Idiopathic normal pressure hydrocephalus case series

2023

119 patients with NPH coding at the University Clinic Münster from January 2009 to June 2017 were examined. The study primarily concentrated on examining symptoms, comorbidities, and radiological measurements, including callosal angle (CA) and Evans index (EI). To evaluate the progression of symptoms, a novel scoring system was developed to quantitatively assess the course at specific time points: 5-7 weeks, 1-1.5 years, and 2.5 years after the operation. This scoring system aimed to provide a standardized approach for measuring and tracking the development of symptoms over time. Logistic regression analyses were employed to identify predictors associated with three key outcomes: shunt implantation, surgical success, and the development of complications.

Among the comorbidities observed, hypertension was the most prevalent. Gait disturbance, in the absence of polyneuropathy, was identified as a predictor of a favorable surgical outcome. Hygroma development was associated with a combination of vascular factors and cognitive disorders. The presence of spinal/skeletal changes, diabetes, and vascular constellations was found to increase the likelihood of developing complications.

The evaluation of comorbidity holds significant importance and necessitates meticulous observation, expertise, and multidisciplinary care [1)].

2022

Twelve patients with iNPH (mean age: 78.08 years; 5 females), 20 with AD (mean age: 75.40 years; 13 females), and 10 normal cognition (NC) participants (mean age: 76.60 years; 7 females) were recruited. The extent and distribution of WMLs and the lateral ventricular volume (LV-V) were evaluated on MRI using voxel-based morphometry analysis. Concentrations of cerebrospinal fluid biomarkers, such as amyloid-β protein (Aβ)42, Aβ40, Aβ38, and tau species, were also measured. Risk factors for small vessel disease (SVD) were assessed by blood examination and medical records.

The periventricular WML volume (PWML-V) and deep WML volume (DWML-V) were significantly larger in iNPH than in AD and NC. The DWML-V was dominant in iNPH, while the PWML-V was dominant in AD and NC. GM-V was significantly smaller in AD than in iNPH and NC. The LV-V positively correlated with WML-V in all participants. There was a significant negative correlation between LV-V and Aβ38 in iNPH. Furthermore, there was no significant difference in SVD risk factors between the groups.

The differences in the extent and distribution of WMLs between iNPH and AD, especially the predominance of DWML-V over PWML-V in iNPH, may reflect decreased fluid and Aβ clearance [2)].

Twenty-seven patients with iNPH were assigned to two groups based on their scores on the neuropsychiatric inventory items related to apathy; 18 patients were assigned to the group with apathy (iNPH + APA) and 9 to the group without apathy (iNPH - APA). The magnetic resonance images

and cerebral blood flow single-photon emission computed tomography data of the two groups were compared using statistical parametric mapping 12. The regional gray matter volume of the right precuneus was significantly larger in the iNPH + APA group than in the iNPH - APA group, but the regional cerebral blood flow in any region of the brain was not significantly different between the two groups. These results suggested that the larger gray matter volume, which is thought to reflect gray matter compression, in the precuneus might be involved in apathy in iNPH [3].

Optic nerve sheath diameters were evaluated using magnetic resonance by an expert radiologist in a cohort of patients with suspected idiopathic normal pressure hydrocephalus. Magnetic resonance findings were evaluated twice. In the first half of this cohort, optic nerve sheath diameters were measured using B-mode only, in the second half applying color-Doppler. Measurements obtained using these two techniques were compared to magnetic resonance imaging measurements. The Bland-Altman analysis and concordance correlation coefficient were computed to quantify the strength of agreement between the two magnetic resonance assessments. Box plots and average (± SD) were used to compare assessments by sonographic and magnetic resonance methods.

Fifty patients were included. MRI assessment showed a moderate concordance correlation coefficient. Optic nerve sheath diameters measured applying color-Doppler were lower ($p < 0.001$) and less scattered compared to B-mode assessment, which approached more to magnetic resonance measurements.

In this cohort of patients, magnetic resonance showed high intra-rater variability in optic nerve sheath diameter assessments. Optic nerve sheath diameter assessments using color-Doppler yielded lower and less scattered diameters compared to B-mode only [4]

A total of 28 patients were operated on for normal pressure hydrocephalus NPH in our institution in the period ranging between January 2015 and December 2019. All the patients underwent magnetic resonance imaging of the brain with standard sequences, calculation of the Evans index and corpus callosum angle, and evaluations by means of Montreal Cognitive Assessment (MOCA), Mini-Mental State Examination, and Frontal Assessment Battery (FAB) neuropsychological tests preoperatively and at 1 and 6 months. A preoperative lumbar infusion test (LIT) with fine measurement of the intrathecal pressures at the beginning and at the end of the procedures was performed.

Results: MOCA and FAB proved an overall improvement of the neurocognitive conditions at 1 month postoperatively. The mean pressure at the beginning of the LIT, was negatively associated with the neuropsychological outcome variables (Mini-Mental State Examination, FAB, and MOCA) in the 3 different evaluations, with FAB and MOCA at 6 months. We found a strong positive correlation between the Evans index as measured on the first magnetic resonance imaging scan both with the diastolic and systolic pressure at the beginning of the test.

Neuropsychological tests, combined with LIT with intrathecal pressure managements aids the diagnostic process in patients affected by NPH. It allows standardizing in a rigorous fashion the follow-up evaluation of patients undergoing surgery for a ventriculoperitoneal shunt [5].

A total of 47 patients who underwent Shunt for Idiopathic normal pressure hydrocephalus treatment at The First Affiliated Hospital of Shenzhen University, Shenzhen between 2018 and 2020 were included in a study. The modified Rankin Scale (mRS) and iNPH grading scale (iNPHGS) were used to evaluate and quantify the clinical symptoms before and after shunt surgery. The disproportionately enlarged subarachnoid space hydrocephalus (DESH) and iNPH Radscale scores were used to evaluate the preoperative MR images. The primary endpoint was improvement in the mRS score a year after surgery, and the secondary endpoint was the iNPHGS after 1 year. The preoperative imaging features of the improved and non-improved groups were compared.

The rates of the primary and secondary outcomes were 59.6% and 61.7%, respectively, 1 year after surgery. There were no significant differences in preoperative DESH score, iNPH Radscale, Evans' index (EI), or callosal angle (CA) between the improved and non-improved groups. Significant correlations were observed between the severity of gait disorder and EI and the CA.

The value of structural neuroimaging in predicting the prognosis of shunt surgery is limited, and screening for shunt surgery candidates should not rely only on preoperative imaging findings.

Key points: • Early shunt surgery can significantly improve the clinical symptoms and prognosis of patients with idiopathic normal-pressure hydrocephalus (iNPH). • Structural imaging findings have limited predictiveness for the prognosis of patients with iNPH after shunt surgery. • Patients should not be selected for shunt surgery based on only structural imaging findings [6].

A total of 32 patients with diagnosed Idiopathic normal pressure hydrocephalus and 18 age-matched healthy controls (HCs) were involved in a study. All subjects underwent magnetic resonance imaging (MRI), including 3D pulsed arterial spin labeling (PASL) for non-invasive perfusion imaging, and clinical symptom evaluation at baseline, and all patients with INPH were reexamined with clinical tests 1 month postoperatively. Patients with INPH had significantly lower whole-brain CBF than HCs, with the most significant differences in the high convexity, temporal lobe, precuneus, and thalamus. At baseline, there was a significant correlation between the CBF in the middle frontal gyrus, calcarine, inferior and middle temporal gyrus, thalamus, and posterior cingulate gyrus and poor gait manifestation. After shunting, improvements were negatively correlated with preoperative perfusion in the inferior parietal gyrus, inferior occipital gyrus, and middle temporal gyrus. Preoperative CBF in the middle frontal gyrus was positively correlated with the severity of preoperative cognitive impairment and negatively correlated with the change of postoperative MMSE score. There was a moderate positive correlation between anterior cingulate hypoperfusion and improved postoperative urination. The study revealed that widely distributed and intercorrelated cortical and subcortical pathways are involved in the development of INPH symptoms, and preoperative CBF may be correlative to short-term shunt outcomes [7].

Di Rienzo et al. retrospectively collected data on a 10-year series of VP-shunted patients with Idiopathic normal pressure hydrocephalus showing transient or minimal improvement of symptoms within 3 weeks from surgery. A full workup (including noninvasive diagnostic, cognitive, and invasive tests) was performed. After ruling out mechanical ventriculoperitoneal shunt malfunction, they performed a tap test followed by a Katzman test 2 weeks later. The confirmed persistence of disturbance of cerebrospinal fluid dynamics was treated by shunt revision and, if found working, by its replacement into the atrial cavity.

Twenty patients were diagnosed with shunt insufficiency. At surgery, the distal end of the shunt was

easily extruded and found working in all cases. It was then repositioned into the right atrium (the first 8 patients of the series also underwent failed contralateral abdominal replacement). Early postoperative clinical improvement was always confirmed. In 1 case, shunt overdrainage was corrected by valve upregulation.

Inadequate distal end placement of a shunt might be one of the reasons needing investigation in patients with iNPH failing improvement after surgery. In such situations, the conversion to a ventriculoatrial shunt proved to be a low-cost and successful treatment option [8].

2021

retrospectively assessed the Evans' index (EI) of 235 consecutive patients aged 60-89 who presented after falls between May and October 2020. We also assessed the presence of the iNPH triad (gait disturbance, cognitive impairment, and urinary incontinence). Patients with EI > 0.3 and with all 3 triad were defined as having possible iNPH; those with clinical improvement after a cerebrospinal fluid (CSF) tap test as having probable iNPH; and those with clinical improvement after a shunt surgery as having definite iNPH. We also examined the 235 patients' EI, and performed a case-control study of EI using sex- and age-matched control patients.

Results: Among the included 235 cases presenting after falls, 44 (18.7%) were diagnosed with possible iNPH, 29 (12.3%) with probable iNPH, and 25 (10.6%) with definite iNPH. The mean EI of these 235 patients was significantly larger than that of controls (0.30 ± 0.04 vs 0.26 ± 0.02, $p < 0.0001$). The proportion of possible iNPH in the cases was 44 out of 235 (18.7%), significantly higher than that of the controls (0%, $p < 0.0001$).

Conclusion: Screening for iNPH in the elderly presenting after falls can possibly identify iNPH patients in the earlier stage who may benefit more from surgical treatments [9]

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22 patients suspected to have iNPH were examined before and after the lumbar tap and were divided into patients who showed symptomatic improvements (positive group, n = 17) and those without improvement (negative group, n = 5) after the lumbar tap. Seven patients in the positive group were examined after the shunt surgery.

Field strength/sequence: 1.5T, electrocardiographically synchronized single-shot diffusion echo-planar imaging.

Assessment: The frontal white matter ΔADC and mean ADC (ADCmean) were compared between before and 24 hours after lumbar tap and from 1 week to 1 month after the shunt surgery.

Statistical tests: Wilcoxon signed-rank test was used. $P < 0.05$ was considered statistically significant.

Results: The deltaADC after the lumbar tap in the positive group was significantly lower than that before ($P < 0.05$), whereas no significant difference was found in the negative group ($P = 0.23$). After the lumbar tap, deltaADC decreased in 16 of 17 patients in the positive group, whereas ADCmean did not significantly change ($P = 0.96$). After the shunt surgery, deltaADC decreased in all seven patients ($P < 0.05$), whereas ADCmean did not significantly change ($P = 0.87$).

Data conclusion: The frontal white matter deltaADC in iNPH decreased after the lumbar tap and shunt surgery. deltaADC analysis may provide detailed information regarding changes in the hydrodynamic and biomechanical properties through CSF drainage.

Level of evidence: 4.

Technical efficacy stage: 4 [10)]

Nakajima et al., examined 1,423 patients (581 women) aged ≥60 years (median age [25%-75%]: 77 [73-80] years) who were diagnosed with iNPH following a hospital visit in 2012. Patients who experienced an improvement of at least one modified Rankin Scale (mRS) grade after the CSF shunt were classified as “improvement” while the remaining patients were classified as “non-improvement.” The efficacy of the shunt intervention (n = 842) was analyzed using a binomial logistic regression analysis.

An analysis of risk factors associated with shunt placement in patients with mRS grade 2 at study entry revealed an association between comorbid chronic ischemic lesions (odds ratio [OR], 2.28; 95% confidence interval [CI], 1.11-4.67; p = 0.025) and cervical spondylosis (OR, 3.62; 95% CI, 1.15-11.34; p = 0.027). Patients with mRS grade 3 at study entry had an association with comorbid Alzheimer's disease (OR, 3.02; 95% CI, 1.44-6.31; p = 0.003).

The results presented here showed that any age-related risk is minimal and should not be cause for rejection of surgical treatment options. Clinical decisions regarding CSF shunt should be individualized to each patient, with adequate consideration of the relative risks and benefits, including maximizing a healthy life expectancy [11)].

2020

To assess automated volumetric analysis as a potential presurgical diagnostic tool or as a method to potentially shed light on normal pressure hydrocephalus pathophysiology. MRI imaging according to a protocol was performed in 29 NPH patients, 45 non-NPH (but suspected) patients and 15 controls. Twenty patients underwent a second MRI 3 months after ventriculoperitoneal (VP) shunt surgery. All structures relevant to NPH diagnosis were automatically segmented using commercial software. The results were subsequently tested using ANOVA analysis. Significant differences in the volumes of the corpus callosum, left hippocampus, internal globus pallidus, grey and white matter and ventricular volumes were observed between NPH group and healthy controls. However, the differences between NPH and non-NPH groups were non-significant. Three months after, VP shunt insertion decreased ventricular volume was the only clearly significant result (p value 0.0001). Even though a detailed volumetric study shows several significant differences, volumetric analysis as a standalone method does not provide a simple diagnostic biomarker, nor does it shed a light on an unknown NPH aetiology [12)].

2018

Thirty subjects with iNPH underwent both CBF SPECT and MRI. After normalization, voxel-wise two-sample t tests between patients and 11 normal controls were conducted to compare the regional

alteration in the gray matter density and rCBF.

The rCBF reduction and the gray matter decrease were seen in almost similar regions surrounding Sylvian fissure, the left parietotemporal region and frontal lobes, whereas they did not find rCBF increase at the top of the high convexity, where the increase of the gray matter density was the highest ($p < 0.05$).

This study showed regional associations and dissociations between the relative gray matter density and rCBF in patients with iNPH [13].

Subramanian et al., reviewed the Idiopathic normal pressure hydrocephalus outcome who underwent ventriculoperitoneal shunt surgery between January 2012 and March 2016. Semi-structured telephone interviews were conducted with 31 patients. Interviews were analyzed using the principles of grounded theory.

Thirty-one patients who underwent shunt surgery for iNPH were interviewed to reach saturation of themes. Seven themes were identified: 1) long preoperative course causes morbidity; 2) the decision to have shunt surgery is easy to make; 3) patients primarily desire to gain independence; 4) patients display variable levels of anxiety; 5) comorbid conditions interfere with postoperative assessment; 6) patients stand by their decision to have shunt surgery; 7) outside information is utilized prior to surgery.

Patients often present to the neurosurgeon frustrated and desperate after a long preoperative course. It is important to acknowledge the uncertainty regarding diagnosis and response to shunting when counseling patients. Comorbid conditions interfere with the ability to assess progression of iNPH and the effectiveness of the shunt. Patient caregivers play a large role in decision-making and clinical course, and should be included when counseling patients [14].

Kotagal et al., from the University of Michigan, United States; Veterans Affairs Ann Arbor Health System (VAAAHS), conducted a retrospective review of 162 consecutive patients who have undergone work-up over a 47 month time period (2/2014-12/2017). Of these, 22 ultimately underwent neurosurgical ventricular shunt surgery as treatment for NPH. Clinical records were reviewed for serious adverse event (SAE)s categorized as possibly/probably/definitely related to NPH surgery.

In 10/22 (45.5%) operated subjects, there were 11 qualifying SAEs over this 3-year period: 1 central nervous system infections, 4 subdural hematomas, 2 seizures resulting in hospitalization, 1 catheter malfunction, 2 perioperative AEs, and 1 death of uncertain cause. Eight SAEs were coded as probably/definitely related. Six occurred >3 months from the time of surgery.

SAEs following NPH surgery are common. Additional studies are needed to determine the long-term safety of NPH surgery in older adults [15].

A cohort of 536 patients with possible NPH from a defined population with a median follow-up time of 5.1 years (range 0.04-19.9) was included in a study. Patients were evaluated by brain imaging and intraventricular pressure monitoring with a brain biopsy immunostained against amyloid-β and

hyperphosphorylated tau. Hospital records were reviewed for vascular diseases and type 2 diabetes mellitus (T2DM). Death certificates and yearly population of the catchment area were obtained from national registries.

A total of 283 patients had a clinical diagnosis of iNPH leading to a median annual incidence of 1.58 iNPH patients per 100,000 inhabitants (range 0.8-4.5). Alzeimer's disease-related brain biopsy findings were less frequent in iNPH compared to the non-iNPH patients ($p<0.05$). An overrepresentation of hypertension (52% vs. 33%, $p<0.001$) and T2DM (23% vs. 13%, $p=0.002$) was noted in iNPH patients. Age (hazards ratio (HR) 1.04/year, 95% confidence interval (CI) 1.03-1.06, $p<0.001$) and T2DM (HR 1.63, 95% CI 1.23-2.16, $p<0.001$) increased the risk of death in the iNPH patients and in the total population. iNPH was associated with decreased risk of death (HR 0.63, 95% CI 0.50-0.78, $p<0.001$). The most frequent causes of death were cardiovascular and cerebrovascular disease. Dementia as a cause of death was more common in non-iNPH patients (27% vs. 10%, $p<0.001$).

Hypertension and T2DM are common in iNPH and the latter causes excess mortality in the affected patients [16].

2017

Twenty-five participants (sixteen NPH patients and nine healthy controls) underwent DTI, pre-operatively and at two weeks post-intervention in patients.

Keong et al. interrogated 40 datasets to generate a full panel of DTI measures and corroborated findings with plots of isotropy (p) vs. anisotropy (q).

Concurrent examination of DTI measures revealed distinct profiles for NPH patients vs. controls. PQ plots demonstrated that patterns of injury occupied discrete white matter districts. DTI profiles for different white matter tracts showed changes consistent with i) predominant transependymal diffusion with stretch/ compression, ii) oedema with or without stretch/ compression and iii) predominant stretch/ compression. Findings were specific to individual tracts and dependent upon their proximity to the ventricles. At two weeks post-intervention, there was a 6·7% drop in axial diffusivity ($p = 0·022$) in the posterior limb of the internal capsule, compatible with improvement in stretch/ compression, that preceded any discernible changes in clinical outcome. On PQ plots, the trajectories of the posterior limb of the internal capsule and inferior longitudinal fasciculus suggested attempted 'round trips'. i.e. return to normality.

DTI profiling with p:q correlation may offer a non-invasive biomarker of the characteristics of potentially reversible white matter injury [17].

Hickman et al. reviewed the medical records of 529 patients who underwent shunt placement for iNPH at their institution between July 2001 and March 2015. Variables associated with shunt-responsive iNPH were identified using bivariate and multivariate analyses. Detailed alcohol consumption information was obtained for 328 patients and was used to examine the relationship between alcohol and shunt-responsive iNPH. A computerized patient registry from 2 academic medical centers was queried to determine the prevalence of alcohol abuse among 1665 iNPH patients.

Bivariate analysis identified associations between shunt-responsive iNPH and gait difficulty (OR 4.59, 95% CI 2.32-9.09; p < 0.0001), dementia (OR 1.79, 95% CI 1.14-2.80; p = 0.01), incontinence (OR 1.77, 95% CI 1.13-2.76; p = 0.01), and alcohol use (OR 1.98, 95% CI 1.23-3.16; p = 0.03). Borderline significance was observed for hyperlipidemia (OR 1.56, 95% CI 0.99-2.45; p = 0.054), a family history of hyperlipidemia (OR 3.09, 95% CI 0.93-10.26, p = 0.054), and diabetes (OR 1.83, 95% CI 0.96-3.51; p = 0.064). Multivariate analysis identified associations with gait difficulty (OR 3.98, 95% CI 1.81-8.77; p = 0.0006) and alcohol (OR 1.94, 95% CI 1.10-3.39; p = 0.04). Increased alcohol intake correlated with greater improvement after CSF drainage. Alcohol abuse was 2.5 times more prevalent among iNPH patients than matched controls.

Alcohol consumption is associated with the development of shunt-responsive iNPH [18].

A method was developed for the computerized volumetric assessment of the intracranial cerebrospinal fluid (CSF) distribution. The study involved 62 patients differentiated into two groups: with CSF resorption disorders (normal pressure hydrocephalus - 30 patients) and without CSF resorption disorders (various types of brain atrophy - 32 patients). The goal of the study was to ascertain whether the assessment, depending on the linear discriminant analysis of volumetric brain features, could be an effective tool differentiating the two groups. Volumetric measurements were performed using VisNow software. For each patient, five features were determined and subjected to discriminant analysis: CSF volume in the subarachnoid space and basal cisterns (SV), CSF volume in the intracranial ventricular system (VV), brain volume (BV), total intracranial CSF volume (FV), and total intracranial volume (TV). Discriminant analysis enables the achievement of a high percentage of correct classification of patients to the appropriate group determined on the result of a lumbar infusion test. The discriminator, based on three features: BV, SV, and VV, showed a complete separation of the groups; irrespective of age. The squared Mahalanobis distance was 70.8. The results confirmed the applicability of the volumetric method. Discriminant analysis seems a useful tool leading to the acquisition of a computer-aided method for the differential diagnosis of CSF resorption disorders [19].

Retrospective analysis of clinical records of all patients over the age of 80 years, who presented to the Victor Horsley Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, Queen Square, London between 2006 and 2016. Results were analysed for co-morbidities, immediate and delayed complications, change in mobility/cognitive function post shunting of hydrocephalus.

39 patients (24 male, 15 female) met criteria. Mean [SD] age at the time of shunt insertion was 84 years (+/- 3.22) (range 80-94). No patients developed immediate CSF infection or sub-dural collection, or extended length of stay due to surgical or anaesthetic complications. There were no peri-operative or anaesthetic complications. 4 patients required a delayed surgical revision to encourage greater CSF drainage. 3 patients went on to develop delayed subdural haematoma, 1 of which was associated with trauma, 2 through overdrainage. 1 patient experienced poor post-operative wound healing and subsequently underwent removal of shunt. Of the 34 patient followed up, 27 patients (79.4%) improved in their mobility. (64.7%) patients/families reported symptomatic improvement in their cognition and memory. 6 (17.7%) patients did not experience an improvement in either mobility or cognitive function.

The data supports the assertion that, with proper patient selection, shunting of the over 80s with iNPH

is a safe and effective procedure [20].

2016

Twelve of 56 patients with NPH-like symptoms presented with morphological aqueductal stenosis (AS) (21.4 %). Patent aqueduct and non-patent aqueduct groups had similar values of mean opening lumbar pressure (8.2 vs. 8.1 mmHg), and mean opening pulse amplitude (3.1 vs. 2.9 mmHg). Mean pressure in the plateau stage (28.6 vs. 23.2 mmHg), and mean pulse amplitude in the plateau stage (12.5 vs. 10.6 mmHg) were higher in the patent aqueduct group. These differences were not statistically significant. Only Rout was significantly higher in the patent aqueduct group (13.6 vs. 10.1 mmHg/ml/min). One-third of NPH patients with AS presented Rout >12 mmHg/ml/min.

No differences in mean pressure or pulse amplitude during basal and plateau epochs of the lumbar infusion test in NPH patients were detected, regardless of aqueductal patency. However, Rout was significantly higher in patients with patent aqueduct [21].

Bir et al., retrospectively reviewed the clinical notes of 2001 patients with adult-onset hydrocephalus who presented to Louisiana State University Health Sciences Center within a 25-year span. Significant differences between the groups were analyzed by a chi-square test; $p < 0.05$ was considered significant.

The overall mean (± SEM) incidence of adult hydrocephalus in this population was 77 ± 30 per year, with a significant increase in incidence in the past decade (55 ± 3 [1990-2003] vs 102 ± 6 [2004-2015]; $p < 0.0001$). Hydrocephalus in a majority of the patients had a vascular etiology (45.5%) or was a result of a tumor (30.2%). The incidence of hydrocephalus in different age groups varied according to various pathologies. The incidence was significantly higher in males with normal-pressure hydrocephalus ($p = 0.03$) or head injury ($p = 0.01$) and higher in females with pseudotumor cerebri ($p < 0.0001$). In addition, the overall incidence of hydrocephalus was significantly higher in Caucasian patients ($p = 0.0002$) than in those of any other race.

Knowledge of the demographic variations in adult-onset hydrocephalus is helpful in achieving better risk stratification and better managing the disease in patients. For general applicability, these results should be validated in a large-scale meta-analysis based on a national population database [22].

A detailed screening process included neurological, neurosurgical and neuropsychological evaluations, followed by cerebrospinal fluid (CSF) tap test (TT) and resistance outflow (Ro) measurement. Outcome was evaluated through the Japanese NPH grading scale-revised (JNPHGSR) and the motor (third) section of the Unified Parkinson's Disease Rating Scale (UPDRS-m). Friedman's analysis of variance with Wilcoxon post-hoc test was used to evaluate the difference in JNPHGSR and UPDRS-m scores between pre-treatment and follow-up (12 months) in the two groups, while Kruskal-Wallis statistic and post-hoc Mann-Whitney test was used to compare the change in JNPHGSR and UPDRS-m scores between the two groups.

32/54 (59%) patients (mean age 73.2) screened in 36 months met the inclusion criteria, but only 30 were enrolled (two refused surgery), 15 in each group. Preoperative 123I-Ioflupane-cerebral SPECT (DaTSCAN) revealed striatal dopaminergic deficit in 14/30 patients (46.5%). At the final 12 months

follow-up, both groups improved JNPHGSR and UPRDS-m scores. The UPDRS-m score improvement was significant in both groups, but greater in group A (p0.003); JNPHGSR score improvement was similar in the two groups.

iNPH associated with parkinsonism may be a frequent finding. In these cases, patients may benefit from VP shunt plus dopamine oral therapy [23)].

From 2008 to 2013, consecutive patients diagnosed with INPH based on clinical and radiological criteria were included in a single-centre study. All patients received programmable-valve ventriculoperitoneal shunts. Outcome measures were assessed at baseline, 3, 6 and 12months post-operatively. Outcomes included gait time and scores on the Unified Parkinson's Disease Rating Scale part III (UPDRS-III), the Addenbrooke's Cognitive Examination Revised (ACE-R) and the Mini-Mental State Examination (MMSE). Thresholds for improvements were set a priori as ⩾20% decrease in gait time, ⩾10point decrease in UPDRS-III score, ⩾5point increase in ACE-R score and ⩾2point increase in MMSE score at last follow-up. The proportion of patients improving varied between measures, being gait time (60%), UPDRS-III (69%), MMSE (63%), and ACE-R (56%). Overall, improvement in at least one outcome measure was observed in 85% of patients and 38% improved in gait time, UPDRS-III score and cognitive scores. Only 15% of patients experienced no improvement on any measure. This study demonstrates that the majority of INPH patients can sustain improvements in multiple symptoms up to 12months after shunting [24)].

Vakili et al., conducted a retrospective review of 393 cases of iNPH involving patients treated with ventriculoperitoneal shunting. The duration of symptoms prior to the operative intervention was recorded. The following outcome variables were assessed at baseline, 6 months postoperatively, and at last follow-up: gait performance, urinary continence, and cognition.

The patients' median age at shunt placement was 74 years. Increased symptom duration was significantly associated with worse gait outcomes (relative risk (RR) 1.055 per year of symptoms, p = 0.037), and an overall absence of improvement in any of the classic triad symptomology (RR 1.053 per year of symptoms, p = 0.033) at 6 months postoperatively. Additionally, there were trends toward significance for symptom duration increasing the risk of having no 6-month postoperative improvement in urinary incontinence (RR 1.049 per year of symptoms, p = 0.069) or cognitive symptoms (RR 1.051 per year of symptoms, p = 0.069). However, no statistically significant differences were noted in these outcomes at last follow-up (median 31 months). Age stratification by decade revealed that prolonging symptom duration was significantly associated with lower Mini-Mental Status Examination scores in patients aged 60-70 years, and lack of cognitive improvement in patients aged 70-80 years.

Patients with iNPH with longer duration of preoperative symptoms may not receive the same short-term benefits of surgical intervention as patients with shorter duration of preoperative symptoms. However, with longer follow-up, the patients generally reached the same end point. Therefore, when managing patients with iNPH, it may take longer to see the benefits of CSF shunting when patients present with a longer duration of preoperative symptoms [25)].

Radovnický et al., analysed 1.5-T MRI scans of patients fulfilling the criteria of probable or possible iNPH and positive supplementary tests before and after surgery (ventriculo-peritoneal shunt). FA was measured in the anterior and posterior limb of the internal capsule (PLIC) and in the corpus callosum. Patients were divided into the Disproportionately enlarged subarachnoid space hydrocephalus (DESH) and non-DESH group. These data were also compared to FA values in the control group.

Twenty-seven patients and 24 healthy controls were enrolled. DESH was present in 15 patients and lacking in 12. Twenty-three iNPH patients were shunt responders (85.2 %), and 4 were non-responders (14.8 %). All patients in the DESH group were shunt responders. In the non-DESH group, eight patients were responders (66.7 %). A significant difference between the DESH and non-DESH group was found in the FA of the PLIC. The mean value of FA in the PLIC was 0.72 in the DESH group and 0.66 in the non-DESH group. After the surgery FA decreased in both groups. In the DESH iNPH group FA PLIC decreased to 0.65 and in the non-DESH iNPH group to 0.60. In the healthy controls, the mean FA in the PLIC was 0.58.

DESH on MRI scans is related to a higher FA in the PLIC with a decrease after the surgery. It reflects a more severe compression of the white matter than in non-DESH patients or healthy volunteers. DESH patients had better outcome than non-DESH patients. This study confirmed the importance of DESH as a supportive sign for iNPH [26].

Eighty-three patients with iNPH (age 60 to 85 years) who presented with ventriculomegaly and high-convexity and medial subarachnoid space tightness on MR images were recruited from 20 neurological or neurosurgical centers in Japan between March 1, 2010, and October 19, 2011. The primary outcome was the modified Rankin Scale (mRS) score 1 year after surgery, and the secondary outcome included scores on the iNPH grading scale (iNPHGS). A previously conducted VPS cohort study with the same inclusion criteria and primary and secondary end points was used as a historical control.

The proportion of patients who achieved a favorable outcome (i.e., improvement of at least 1 point in their mRS score) was 63% (95% CI 51%-73%) and was comparable to values reported with VPS implantation (69%, 95% CI 59%-78%). Using the iNPHGS, the 1-year improvement rate was 75% (95% CI 64%-84%) and was comparable to the rate found in the VPS study (77%, 95% CI 68%-84%). The proportion of patients experiencing serious adverse events (SAEs) and non-SAEs did not differ significantly between the groups at 1 year after surgery (SAEs: 19 [22%] of 87 LPS patients vs 15 [15%] of 100 VPS patients, p = 0.226; non-SAEs: 24 [27.6%] LPS patients vs 20 [20%] VPS patients, p = 0.223). However, shunt revisions were more common in LPS-treated patients than in VPS-treated patients (6 [7%] vs 1 [1%]).

The efficacy and safety rates for LPSs with programmable valves are comparable to those for VPSs for the treatment of patients with iNPH. Despite the relatively high shunt failure rate, an LPS can be the treatment of choice because of its minimal invasiveness and avoidance of brain injury [27].

In a prospective double blind study, randomized controlled trial, double-center study on patients with iNPH, a ventriculoperitoneal shunt with an adjustable Codman Hakim programmable valve was implanted in 68 patients randomized into 2 groups.

In 1 group (the 20-4 group) the valve setting was initially set to 20 cm H2O and gradually reduced to 4 cm H2O over the course of the 6-month study period. In the other group (the 12 group), the valve

was kept at a medium level of 12 cm H2O during the whole study period. All patients were clinically evaluated using 4 tests preoperatively as well as postoperatively at 1, 2, 3, 4, and 6 months. The test scores between the 2 groups (20-4 and 12) were compared for each clinical evaluation.

Fifty-five patients (81%) were able to complete the study. There were no significant differences between the 2 groups (20-4 and 12) preoperatively or at any time postoperatively. Both groups exhibited significant clinical improvement after shunt insertion at all valve settings compared with the preoperative score, with the greatest improvement observed at the first postoperative evaluation. The clinical improvement was significant within the first 3 months, and thereafter no significant improvement was seen in either group.

Gradual reduction of the valve setting from 20 to 4 cm H2O did not improve outcome compared with a fixed valve setting of 12 cm H2O. Improvement after shunt surgery in iNPH patients was evident within 3 months, irrespective of valve setting [28].

Forty-four patients with normal pressure hydrocephalus (23 idiopathic and 21 secondary cases) were included in a prospective observational study. The male:female sex ratio was 1.44, the age range was 21-87 years (mean age 64.3 years), and the range of the follow-up period was 1-3 years (mean 20 months). Patients were implanted with a Sophy SU8 adjustable-pressure valve as the ventriculoperitoneal shunt. The phase shifts of otoacoustic emissions in response to body tilt were measured preoperatively, immediately postoperatively, and at 3-6 months, 7-15 months, 16-24 months, and more than 24 months postoperatively. Three groups were enrolled: Group 1, 19 patients who required no valve opening-pressure adjustment; Group 2, 18 patients who required valve opening-pressure adjustments; and Group 3, 7 patients who required valve replacement.

In Group 1, phase shift, which was positive before surgery, became steadily negative after surgery and during the follow-up. In Group 2, phase shift, which was positive before surgery, became negative immediately after surgery and increasingly negative after a decrease in the valve-opening pressure. In Group 3, phase shift was positive in 6 cases and slightly negative in 1 case before revision, but after revision phase shift became significantly negative in all cases.

Otoacoustic emissions noninvasively reflect cerebrospinal fluid shunt function and are impacted by valve-opening pressure adjustments. Otoacoustic emissions consistently diagnosed shunt malfunction and predicted the need for surgical revision. The authors' diagnostic test, which can be repeated without risk or discomfort by an unskilled operator, may address the crucial need of detecting valve dysfunction in patients with poor clinical outcome after shunt surgery [29].

An observational cohort study included all patients with iNPH managed during the years 2002-2012 in whom overnight intracranial pressure monitoring was part of the preoperative work-up. Clinical data were retrieved from a quality registry and ICP scores from a pressure database.

The study included 472 patients, 316 in the surgery group and 156 in the nonsurgery group. Among those treated surgically, 278 (90%) showed clinical improvement (Responders) whereas 32 (10%) had no improvement (Nonresponders). Among Responders, only about one third reached the best clinical scores; moreover, the difference in clinical score between Responders and Nonresponders declined with time after surgery, particularly after 3-4 years. The surgery was accompanied by acute

intracranial hematomas in 11 patients (3.5%), of whom 4 (1.3%) died. Survival (age at death) was significantly greater among the Responders than in Nonresponders. Although the static ICP was normal in all patients, the pulsatile ICP was significantly greater in Responders than in Non-responders.

The pulsatile ICP was greater in shunt Responders than Nonresponders. Although the clinical improvement declined over time and the majority did not experience complete relief of symptoms, shunt Responders lived significantly longer than Nonresponders. The present observations suggest that the current surgical treatment regimens for iNPH (primarily shunt surgery) address only some aspects of the disease process, in particular the aspect of brain water disturbance [30].

2015

In a retrospective cohort study, Kojoukhova et al evaluated brain CT or MRI scans of 390 patients with suspected iNPH. Based on a 24-h intraventricular pressure monitoring session, patients were classified into a non-NPH (n = 161) or probable iNPH (n = 229) group. Volumes of cerebrospinal fluid compartments (lateral ventricles, sylvian and suprasylvian subarachnoid spaces and basal cisterns) were visually assessed. Disproportionally enlarged subarachnoid spaces, flow void, white matter changes, medial temporal lobe atrophy and focally dilated sulci were evaluated. Moreover, we measured quantitative markers: Evans' index (EI), the modified cella media index, mean width of the temporal horns and callosal angle.

iNPH was more likely in patients with severe volumetric disproportion between the suprasylvian and sylvian subarachnoid spaces than in those without disproportion (OR 7.5, CI 95 % 4.0-14.1, $P < 0.0001$). Mild disproportion (OR 2.6, CI 95 % 1.4-4.6, $P = 0.001$) and narrow temporal horns (OR per 1 mm 0.91, CI 95 % 0.84-0.98, $P = 0.014$) were also associated with an iNPH diagnosis. Other radiological markers had little association with the iNPH diagnosis in the final combined multivariate model. Interestingly, EI was higher in non-NPH than iNPH patients (0.40 vs. 0.38, $P = 0.039$). Preoperative radiological markers were not associated with shunt response.

Visually evaluated disproportion was the most useful radiological marker in iNPH diagnostics. Narrower temporal horns also supported an iNPH diagnosis, possibly since atrophy was more pronounced in the non-NPH than iNPH group [31].

A study included 29 patients with a mean age of 73.9 years; 62.1% were male and 65.5% had hypertension. Clinical improvement (complete or partial) was observed in 58% after one year and in 48% by the end of the follow-up period (mean follow-up time was 37.8 months). Older age, presence of hypertension, and surgery-related complications were more prevalent in the group responding poorly to treatment. One patient died, 20.7% experienced severe complications, and 69% were dependent (mRS ≥ 3) by the end of the follow-up period. Age at diagnosis was independently associated with poorer clinical response at one year and a higher degree of dependency by the end of follow-up.

Symptomatic benefits offered by VPS were partial and transient; treatment was associated with a high complication rate and poor functional outcomes in the long term, especially in the oldest patients [32].

2010

Fifty-one patients were included after confirmation of the diagnosis by extensive clinical and diagnostic investigations. Surgery included ventriculoatrial or ventriculoperitoneal shunting with differential pressure valves in the majority of patients. For each of the cardinal symptoms, postoperative outcome was assessed separately with the Krauss Improvement Index, yielding a value between 0 (no benefit) and 1 (optimal benefit) for the overall outcome.

Mean age at surgery was 70.2 years (range, 50-87 years). Thirty patients were women, and 21 were men. Short-term (18.8 +/- 16.6 months) follow-up was available for 50 patients. The Krauss Improvement Index was 0.66 +/- 0.28. Long-term (80.9 +/- 51.6 months) follow-up was available for 34 patients. The Krauss Improvement Index was 0.64 +/-0.33. Twenty-nine patients died during the long-term follow-up at a mean age of 75.8 years (range, 55-95 years). The major causes of death were cardiovascular disorders: cardiac failure (n = 7) and cerebral ischemia (n = 12). Other causes were pneumonia (n = 2), acute respiratory distress syndrome (n = 1), pulmonary embolism (n = 1), cancer (n = 2), renal failure (n = 1), and unknown (n = 3). There was no shunt-related mortality.

Idiopathic normal pressure hydrocephalus patients may benefit from shunting over the long term when rigorous selection criteria are applied. Shunt-related mortality is negligible. The main cause of death is vascular comorbidity [33)].

2006

A total of 54 patients with normal-pressure hydrocephalus (NPH) were treated; 30 patients received an Aesculap-Miethke GA-Valve (Miethke GAV; counterbalancer), and in 24 patients an Aesculap-Miethke Dual-switch-Valve (DSV; switcher) was implanted. The opening pressure of the posture-independent valve was 5 cm H2O in both devices. The outcome was clearly better with the usage of the GAV than with the DSV. The frequency and severity of complications was pronounced in the DSV group. We recommend the Aesculap-Miethke-GAV valve with a low opening pressure in a posture-independent valve for patients with NPH [34)]

1998

In 17 patients with IAHS polysomnographic investigations were performed before and after lumbar CSF drainage and after shunt operation.

RESULTS: Baseline investigations documented a high prevalence of sleep related obstructive respiratory events (respiratory disturbance index >10 in 65% of the patients) and impaired sleep structure. There was no correlation between respiratory disturbance index and CSF pressure. Minimum oxygen saturation was highly correlated with cognitive function. Neither lumbar CSF drainage nor shunting alleviated the respiratory disturbance index. REM and delta sleep increased initially after shunting but there was no sustained effect on sleep quality.

CONCLUSIONS: Sleep disordered breathing is a prevalent finding in patients with IAHS. The shortcoming of CSF drainage to improve sleep disordered breathing either transiently or permanently

implies that sleep disordered breathing is a coexistent condition, or an irreversible consequence of the hydrocephalus, with a potential of causing additional dysfunction in IAHS [35].

1997

Tanaka et al., studied the cerebral blood flow (CBF) and vascular response to acetazolamide in the white matter, cortex, and thalamus of 21 patients with normal pressure hydrocephalus, comparing patients who improved clinically after shunting with those who did not. We used xenon-enhanced computed tomography for the CBF measurements.

Preoperatively, both groups had globally reduced CBF, but the reduction was more pronounced in the unimproved patients. The vascular response was impaired only in the white matter of the patients who improved later. After shunting, restoration of CBF, more marked in the white matter, and recovery of vascular response in the white matter paralleled clinical improvement and a reduction in ventricular dilation and periventricular lucency on computed tomographic scans in nine patients. The CBF reduction, however, deteriorated in the 12 patients who did not improve clinically.

They conclude that the underlying disease in the improved patients was ischemia, with a loss of autoregulatory capacity in the periventricular white matter caused by cerebrospinal fluid diffusion. Those who did not improve had irreversible brain damage in which the CBF reduction was secondary to metabolic depression and autoregulation was preserved. We also conclude that patients suspected of having normal pressure hydrocephalus will improve clinically after shunting if preoperative hemispheric CBF is greater than 20 ml/100 g per minute and the vascular response to acetazolamide is impaired only in the periventricular white matter. They will not improve, however, if the preoperative CBF is less than 20 ml/100 g per minute and the vascular response to acetazolamide is intact [36].

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