al. reported that marked improvement occurred in 52% of patients with sNPH, lowering to 15% when only patients with iNPH were considered.⁷⁰ They further conducted a literature review of 1047 patients in which they showed that studies in patients with iNPH found marked improvement in 33%, whereas studies with mixed patients found marked improvement in 50%. They concluded that the etiology of NPH has a significant effect on outcome. Larsson et al. reported that patients with sNPH had a better prognosis than did those with iNPH (94% SAH, 79% posttraumatic, 77% idiopathic).³⁰

The duration of preoperative symptoms has been reported to be a significant factor in the prognosis of NPH.^{16,30} Patients with sNPH present with a shorter duration of preoperative symptoms, because the presence of a known etiology can lead to an earlier investigation and detection of NPH symptoms. Similarly, Thomsen et al. reported that patients with NPH of a known cause had a better outcome than patients with iNPH, and that disease duration of less than 12 months was an important factor for successful outcome. They reported that patients with sNPH usually have a more abrupt onset of dementia, whereas patients with iNPH usually experience gradual deterioration.⁶⁵ Wood et al. reported that symptom duration of less than 6 months is

a good prognostic factor for improvement after shunting. However, their study was one of the few to conclude that etiology did not have an important prognostic value.⁸⁰

Other studies have further suggested that patients with sNPH may have a more favorable shunt outcome than patients with iNPH, because patients with iNPH may have brain atrophy in addition to hydrocephalic features, whereas sNPH patients only have a CSF circulatory disorder.^{64,67} Although our results support the separation of iNPH and sNPH based on outcome, iNPH and sNPH do not represent separate entities; rather, they represent a clinical syndrome associated with a subset of patients with acquired hydrocephalus—patients of different ages with different etiologies and vastly different pathophysiology. Both iNPH and sNPH represent a disorder of CSF flow and absorption, although iNPH may be associated with other factors including white matter ischemic changes, increased transmantle pressure, asymptomatic fibrosing meningitis, and insufficiency of the transcortical subarachnoid space.^{20,37}

Both VP and VA shunting have been used successfully in the management of sNPH. The most important factor to consider in the treatment of patients with sNPH is early intervention. Wen et al. reported that shunt placement should be performed within 6 months of the onset of posttraumatic hydrocephalus.⁷⁸ Some studies that used programmable valves observed a higher rate of reprogramming in patients with iNPH. Zemack and Romner reported that in the iNPH group 49% of patients required valve adjustments, versus 32.4% of patients with sNPH (because of overdrainage, underdrainage, and subdural hematoma).⁸³ Similarly, Yamashita et al. reported that shunt reprogramming was more frequently performed in patients with iNPH than in patients with sNPH after SAH.⁸² The best response to treatment was observed in the SAH, head trauma, and intracranial malignancy groups. These patients may benefit the most from shunt surgery for sNPH.

Patients with sNPH who require surgical shunt placement are often being treated with anticoagulation and antiplatelet agents to manage the primary disease, including stroke or endovascular interventions for aneurysm treatment in patients with SAH, or these patients may be on anticoagulation therapy for the management of other comorbid conditions (atrial fibrillation, deep venous thrombosis, valvular heart disease, and so on). Whether shunting should be performed in these patients is controversial.¹³ The benefits-to-risk ratio should be assessed for each individual. The feared complications of shunting in patients on anticoagulation therapy include ICH, subdural hematoma, abdominal bleeding, and thromboembolic complications after discontinuation of antithrombotic agents. Goodwin et al. reported a low rate of subdural hematoma (6.7%) in patients on long-term warfarin therapy, and they observed no thromboembolic complications when they stopped warfarin prior to shunting.¹⁵ They concluded that anticoagulation was not a contraindication for shunting in patients with NPH. Perioperative management of antithrombotic therapy can be accomplished safely, and anticoagulation treatment should not prevent the placement of a shunt in patients with sNPH.

The combination of several factors supports the existence of sNPH, including the facts that sNPH can occur in

any age group, versus iNPH, which occurs most commonly in the elderly population; that an acute or subacute onset is associated with sNPH following the suspected etiology, versus a slow, gradual onset in patients with iNPH; that typical symptoms of NPH may not always be present with sNPH and atypical symptoms may occur; and that there are higher rates of improvement after shunt placement in patients with sNPH compared with iNPH, which plays an important role in patient selection for shunting. Although we evaluated the various sNPH etiologies, further separation of cases based on etiology is not clearly supported from our data and requires further studies.

The limitations of this review relate to paucity of the literature on the topic of sNPH; the search strategy with the inclusion of smaller studies and older studies; and the inclusion of heterogeneous studies that have a wide variation in the size, population, methodology (both prospective and retrospective studies), and outcome definition. In addition, the lack of randomization of the included studies, with each one having its own reporting bias, should be highlighted as well. It is important to assess the likely extent of the bias and its potential impact on the conclusions. Nevertheless, for this rarely discussed subject, Class I or II evidence is difficult to obtain. This review paper evaluates patients with one clinical pattern of acquired hydrocephalus (NPH) and cannot be generalized to the entire acquired hydrocephalus population. Because of the limitations of this review, further studies are recommended.

Conclusions

Secondary NPH does indeed exist and should be differentiated from iNPH based on outcome as well as clinical, pathophysiological, and epidemiological characteristics but should not be considered as a separate entity. Evaluation of patients with NPH to identify a known cause is recommended because the response to treatment varies considerably. Although clinical presentation is often the same, a multitude of primary etiologies can lead to the development of sNPH. The most common etiologies of sNPH include SAH, traumatic brain injury, intracranial malignancies, meningitis, and stroke. Further studies are required to investigate differences in management and outcome among the diverse etiologies of sNPH.

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Disclosures

Dr. Tjoumakaris is a consultant for Medtronic and Stryker.

Author Contributions

Conception and design: all authors. Acquisition of data: Daou, Klinge. Analysis and interpretation of data: Jabbour, Daou, Tjoumakaris. Drafting the article: Jabbour, Daou. Critically revising the article: Jabbour, Daou, Tjoumakaris. Reviewed submitted version of manuscript: Jabbour, Daou, Tjoumakaris, Rosenwasser. Approved the final version of the manuscript on behalf of all authors: Jabbour. Administrative/technical/material support: Rosenwasser. Study supervision: Jabbour, Klinge, Rosenwasser.

Correspondence

Pascal M. Jabbour, Division of Neurovascular Surgery and Endovascular Neurosurgery, Department of Neurological Surgery, Thomas Jefferson University Hospital, 901 Walnut St., 3rd Fl., Philadelphia, PA 19107. email: pascal.jabbour@jefferson.edu.