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iNPH Guideline

Guidelines for Management of Idiopathic Normal Pressure Hydrocephalus: Second Edition

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Abstract

Among the various disorders manifesting dementia, gait disturbance, and urinary incontinence in the elderly population, idiopathic normal pressure hydrocephalus (iNPH) is becoming of great importance. After the publication of the first edition of the Guidelines for Management of Idiopathic Normal Pressure Hydrocephalus in 2004 (the English version was published in 2008), clinical awareness of iNPH has risen dramatically, and the number of shunt surgeries has increased rapidly across Japan. Clinical and basic research on iNPH has increased significantly, and more high-level evidence has since been generated. The second edition of the Japanese Guidelines was thus published in July 2011, to provide a series of timely evidence-based recommendations related to iNPH. The revision of the Guidelines has been undertaken by a multidisciplinary expert working group of the Japanese Society of Normal Pressure Hydrocephalus in conjunction with the Japanese Ministry of Health, Labour and Welfare research project on ''Studies on the epidemiology, pathophysiology, and treatment of normal pressure hydrocephalus.'' This English version of the second edition of the Guidelines was made to share these ideas with the international community and to promote international research on iNPH.

Key words: clinical guideline, idiopathic normal pressure hydrocephalus, diagnosis, treatment

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CHAPTER I: CREATING THE GUIDELINES

1. Introduction

With the rapid aging of Japanese society, medical care of the elderly has become an important social issue. Among the various disorders manifesting dementia, gait disturbance, and urinary incontinence in the elderly population, normal pressure hydrocephalus (NPH) is becoming of great importance.

NPH, which was first reported by Hakim and Adams in 1965,[1,3] attracted attention as a syndrome of the clinical triad of dementia, gait disturbance, and urinary incontinence, with ventricular dilation and normal cerebrospinal fluid (CSF) pressure, and these symptoms could be reversed by CSF shunt surgery. NPH is classified into secondary NPH (sNPH) of known etiology, such as subarachnoid hemorrhage and meningitis, and idiopathic NPH (iNPH) of unknown etiology. In contrast to sNPH, iNPH is difficult to distinguish from neurological or non-specific conditions causing locomotor, cognitive, and urinary disorders in the elderly. Ventriculomegaly on cranial computed tomography (CT) and magnetic resonance imaging (MRI) is sometimes misinterpreted as brain atrophy, and iNPH has been misdiagnosed as Alzheimer's disease or other neurodegenerative diseases. In the past, iNPH has been overly emphasized and operated upon as a ''treatable dementia,'' and, as a result, was neglected. The conflation of iNPH and sNPH as communicating hydrocephalus made it difficult to understand iNPH. Although a half century has passed since the first report appeared, the prefix ''idiopathic'' remains to be attached; its etiology and pathomechanism have not yet been elucidated. Even pathological and epidemiological studies are lacking, which are the fundamental approaches used to understand a disease. It is no exaggeration to say that iNPH has not yet benefited from recent advances in neuroscience and biomedicine.

2. History of the Guidelines

In 1996, iNPH was first selected as a main research subject by the Committee for Scientific Research on Intractable Hydrocephalus of the Japanese Ministry of Health, Labour and Welfare (MHLW) (principal investigator: Professor Koreaki Mori, Department of Neurosurgery, Kochi Medical School) during its long history of hydrocephalus research. In consideration of its continuing social importance, the Japanese Society of Normal Pressure Hydrocephalus (JSNPH) was established in 1999 for the purpose of continuing research. At the 3rd board meeting of the JSNPH in 2002, it was decided to create Guidelines for the diagnosis and treatment of iNPH. Members specializing in the fields of neurosurgery, neurology, psychiatry, and clinical epidemiology met and discussed this matter. The first edition of the Guidelines[5] was published in May 2004 after a public consultation and peer review on the draft version of the Guidelines. Our Guidelines were published more than a year before the international guidelines for iNPH by the group of Marmarou.[2,6–9] As there are some differences in emphasis between their guidelines and ours, including diagnostic criteria, to increase worldwide knowledge of our Guidelines, an English version of the 2004 Guidelines, with some updates, was published in 2008 as a supplement issue of *Neurologia medico-chirurgica* with the assistance of the Japan Neurosurgical Society.[4]

After the publication of the first edition of the Guidelines, clinical awareness of iNPH has risen dramatically, and the number of shunt surgeries has rapidly increased across the country. Clinical and basic research on iNPH have increased significantly; a MEDLINE search revealed that the number of articles published between 2003 and 2010 was in excess of those appearing between 1965 and 2002, which were used as the source material for the first edition of the Guidelines. More high-level evidence has since been generated. Therefore, the JSNPH decided that there was a need to revise the Guidelines, and promoted such revision in conjunction with the MHLW research project on ''Studies on the epidemiology, pathophysiology, and treatment of normal pressure hydrocephalus'' (principal investigator: Professor Hajime Arai).

3. Purpose of the Guidelines

The Guidelines for the management of iNPH were created to facilitate a more accurate diagnosis for iNPH in the elderly, to select appropriate patients for whom CSF shunt surgery is effective, and to maintain the long-term effect of shunt surgery. The Guidelines are useful not only for neurosurgeons, neurologists, and psychiatrists, who often treat neurological disorders in the elderly, but also for radiologists, gerontologists, internists, and general practitioners. The English version of the first edition of the Guidelines was published in 2008, and the second edition of the Guidelines was published in Japanese in July 2011. This English version of the second edition was made to show the diagnosis and treatment of iNPH with reference to the socio-

medical background in Japan, to share these ideas with the worldwide community, and to promote international research on iNPH. It is necessary to understand that these Guidelines are not intended to override the diagnosis and treatment decisions of experienced practitioners, and they are not intended as a denial of treatment policies not included in these Guidelines.

4. Methods

As with the first edition, the Guidelines were created in compliance with evidence-based medicine. Initially, all clinical questions related to this syndrome are raised, and a bibliographic search using MEDLINE was carried out to obtain solutions to these problems. In order to minimize bias in selecting publications by investigators, a list was made for each section of diagnosis and therapy utilizing the same search terms as in the first edition and some additional ones related to neuroimaging, biomarkers, and rehabilitation: 1429 publications were identified in the diagnosis section (Table 1) and 945 were identified in the treatment section (Table 2), which represent a two-fold increase from the first edition.

The literature was selected as follows: 1) we screened candidate papers that were relevant to the research questions by reviewing the abstract or text, whenever necessary, of those identified in the database search; 2) we assessed the level of evidence of the selected papers through a critical review; 3) we adopted those papers with at least level 4 evidence according to the classification of the Oxford Centre for Evidence-based Medicine (Table 3); and 4) we gave priority to the highest-level evidence when there was disagreement among the reports. Studies dealing with iNPH were the principal sources, and those dealing with both iNPH and sNPH, or that did not identify these two, were considered to be lower-level evidence. Case reports were adopted only when serious side effects or accidents were dealt with. Publications that did not match with the theme of the individual section, but contained necessary information, were adopted, with their evidence level described as ''non-classifiable.''

Table 1 MEDLINE search strategy for the diagnosis

Search	Most recent queries	Results
#37	Search #33 OR #34 OR #35 OR #36	1429
#36	Search #3 AND #30 AND ''pubstatusaheadofprint''	6
#35	Search #3 AND #29 AND ''pubstatusaheadofprint''	4
#34	Search #3 AND #30 Limits: All Adult: 19+ years, Publication Date from 1965 to 2010/11/22	1175
#33	Search #3 AND #29 Limits: All Adult: 19+ years, Publication Date from 1965 to 2010/11/22	791
#32	Search #3 AND #30	1959
#31	Search #3 AND #29	1093
#30	Search #23 OR #24 OR #25 OR #26 OR #27 OR #28	756900
#29	Search #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	1975158
#28	Search ''cerebrospinal fluid'' OR ''CSF''	117025
#27	Search cysternograph*	26
#26	Search ''cerebral blood flow'' OR ''CBF''	25633
#25	Search ''single photon'' OR ''SPECT''	30571
#24	Search ''magnetic resonance'' OR ''MRI''	412146
#23	Search ''computed tomography'' OR ''CT''	256542
#22	Search mmse	4498
#21	Search apath*	3209
#20	Search abulia	93
#19	Search depressi*	261055
#18	Search neuropsychiatr*	21449
#17	Search incontinen*	39042
#16	Search gait	26290
#15	Search working memory	23519
#14	Search executi*	40062
#13	Search attenti*	219679
#12	Search frontal lobe	52046
#11	Search frontal function	47449
#10	Search neuropsychologi*	65099
#9	Search cogniti*	202423
#8	Search amnes*	20974
#7	Search dementi*	72449
#6	Search ''neurologic manifestations'' [MESH]	674599
#5	Search ''behavioral sciences'' [MESH]	189949
#4	Search ''mental disorders'' [MESH]	783013
#3	Search #1 AND #2	2693
#2	Search hydrocephal*	23420
#1	Search normal pressure OR normotensive OR low pressure	181043

CBF: cerebral blood flow, CSF: cerebrospinal fluid, CT: computed tomography, MRI: magnetic resonance imaging, SPECT: single photon emission computed tomography.

Table 2 MEDLINE search strategy for the treatment

Search	Most recent queries	Results
#15	Search #11 OR #12 OR #13 OR #14	945
#14	Search #3 AND #7 AND ''pubstatusaheadofprint''	1
#13	Search #3 AND #8 AND ''pubstatusaheadofprint''	7
#12	Search #3 AND #7 Limits: All Adult: 19+ years, Publication Date from 1965 to 2010/11/22	42
#11	Search #3 AND #8 Limits: All Adult: 19+ years, Publication Date from 1965 to 2010/11/22	920
#10	Search #3 AND #7	60
#9	Search #3 AND #8	1426
#8	Search #4 OR #5 OR #6	56680
#7	Search rehabilitation OR physical therapy	418386
#6	Search shunt OR shunts OR shunting	55655
#5	Search ventriculostom*	1778
#4	Search ''cerebrospinal fluid shunts'' [MESH]	8733
#3	Search #1 AND #2	2693
#2	Search hydrocephal*	23420
#1	Search normal pressure OR normotensive OR low pressure	181043

Table 3 Oxford Centre for Evidence-based Medicine—Levels of Evidence*

Level	Therapy/Prevention, Etiology/Harm	Diagnosis
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) of Level 1 diagnostic studies; CDR with Level 1b studies from different clinical centers
1b	Individual RCT (with narrow confidence interval)	Validating cohort study with good reference standards or CDR tested within one clinical center
1c	All or none	A diagnostic finding whose specificity is so high that a positive result supports the diagnosis, or a diagnostic finding whose sensitivity is so high that a negative result rules out the diagnosis
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of Level >2 diagnostic studies
2b	Individual cohort study (including low quality RCT, e.g., <80% follow-up)	Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or databases
2c	''Outcomes'' research; ecological studies	
3a	SR (with homogeneity) of case-control studies	SR (with homogeneity) of Level 3b and better studies
3b	Individual case-control study	Non-consecutive study or without consistently applied reference standards
4	Case series (and poor quality cohort and case-control studies)	Case-control study, poor or non-independent reference standards
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or ''first principles''	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or ''first principles''

*Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, and Martin Dawes since November 1998. Updated by Jeremy Howick, March 2009. CDR: clinical decision rule, RCT: randomized controlled trial, SR: systemic review.

The recommendations were classified into the following 5 grades, considering the actual state and benefit in the treatment field in addition to the evidence level: A, Strongly recommended (at least one study of level Ia or Ib); B, recommended (at least one study of level IIa or IIb); C1, can be considered, although scientific evidence is inconclusive; C2, not recommended due to a lack of scientific evidence; and D, not recommended.

The second edition of the Guidelines consisted of 3 parts: text, evidence table, and question and answer which were published in Japanese in July 2011. In this English version, the evidence table and question and answer are omitted due to space limitations.

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CHAPTER II: CONCEPT AND EPIDEMIOLOGY

1. What is iNPH?

iNPH is a clinical syndrome that includes dementia and urinary incontinence in addition to gait disturbance as major manifestations in the absence of preceding disorders, including subarachnoid hemorrhage and meningitis, but with ventricular dilation caused by an impairment of CSF circulation. iNPH develops in elderly patients, and its symptoms usually progress slowly. The symptoms can be improved by appropriate CSF shunt surgery.

The conventional definition of iNPH included the condition that NPH symptoms improved following CSF shunt surgery. However, preoperative diagnosis is impossible by this definition; therefore, ''concept'' is used rather than ''definition'' in these Guidelines.

1-A. Disproportionately enlarged subarachnoid space hydrocephalus

Hydrocephalus is a condition in which there is excessive accumulation of CSF in the brain, primarily in the ventricles. Ventriculomegaly on neuroimaging is the primary requisite for a diagnosis of hydrocephalus. The accumulation of CSF in the subarachnoid spaces had not been considered to be a major finding of hydrocephalus. Kitagaki et al.[21] first reported the MRI findings of narrowed CSF spaces in the high convexity and midline, and increased CSF spaces in the sylvian fissure and basal cistern of iNPH patients using volumetry. The multicenter prospective cohort study named Study of INPH on neurological improvement (SINPHONI) confirmed these findings in iNPH patients. One of the entry criteria of SINPHONI was high convexity tightness on coronal MRI. This study enrolled 100 suspected iNPH patients. All patients had a ventriculoperitoneal shunt with a programmable valve and were followed for up to 1 year after surgery. In this study, the majority of patients showed dilation of the sylvian fissure in association with tight high convexity. This peculiar contrast in the subarachnoid space in iNPH patients led us to call it disproportionately enlarged subarachnoid space hydrocephalus (DESH)[15] (Fig. 1).

On the basis of the SINPHONI multicenter prospective cohort study,[15] iNPH patients with MRI findings of DESH are regarded as a major group among iNPH patients. However, there are some patients without DESH; thus, iNPH can be divided into DESH and non-DESH types. In either case, iNPH can be classified as a communicating hydrocephalus. The pathophysiology of DESH in iNPH patients is important to understand the production and absorption of CSF, but it remains to be clarified.

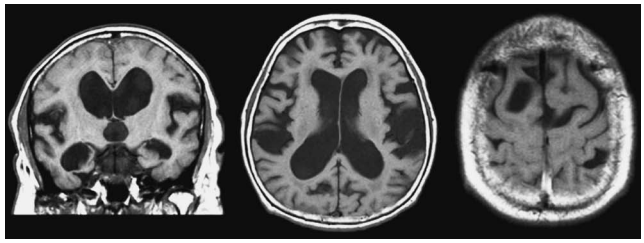

Fig. 1 Magnetic resonance imaging features of disproportionately enlarged subarachnoid space hydrocephalus. The features include tight high convexity and medial subarachnoid spaces and enlarged sylvian fissure associated with ventriculomegaly. Cerebrospinal fluid is distributed disproportionately between the superior and inferior subarachnoid spaces.

1-B. Proposal of new NPH classification

In contrast to iNPH, sNPH develops several months to several years after preceding disorders such as subarachnoid hemorrhage or meningitis, which are known to be acquired. The diagnosis is not difficult since careful follow-up of the patients with preceding disorders will show the development of NPH symptoms and ventriculomegaly within several weeks or months.

In the international iNPH guidelines,[27] as the age at onset was defined as 40 years or older, individuals younger than 60 years in whom occult congenital hydrocephalus manifests in adulthood would be included as iNPH. In fact, a study reported large head size in patients with ''iNPH,''[32] suggesting inclusion of patients with hydrocephalus of congenital or developmental origin. However, in studies including a large number of patients with iNPH, the mean age of onset of iNPH is approximately 75 years, and patients aged in their 40s and 50s are very uncommon.[24,33] Oi et al. first described cases of longstanding overt ventriculomegaly in adults (LOVA), showing severe ventriculomegaly that was associated with macrocephalus and aqueductal stenosis[25] (Fig. 2). They were successfully treated by shunt surgery with a programmable pressure valve or an endoscopic procedure. There are some patients with NPH symptoms in adulthood showing a posterior fossa

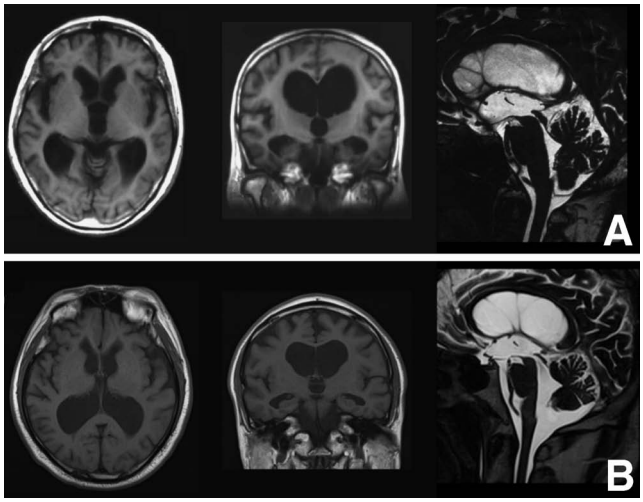

Fig. 2 Magnetic resonance imaging features of longstanding overt ventriculomegaly in adults (LOVA) (A) and hydrocephalus associated with Blake's pouch cyst in adults (B). In both disorders, marked ventriculomegaly and downward bulging of the third ventricle are characteristic. The subarachnoid spaces are neither enlarged nor tightened, and are comparable between the dorsal and ventral sides. In the case of LOVA, stenosis of the aqueduct and lack of expansion of the fourth ventricle are apparent on midsagittal sections.

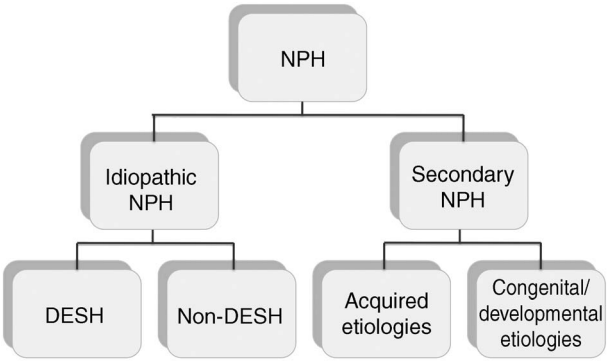

Fig. 3 Classification of normal pressure hydrocephalus (NPH). DESH: disproportionately enlarged subarachnoid space hydrocephalus.

cyst such as Blake's pouch cyst. Blake's pouch cyst is defined by a failure of the embryonic assimilation of the area membranacea anterior within the tela choroidea associated with imperforation of the foramen of Magendie. The patients range from being asymptomatic to showing symptoms of increased intracranial pressure (ICP) and NPH symptoms in adulthood.[7] It is not well understood whether these cystic lesions in the posterior fossa impair the communication between the fourth ventricle and subarachnoid space. There is a case study describing hydrocephalic infants with an extraventricular intracisternal obstruction who were successfully treated with third ventriculostomy.[20] If these symptoms developed in adulthood, a diagnosis of NPH could be established. Although the development of hydrocephalus was congenital or developmental, the development of symptoms can be delayed until young adulthood or old age. If NPH symptoms develop in the elderly, these cases could include NPH. However, such cases were not idiopathic, so were defined as congenital/developmental etiologies in secondary NPH.

If NPH is defined as a shunt-responsive syndrome with NPH symptoms, ventriculomegaly, and normal CSF pressure, the above-stated non-communicating hydrocephalus can be included in NPH. Since cases with LOVA or a Blake's pouch cyst are defined as congenital/developmental etiologies, it could be better to classify them as secondary NPH. Thus, the Guidelines propose a comprehensive classification of NPH as shown in Fig. 3. In this scheme, NPH is classified into idiopathic and secondary. Idiopathic NPH is classified into DESH and non-DESH. Secondary NPH is classified into acquired or congenital/developmental etiologies. To establish the classification of NPH, further studies on CSF production and absorption are necessary.

2. Epidemiology

Patients with iNPH show cognitive impairment, gait disturbance, and/or urinary incontinence, which are non-specific symptoms often seen in the elderly with other diseases. The diagnosis of iNPH requires a CSF examination, which is somewhat invasive. Therefore, most studies on the prevalence of iNPH are based on the number of iNPH patients diagnosed at a hospital or a group of hospitals (hospital-based studies). Conversely, population-based studies, which examine individuals in a general population, have rarely been performed up to the present time. Previous studies differed in terms of the subjects examined (hospital patients vs. community residents) and the diagnostic criteria of iNPH employed (presence or absence of CSF examination and shunt operation); therefore, in a strict sense, it does not seem reasonable to compare the results of such studies. It also remains undetermined whether there are differences in the prevalence and incidence of iNPH between different ethnicities and races.

2-A. Population-based studies on the prevalence of iNPH

MRI-based epidemiological studies on the

prevalence of iNPH have recently been reported in Japan. These studies examined all of the members of a community using brain MRI and estimated the prevalence of ''possible iNPH with MRI support'' in a general Japanese population. As described in the present Guidelines, the term ''possible iNPH with MRI support'' is defined by the MRI features of iNPH (i.e., enlargement of the ventricles and disproportionate narrowing of the subarachnoid space and cortical sulci at the high convexity of the cerebrum) and the presence of one or more symptoms of iNPH. Using these criteria, the prevalence of possible iNPH with MRI support was estimated to be 2.9%[16] and 1.4%[30] in residents aged 65 years or older and 0.5%[17] in those aged 61 years or older. The weighted mean of these 3 studies was 1.1% in the elderly living in a Japanese community. In these studies, all of the participants, with or without symptoms, in a community underwent a brain MRI examination. However, there were some limitations; because of its invasive nature, no CSF examination or tap test was performed. Furthermore, no information was available regarding the shunt operation. Therefore, these studies do not show the prevalence of ''probable'' or ''definite'' iNPH. In spite of these limitations, it can be speculated that there may be even more patients with iNPH, mostly undiagnosed, in a general population than expected from the hospital-based studies described in the next section.

2-B. Hospital-based studies on the prevalence of iNPH

Some previous studies counted the number of NPH patients who had shunt operations in the neurosurgery departments of certain hospitals and estimated the prevalence of NPH among the population that was covered by the hospitals. The only hospital-based study that recruited iNPH patients was performed in Norway.[4] In that study, structured and intensive efforts were directed toward the public and healthcare professionals to recruit patients with iNPH. On the basis of the symptoms, neuroimaging, and opening CSF pressure, the prevalence of iNPH was estimated to be 21.9/100,000 population.

2-C. Other studies on the prevalence of iNPH

One study focused on iNPH and estimated its prevalence as 3.5% among a series of 400 patients who visited a memory clinic[3]; another estimated it as 19% among residents who were suspected of parkinsonism.[31] On the basis of these studies, however, it does not seem possible to estimate the prevalence of iNPH in a general population.

3. Asymptomatic Ventriculomegaly with Features of iNPH on MRI

An MRI-based epidemiological study was carried out on the elderly inhabitants of the Town of Takahata and the City of Sagae, Yamagata Prefecture, Japan. All of the participants, with or without symptoms, underwent a brain MRI examination, and it was found that 1% of the elderly had brain MRI features consistent with iNPH without any neurological symptoms. The condition was called ''asymptomatic ventriculomegaly with features of iNPH on MRI'' (AVIM).[17] During a follow-up period of 4–8 years, 25% of the subjects with AVIM developed dementia and/or gait disturbance, suggesting that AVIM may represent a preclinical stage of iNPH.[17] It remains unknown, however, whether AVIM really develops into shunt-responsive, definite iNPH. The natural course of AVIM is an important issue in the study of iNPH.

4. Risk Factors for iNPH

There are only a few case-control studies on risk factors for iNPH in which hypertension, diabetes mellitus, and a low serum level of high-density lipoprotein cholesterol were indicated as significant risk factors for iNPH.[5,6,13,18,22] Because these are well-known risk factors for vascular diseases, it is considered that vascular changes may be involved in the pathogenesis of iNPH. It has been demonstrated that, during the Valsalva maneuver, iNPH patients showed a significantly greater frequency of retrograde jugular venous flow than control subjects, suggesting a high resistance to CSF outflow in iNPH patients.[23] A higher incidence of glaucomatous disease in iNPH patients than in those without iNPH has been reported, suggesting the possibility of a common, increased neural susceptibility to pressure-related dysfunction underlying both diseases.[6] In the present Guidelines, the age of onset of iNPH is defined as 60 years or older; however, most iNPH patients are older than 70 years of age, indicating that age is an important risk factor for iNPH.

5. Pathology and Etiology of iNPH

5-A. Pathology

As shown in Table 4, various pathological changes have been reported in the brains of iNPH patients: 1) thickening and fibrosis of the leptomeninges and arachnoid membrane, 2) inflammation of the arachnoid granulation, 3) ventricular ependymal disruption, 4) subependymal gliosis, 5) multiple infarcts due to arteriosclerotic and/or hypertensive vascular disease, and 6) pathological changes of Alzheimer's disease (senile plaques and

Table 4 Pathological findings in idiopathic normal pressure hydrocephalus

Author (Year)	Meningeal thickening	Inflammation of arachnoid villi	Subependymal gliosis	AD pathology	Vascular pathology
DeLand et al. (1972)[9]	+	+	+	/	/
Stein and Langfitt (1974)[28]	/	/	/	+	+
Earnest et al. (1974)[11]	−	−	/	/	+
Di Rocco et al. (1977)[10]	+	/	+	+	+
Bech et al. (1999)[1]	+	/	/	+	+
Golomb et al. (2000)[12]	/	/	/	+	/
Bech-Azeddine et al. (2007)[2]	/	/	/	+	+
Hamilton et al. (2010)[14]	/	/	/	+	AA

AA: amyloid angiopathy, AD: Alzheimer's disease.

neurofibrillary tangles).[1,2,9–12,14,28] Different pathological changes or no changes at all were observed in different cases of iNPH; therefore, no pathological basis of iNPH has yet been established. Many studies have also shown no significant correlation between the shunt outcome and the presence of ischemic lesions or Alzheimer-type pathology in the brain, suggesting that the presence of such pathological changes is not necessarily a contraindication for a shunt operation, although this matter should be evaluated further.

5-B. Etiology

As the term ''idiopathic'' implies, the etiology of iNPH remains unknown. Because CSF shunting has a beneficial effect on the neurological symptoms of many iNPH patients, it seems plausible that the disturbance of CSF circulation is involved in the pathogenesis of iNPH. It remains undetermined, however, as to what causes the disturbance of CSF circulation. As described above, no specific or common neuropathological changes of iNPH have been established, implying that a variety of causes can disturb the normal flow of CSF, such as leptomeningeal thickening, sclerotic changes of the vessels, reflux of jugular venous flow, and others may eventually result in ventricular dilation and neurological symptoms consistent with iNPH. Therefore, it is possible that iNPH could be regarded as a ''multietiological clinical entity.''[1,2] However, the possibility is not excluded that the majority of iNPH occurs as a result of a single etiology.

From a genetic point of view, some evidence suggested that a genetic factor may be involved in the etiology or pathogenesis of iNPH. Although rare, sibling cases of NPH have been reported, in which the individuals had clinical features indistinguishable from iNPH.[8,26] More recently, a large family with NPH patients in three generations who had clinical and MRI features that were indistinguishable from iNPH has been reported.[29] It has also been suggested that a copy number variation in a certain region of the genome may play a role as a genetic risk factor for iNPH.[19]

Each hypothesis described above does not exclude the others; one hypothesis may focus on the etiology and pathogenesis of iNPH from a single viewpoint, differently from the others. Further study is needed to clarify the exact etiology and pathogenesis of iNPH.

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CHAPTER III: DIAGNOSIS

1. Clinical Symptoms of iNPH

1-A. Characteristics of gait disturbance

The characteristic triad of gait patterns in iNPH consists of a small-stepped gait, magnet gait, and broad-based gait.[124,125,140] Patients with iNPH walk slowly and unstably.[27,124] Their strides become shorter, and instability becomes more pronounced during turning than during walking in a straight line.[17,89] The foot rotation angles are increased and the strides are variable during walking.[124,125] Freezing of gait sometimes becomes apparent when the patients start walking, walk in a narrow place, and turn around.[98] There is little effect of external cues, including verbal commands or visual markings such as lines, on gait improvement in iNPH. This is different from patients with Parkinson's disease.[125] No learning effect is found in patients with iNPH on gait assessments before CSF removal.[123] The improvement of gait disturbance after CSF removal is characterized by an increased stride length and a decreased number of steps during turning.[27,89] This improvement is larger after shunt surgery than after transient CSF tapping.[111] No improvement is seen in leg elevation or instability.[27,124] Although the underlying pathophysiological mechanisms of gait disturbance are unknown, the striatum[102] and corticospinal tract[44] are reported as the candidate regions for gait disturbance in iNPH patients.

1-B. Characteristics of cognitive impairment (dementia)

Psychomotor speed, attention, and working memory are most frequently defective in patients with mild iNPH.[3,19,30,45,91,98,106,133] Memory is frequently impaired in patients with mild iNPH; however, recognition memory is relatively preserved compared with recall.[102] Verbal fluency is also impaired. These are frontal lobe-related functions. Patients with severe iNPH exhibit overall cognitive impairment.[52] The impairments of psychomotor speed, attention, literal fluency, and executive function are more severe, while the impairments of memory and orientation are milder in patients with iNPH than in those with Alzheimer's disease.[98,106] No learning effect is found in patients with iNPH on cognitive tests before CSF removal.[123] The impairments of verbal memory and psychomotor speed appear more likely to respond to shunt surgery.[133] Overall frontal lobe function and visuoconstructive function can improve after shunt surgery[91,110]; however, they rarely return to the normal level.[46] Conversely, in patients with severe verbal memory impairment, their overall cognitive impairments tend not to improve after shunt surgery. In patients with not only verbal memory impairment but also visuoconstructive impairment, the improvement of cognitive deficits after shunt surgery is less pronounced.[133] Although the underlying pathophysiological mechanisms of cognitive impairment are not well described, cognitive impairment and gait disturbance in iNPH patients could share common underlying mechanisms.[44,98,102] The corpus callosum,[91] striatum,[102] superior frontal gyrus, and medial aspect of the frontal lobe, including the anterior cingulate gyrus,[90] are reported as candidate regions for the cognitive impairment of iNPH patients.

1-C. Characteristics of urinary dysfunction

Characteristics of urinary dysfunction in iNPH include overactive bladder, mainly manifesting as increased nocturnal urinary frequency and urgency urinary incontinence, reduction of the maximum flow rate, increase in the residual volume, and reduction of the bladder capacity on a urodynamic test.[114] In addition, overactive bladder was reported to be significantly correlated with enhancement of parasympathetic nerve activity on power spectral analysis of 24-hour electrocardiography-recorded R-R interval variability, and the variation returned to the normal level after a lumbar puncture test and shunt surgery.[76]

1-D. Incidence of the classical triad

Since there have been no reports on a large-scale population-based cross-sectional or longitudinal study on the incidence of iNPH, the accurate incidence of the classical triad is unknown. Although previous hospital-based studies may not have reflected its accurate incidence because the number of cases was small in all studies, summarizing the main reports in other countries, gait disturbance is the earliest common symptom, which developed in 94–100% of cases, followed by cognitive impairment in 78–98% and urinary dysfunction in 76–83%, and these 3 symptoms developed concomitantly in approximately 60% of cases.[36,71,94,100] In Japan, in a multicenter cohort study on the validity of MRI diagnosis of iNPH involving 100 patients, i.e., the SINPHONI, gait disturbance, cognitive impairment, and urinary dysfunction were noted in 91%, 80%, and 60% of patients, respectively. The complete triad was present in 51% of patients, only gait disturbance in 12%, only

cognitive impairment in 1%, and only urinary dysfunction in 3%.[43]

1-E. Other clinical symptoms

Regarding symptoms other than the classical triad, psychiatric symptoms and abnormal neurological findings have been investigated relatively well. Reportedly, psychiatric symptoms were noted in 88% of patients.[79] Apathy and anxiety were frequently noted in 70% and 25% of patients, respectively, whereas delusion, emotional instability, depressive state, or impatience was observed in more than 10%.[63] On neurological examination, bradykinesia, hypokinesia, paratonic rigidity, glabellar reflex, snout reflex, and palmomental reflex were exhibited at a high frequency.[70,79] The association of akinesia and tremor at rest was observed as more prevalent in iNPH than in sNPH.[70] Forced crying, laughing, and convulsion are rarely encountered.[17]

It has been reported that, in addition to motor disturbance in the lower limbs, iNPH may be accompanied by hypokinesia of the upper limbs similar to the upper limb motor dysfunction in Parkinson's disease.[105] The latent presence of slow movement and impaired limb/hand/finger motor functions due to impairment of the supplementary motor area have also been reported.[83,104]

2. Diagnostic Imaging

2-A. CT and MRI

Morphological brain imaging by CT and MRI is essential for screening and clinical diagnosis of iNPH. Although no study has compared the diagnostic performance of CT and MRI, MRI is suitable for detecting morphological changes, and coronal sections are particularly useful in evaluating the condition of the sulci over the high cerebral convexity[43,62] (Recommendation grade B). Axial sections are also comparably useful to coronal sections for imaging of the high convexity[117] (Recommendation grade C1).

2-A-i. Brain morphology

CT and MRI reveal ventricular dilation.[28,50,62,117,138] Evans index (ratio of the maximum width of the frontal horns to the maximum width of the inner table of the cranium) of greater than 0.3 is a hallmark of hydrocephalus. The subarachnoid spaces in the sylvian fissures and over the ventral surface below are dilated (or at least not narrowed), and those over the high cerebral convexity and medial surface are narrowed[55,62,81,117,142] (Figs. 4 and 5). Tight high convexity and medial subarachnoid spaces are usually found in the dorsoposterior part of the brain,

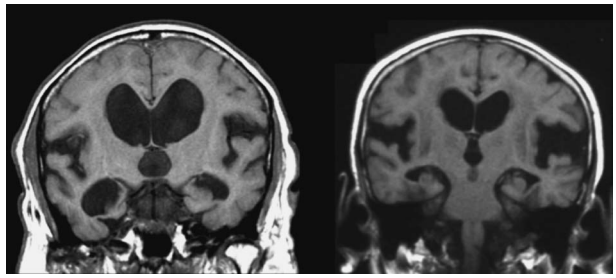

Fig. 4 Magnetic resonance imaging (coronal section): Examples of ventriculomegaly and dilatation of the sylvian fissures and narrowing of the sulci and subarachnoid spaces over the high convexity.

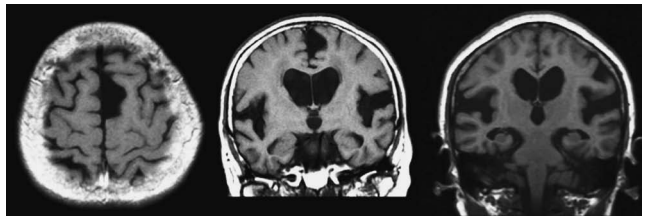

Fig. 5 Magnetic resonance imaging (axial section): Examples of narrowing of the sulci with focal dilation.

and the disappearance of the sulci on two sequential sections of coronal T_1-weighted MRI is a hallmark[43] (Recommendation grade B). In some patients with iNPH, one or more sulci over the medial surface and convexity were elliptically dilated in isolation[62] (Figs. 4 and 5).

CSF is retained in the ventricles and subarachnoid spaces in the sylvian fissures and below them, and decreased in the subarachnoid spaces on the dorsal surface. As CSF is distributed disproportionately between the superior and inferior subarachnoid spaces, the generic term DESH was coined for this type of hydrocephalus[43] (Recommendation grade C1). It should be kept in mind that some of the elderly may present with MRI features consistent with DESH without neurological symptoms, which is called AVIM.[21]

The finding of tight high convexity subarachnoid spaces can differentiate iNPH from cerebral atrophy in patients with Alzheimer's disease with high sensitivity and specificity[55,62,142] (Recommendation grade C1).

The presence of one of the triad symptoms and the MRI features is highly predictive of a positive tap test[81] and shunt responsiveness[43] (Recommendation grade B). All of the MRI features may be partially corrected after shunt surgery (Recommendation grade B).[49,53] In addition, the callosal angle is steep

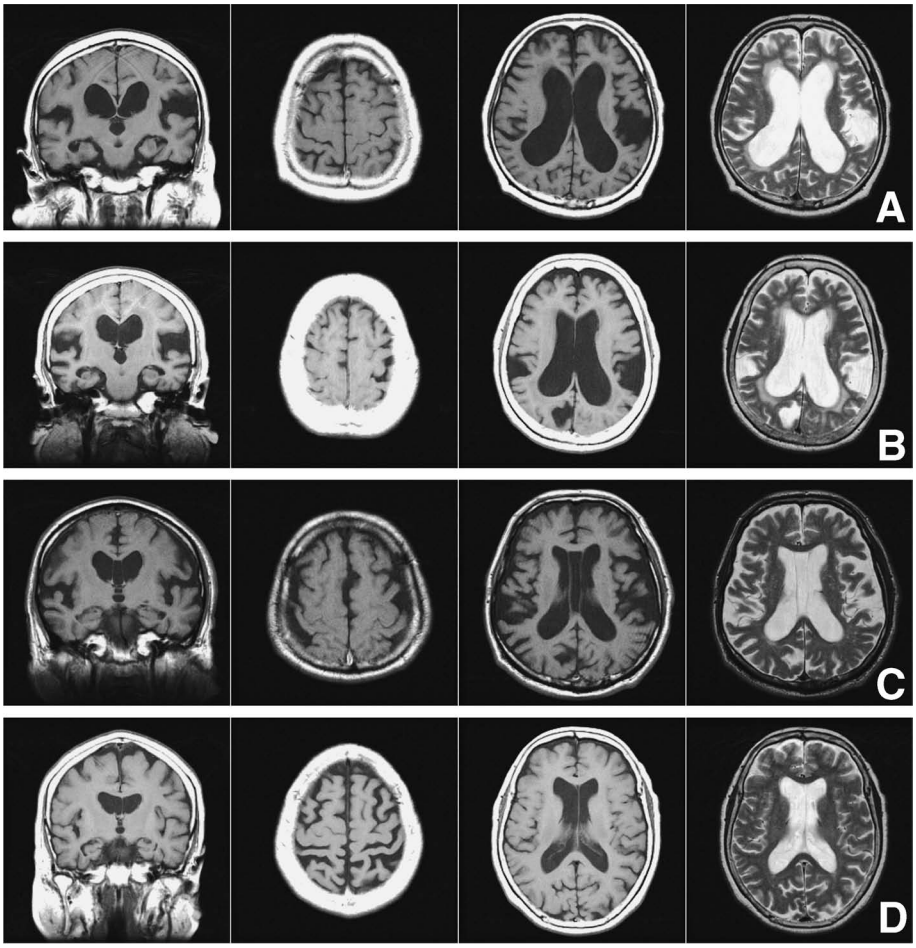

Fig. 6 Magnetic resonance imaging (coronal and axial sections): Comparison between idiopathic normal pressure hydrocephalus (iNPH) (A–C) and Alzheimer's disease (D). Each row contains a coronal T_1-weighted image, a dorsal horizontal T_2-weighted image, a horizontal T_1-weighted image, and a horizontal T_2-weighted image from a single patient. A and B show severe ventriculomegaly and sylvian fissure dilation. The sulci and subarachnoid spaces are narrowed over the high convexity and midline, but not on the ventral surface. Narrowing of the high-convexity/midline sulci and subarachnoid spaces can be detected clearly on the coronal sections. T_2-weighted images show mild to moderate periventricular hyperintensity. B shows focal dilation of the left parieto-occipital sulcus. C shows moderate ventriculomegaly and sylvian fissure dilation. Sulci and subarachnoid spaces are dilated on the ventral surface, but are markedly narrowed over the high convexity. Periventricular hyperintensity is not evident. D shows images of Alzheimer's disease as a comparison with iNPH. In the Alzheimer's sections, the ventricles, sulci, and subarachnoid spaces are evenly dilated. The gyri on the convexity are atrophic, and narrowing of the sulci and subarachnoid spaces is absent.

(less than 90°) on coronal (perpendicular to the anterior commissure-posterior commissure plane) MRI sections through the posterior commissure,[54] and the posterior half of the cingulate sulcus is narrower than the anterior half on sagittal MRI sections (the anterior half is narrower or equal to the posterior half in healthy individuals).[1] Both signs are also useful in the differentiation of iNPH from Alzheimer's disease (Recommendation grade C1).

Cerebral atrophy may be present in some cases, but its presence does not rule out iNPH. Hippocampal atrophy[118] and widening of the parahippocampal sulci[50] are mild compared with Alzheimer's disease, which is useful to differentiate iNPH from Alzheimer's disease[62,138] (Recommendation grade C1). Examples of MRI are shown in Fig. 6 as a reference for the differential diagnosis of both disorders.

The diameter of the midbrain is reportedly decreased in iNPH,[80] negatively correlated with the severity of gait disturbance,[99] and increased after shunt surgery. On the contrary, there are also conflicting reports indicating that the diameter of the midbrain does not change after shunt surgery

and does not correlate with the improvement of gait disturbance.[48,56] The diagnostic value of this finding is uncertain. In iNPH, the cross-sectional area of the corpus callosum on a mid-sagittal MRI section is small compared with healthy controls, and is increased after shunt surgery.[91] The diagnostic value of this finding is also uncertain.

2-A-ii. Periventricular and deep white matter changes

MRI and CT reveal periventricular and deep white matter changes (leukoaraiosis) more often and more severely in patients with iNPH than in healthy elderly individuals; but these findings are not requisite signs for iNPH and rather suggest a complication of chronic cerebral ischemia.[73,74] The response to the tap test is inversely correlated with the degree of white matter changes.[27] Shunt surgery can be effective even when white matter changes are present; however, there are conflicting reports about the relationship between the severity of white matter changes and the magnitude of shunt effects.[69,135] White matter changes cannot be used to predict shunt responsiveness.

2-A-iii. CSF flow void by MRI and CSF flow rate by phase-contrast MRI

In iNPH, a relatively high incidence of CSF flow void phenomenon on MRI, in which no CSF signal is observed in the aqueduct over the adjacent third and fourth ventricles, was noted in some studies,[7] whereas its incidence was not different from that in healthy subjects,[28] although the CSF flow void was noted in other reports,[25,58,72] showing that the diagnostic value of the CSF flow void on MRI is low. Regarding the CSF flow rate measured using phase-contrast MRI, the diagnostic sensitivity for iNPH has been reported to be high,[4,86] but the diagnostic value has not been established.

It is controversial whether the above imaging diagnosis predicts the shunt response,[23,24,32,41,72] but measurements of the preoperative peak flow velocity of CSF[103,122] and stroke volume, reflecting the CSF volume following the cerebral aqueduct,[6,120,121] have been reported to be clinically useful predictors of the shunt response, and these may be considered for preoperative examinations; however, the measurement methods have not been standardized and their diagnostic value has not been established. Reduced venous circulation in the sagittal and straight sinuses and intracranial compliance on heart rate-gated phase-contrast MRI have been reported,[11,12] but their diagnostic values have not been established.

2-A-iv. Magnetic resonance spectroscopy (MRS)

A lactic acid peak was noted around the lateral ventricle in iNPH on MRS, but not in healthy controls or patients with Alzheimer's disease, so the diagnostic value is unclear.[64] The N-acetylaspartate/creatine ratio on ^{1}H-MRS was significantly lower in the healthy controls than in the iNPH patients.[82] A significant correlation was also noted between the recovery of the N-acetylaspartate/creatine ratio after shunt surgery and the improvement of neuropsychological test findings and the triad in some reports,[90] but other reports were negative.[5] The value of MRS as a test to investigate the clinical course, such as conditions before and after shunt surgery, has not been established.

2-A-v. Diffusion tensor imaging (DTI)

DTI, a new MRI method, facilitates the evaluation of the condition of cerebral white matter nerve fibers by determining their fractional anisotropy and mean diffusivity, and its usefulness to differentiate iNPH and Alzheimer's disease has been reported.[44,51] However, the diagnostic value of the white matter evaluation by DTI has not been established.

2-B. Cerebral blood flow (CBF)

Measurements of CBF in NPH, including patients with iNPH, have been conducted by single photon emission computed tomography utilizing radio-labeled materials including iodine-123 N-isopropyl-p-iodoamphetamine,[101,116,128] technetium-99m hexamethylpropyleneamine oxime,[29,74,93] and technetium-99m ethyl cysteinate dimer,[47,67,143] positron emission tomography with ^{15}O-gas[97] and ^{15}O-H_2O,[65,66] and nonradioactive xenon-CT.[130] In a study measuring CBF, hypoperfusion around the corpus callosum and sylvian fissures was observed and frontal dominant hypoperfusion has been reported in many studies, but posterior and diffuse hypoperfusion have also been reported.[67,74,116,129,143] When voxel-based analysis is performed, hypoperfusion around the sylvian fissures and the corpus callosum reflects dilation of the sylvian fissures and lateral ventricles, respectively.[116] Perfusion of the cortices at the high convexity, and medial parietal and frontal lobes is relatively increased due to increased gray matter density and decreased CSF spaces in these regions,[67] which are useful in differentiating iNPH from other dementia illnesses including Alzheimer's disease[67,116] (Recommendation grade C1).

Concerning the correlation of CBF changes and the clinical symptoms, there is a report describing the presence of medial and lateral frontal hypo-

perfusion in iNPH patients with urinary incontinence.[116] There are many studies showing an association between improved symptoms and increased CBF after a shunt procedure[47,74,78,93,95,128,129]; however, other studies report no association between the symptoms and CBF.[66] It was reported that regional CBF in iNPH patients with minimal triad symptoms was significantly lower than in healthy controls, but in all brain regions, there was no significant difference from those with apparent objective triad symptoms.[126] A few studies demonstrated features of CBF in shunt responsiveness, including lower regional CBF in the basal frontal lobes and cingulate gyrus in shunt responders,[101] impaired preoperative cerebrovascular reactivity in responders,[29] and no increase of CBF after a tap test.[74] However, it is unclear whether the disturbance of autoregulation is related to the pathogenesis of iNPH,[95] so the value of CBF measurements in predicting shunt responsiveness has not been established.[47,65]

2-C. Cisternography

Radioisotope (RI) or CT cisternography has been considered to be required for the diagnosis of NPH, which has typical findings of intraventricular reflux and stagnation of the isotope and contrast medium on the brain surface.[77,132] Although these findings are often found in cases of sNPH, there is no report dedicated to iNPH. However, comparing patients with clinical symptoms and CT findings to those with RI cisternography findings as well as clinical symptoms and CT findings, RI cisternography was not shown to improve diagnostic accuracy.[137] Additionally, a study limited to iNPH patients reported improvement of symptoms in 55% of all cases with normal RI cisternography.[17] RI cisternography predicted shunt responsiveness less accurately than repeated lumbar CSF tap test or lumbar external CSF drainage,[61] and the use of RI cisternography did not add any additional information.[16] Because of the invasiveness and low diagnostic accuracy of CT or RI cisternography, it is not necessary for the diagnosis of iNPH (Recommendation grade C2); however, it may be useful in identifying obstructions in the circulation of CSF.

3. CSF Removal Test, ICP Test, and Other Tests

3-A. Tap test and continuous drainage test

The CSF removal test is divided into small volume removal and large volume removal of CSF. Small volume removal of CSF (30–50 ml) is carried out via a lumbar tap (tap test).[43,75,78,115,124] A tap test is less invasive. In contrast, large volume removal of CSF (300–500 ml) is carried out via an external lumbar drain over several days (external lumbar drainage test).[35,39,40,82,83,88,89,94,107,122,139,140,141] Complications such as disconnection or fracture of the indwelling catheter, radicular pain, or meningitis were reported in 2–8% of patients.[39,89,94,139,141] Since patients with iNPH are elderly, attention should be given to spinal canal stenosis or obstruction of the CSF pathway.

Some reports mentioned that patients on anticoagulant or antiplatelet agents were asked to stop their medications at 5–7 days beforehand, when they were examined for the external lumbar drainage test[39,89]; however, no extensive study has been performed on this subject. Care should be taken before the tests since suspected iNPH patients may be prescribed anticoagulant or antiplatelet agents.

A decision on a positive or negative response to the CSF removal tests is primarily based on the clinical symptoms. There are several measurements for the clinical symptoms, including assessment tools for NPH symptoms, and the global assessment of the activity of daily life, such as the modified Rankin scale. Gait can be assessed quantitatively using the 3-meter timed up and go test or the 10-meter straight walk test. The mini-mental state examination, frontal assessment battery, and/or trail-making tests are applied for the assessment of cognition. Although there are many assessment tools, only a few studies have assessed their sensitivity or specificity. In addition, only a few studies have assessed the relationship between the different types of examinations in the same subjects. Standardization of the assessments for the severity of symptoms and the interrelationship between the different grading scales are necessary to compare the data from different studies.

A decrease of CSF flow velocity in the aqueduct in shunt-effective iNPH patients on phase-contrast MRI[122] or increased supplementary motor activity on functional MRI[83] were reported to be useful for the diagnosis of iNPH; however, the case numbers were limited in these studies. CSF studies using MRI are increasing and they may show the high predictability of shunt effectiveness, but a higher level of evidence needs to be established.

Comparing the sensitivity and specificity between the tap and drainage tests, the tap test showed a sensitivity of 28–62% and specificity of 33–100%. For continuous drainage, the sensitivity was reported to be 60–100% and the specificity was 80–100%. The sensitivity tended to be higher for the drainage test[40,89,139,141]; however, there was some difference as to whether the sensitivity or the specificity was high for both tests.[75,88,139] The high

sensitivity indicates a low incidence of false-negative cases, which helps to make a differential diagnosis of the disease. The high specificity indicates a low incidence of false-positive cases, which also helps to establish the diagnosis of the disease. The specificity of both tests is comparable so that both are useful for the high predictability of shunt effectiveness. More precise data are necessary for CSF removal tests, especially for the tap test.

There are two options at present: the tap test (Recommendation grade B) and continuous drainage test (Recommendation grade B). The tap test is less invasive and easy to perform in neurological or neurosurgical wards or outpatient clinics. If the tap test is negative, further exploration may be necessary, including an external lumbar drainage test. The external lumbar drainage test is reported to have a higher accuracy than the tap test, but attention should be given to the complications of this examination such as disconnection, radicular pain, or meningitis.

3-B. ICP monitoring, CSF dynamics test, and other tests

3-B-i. Pressure and condition of CSF

The CSF should be colorless, watery, and clear. Many studies have reported the normal upper limit of CSF pressure to be 200 mmH_2O[133] or 180 mmH_2O.[110] The possibility of iNPH cannot be denied even in cases with higher pressure than this; however, it is necessary to rule out other diseases beforehand, such as benign intracranial hypertension or leptomeningeal carcinomatosis. There are few descriptions of the lower limits of CSF pressure in the elderly.

3-B-ii. ICP monitoring (continuous measurement of ICP)

The measurement period for ICP is approximately 12–48 hours, measured mainly at night.[18,57,68,108,110] Lumbar subarachnoid pressure is the most frequently measured[8,10,18,25,31,57,68,96,108,141]; however, there are also studies measuring parenchymal pressure,[34,35] intraventricular pressure,[110] and epidural pressure.[109,113,127,131]

The following 3 items are examined during the measurement.

1) Baseline ICP: The shunt procedure is effective in cases with high baseline ICP, and the threshold is approximately 90–200 mmH_2O.[10,18,57,68,113] Many cases show pressure that is closer to the upper limit of normal pressure. Conversely, some studies report that there is no correlation between the baseline ICP and the efficacy of shunting.[31,34,35,109]

2) Pressure wave: The incidence of B-waves is high during sleep, especially during rapid eye movement sleep.[68] The higher their incidence becomes (more than 15% of all records), the more effective is the shunt procedure.[18,57,113,131] Conversely, some studies report that there is no correlation between the appearance of B-waves and the efficacy of shunting.[31,108,109,141]

3) CSF pulse pressure: Increased amplitude together with decreased latency of the ICP pulse wave are noted in most of shunt-effective cases.[9,10,22,33,35,110] A high proportion of high amplitude waves of >9 mmHg predicts postsurgical improvement (positive predictive value 96%)[110] (Recommendation grade C1).

3-B-iii. CSF dynamics test (CSF space volume load test)

This test examines the CSF dynamics, the most important factor in iNPH, by injecting a normal saline solution or artificial CSF into the CSF space. The values vary depending on the site of injection (lumbar site[19,22,59,88,113,131]), speed of injection (at a constant injection speed[19,22,59,109,113] or bolus injection[131]), and ICP measurement site (lumbar subarachnoid pressure[19,22,59,88] or epidural pressure[113,131]); however, the values are not affected by lesions of the meninges or cerebral parenchyma.

The following are the major items for examination.

1) CSF outflow resistance (R_{out}): In previous reports, R_{out} was significantly elevated in shunting-effective groups and its positive predictive rate was over 80%.[19,59,113,131] However, the absolute value of R_{out} and the threshold between shunting-effective and -ineffective were reported as approximately 14–20 mmHg/ml/min (positive predictive rate 80–92%),[19,59,131] the value differs according to the method of injection. Moreover, many recent studies report that there is no correlation between R_{out} and the efficacy of shunting.[25,31,109]

2) CSF outflow conductance (C_{out}): Many studies have reported that C_{out} is significantly low in cases for which the shunt procedure is effective,[22,88,113] and the threshold of C_{out} between efficacy and inefficacy was approximately 0.08 ml/min/mmHg (positive predictive value 74–76%).[22,57]

3-C. CSF and serum biochemical tests

Many different molecules in the CSF and serum have been examined as biological markers for: 1) the diagnosis of iNPH and 2) predicting shunt efficacy; however, most of the previous studies included patients with iNPH and sNPH. In recent studies that were strictly aimed at iNPH patients, the measurement of proteins and neuropeptides in the

CSF has been conducted.

Neurofilament light chain,[2,136] transforming growth factor (TGF)-β1, TGF-β type II receptor, and α2-leucine-rich glycoprotein (LRG)[84,85] are significantly increased in the CSF of iNPH patients, whereas acetylcholine esterase activity, lactic acid,[87] β-amyloid-42,[60,112] β trace,[26] a secreted form of β-amyloid precursor protein (APP), and a secreted form of APPα[112] were significantly decreased in the CSF of iNPH patients. Since the levels of total tau (t-tau), but not phosphorylated tau (p-tau), were increased in the CSF of iNPH patients, they were reported to be useful in the differential diagnosis of Alzheimer's disease.[60] However, no definitive conclusion has been reached yet because of inconsistent studies showing low[2] or normal[112] CSF levels of t-tau and p-tau in iNPH patients. There is one report showing that the levels of vasoactive intestinal peptide, neuropeptide Y, and sulfatide in ventricular CSF and the ventricular CSF/serum albumin ratio were inversely correlated with alertness levels and improvement in cognitive tests after shunt surgery, respectively.[134] In one report, the CSF levels of galanin decreased after shunt surgery, and the degree of reduction was correlated with the improvement in cognitive function and clinical severity.[92]

Most of the studies conducted so far have included a small number of subjects, and the reproducibility of their results has not yet been examined. Thus, there are few studies with a high evidence level for the diagnosis of iNPH. However, the low CSF levels of neurofilament light chain and β-amyloid-42 as well as the high CSF levels of LRG have been confirmed in two or more studies. The usefulness of the CSF levels of LRG is especially expected in the clinical diagnosis of iNPH since LRG is a newly detected protein that was specifically increased in the CSF of definite iNPH patients by using unbiased proteomic analyses (Recommendation grade C1).

4. Differential Diagnosis

The characteristic clinical symptoms and imaging are both critical for the diagnosis of iNPH. Careful differentiation between various types of diseases is required: diseases affecting the elderly and causing dementia; diseases causing gait disturbance; diseases causing both dementia and gait disturbance; and diseases causing ventricular dilation on imaging. Differences in the clinical symptoms, including cognitive impairment and gait disturbance, are useful for differential diagnosis.

Clinically, it is especially necessary to differentiate iNPH from Alzheimer's disease, vascular dementia including multiple lacunar infarctions and Binswanger's disease, a mixture of Alzheimer's disease and vascular dementia, dementia with Lewy bodies, Parkinson's disease, progressive supranuclear palsy, vascular parkinsonism, multiple system atrophy, and frozen gait of unknown origin.[15,37,50,52,125] As for cognitive impairment, it is of particular importance to differentiate iNPH from Alzheimer's disease. Impairment of attention, thinking speed, reaction speed, processing speed, and verbal memory are characteristic of iNPH, whereas the impairment of frontal lobe-related functions is minimal in mild Alzheimer's disease.[52] In patients with Alzheimer's disease, recall and recognition memories are impaired; however, recognition memory is relatively preserved in iNPH, which is also useful. As for gait disturbance, it is important to differentiate iNPH from Parkinson's disease or parkinsonism. Walking in iNPH resembles Parkinsonian gait; however, the gait is improved by external cues in Parkinson's disease, whereas external cues are not effective in iNPH.[2] Patients with iNPH do not respond to antiparkinson agents, including levodopa, which is also useful for differential diagnosis.

As for imaging, it is necessary to differentiate iNPH from sNPH, obstructive hydrocephalus, and cerebral atrophy. For the differential diagnosis of sNPH, in addition to diseases occurring in succession in acute clinical conditions, including subarachnoid hemorrhage, head injury, or acute meningitis, relatively rare chronic and latent conditions, such as tuberculous meningitis, fungal meningitis, neurosyphilis, meningeal carcinomatosis, and Paget's disease, should be taken into consideration. It is possible to differentiate many of these conditions from iNPH by examining the CSF. In obstructive hydrocephalus, there are cases with latent symptoms that are found incidentally in adults by imaging, and cases that manifest symptoms in adulthood. In both cases, aqueductal stenosis may be noted, which is differentiated from iNPH by imaging. In order to differentiate iNPH from cerebral atrophy, it is useful to examine the existence of narrowing of the cerebral sulci and subarachnoid spaces over the high cerebral convexity on coronal MRI. Conversely, other diseases, including Alzheimer's disease and Parkinson's disease, may coexist with iNPH. Studies in which brain biopsies were carried out during shunt surgery have demonstrated evidence of Alzheimer's pathology in some patients with iNPH. The efficacy of shunt surgery was demonstrated even in such patients in all studies (Recommendation grade C1); however, the relationship between the concomi-

Table 5 Diagnostic criteria for idiopathic normal pressure hydrocephalus (iNPH) in these revised Guidelines

1. Possible iNPH: meets all of the following five features
   (1) Individuals who develop the symptoms in their 60s or older.
   (2) More than one of the clinical triad: gait disturbance, cognitive impairment, and urinary incontinence.
   (3) Ventricular dilation (Evans' index >0.3).
   (4) Above-mentioned clinical symptoms cannot be completely explained by other neurological or non-neurological diseases.
   (5) Preceding diseases possibly causing ventricular dilation are not obvious, including subarachnoid hemorrhage, meningitis, head injury, congenital hydrocephalus, and aqueductal stenosis.

   Possible iNPH supportive features
   (a) Small stride, shuffle, instability during walking, and increase of instability on turning.
   (b) Symptoms progress slowly; however, sometimes an undulating course, including temporal discontinuation of development and exacerbation, is observed.
   (c) Gait disturbance is the most prevalent feature, followed by cognitive impairment and urinary incontinence.
   (d) Cognitive impairment is detected on cognitive tests.
   (e) Sylvian fissures and basal cistern are usually enlarged.
   (f) Other neurological diseases, including Parkinson's disease, Alzheimer's disease, and cerebrovascular diseases, may coexist; however, all such diseases should be mild.
   (g) Periventricular changes are not essential.
   (h) Measurement of CBF is useful for differentiation from other dementias.

   Possible iNPH with MRI support
   Possible iNPH with MRI support indicates the condition fulfilling the requirements for possible iNPH, where MRI shows narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface (DESH). This class of diagnosis can be used in circumstances where a CSF examination is not available, for example, in a population-based cohort study.

2. Probable iNPH: meets all of the following three features
   (1) Meets the requirements for possible iNPH.
   (2) CSF pressure of 200 mmH_2O or less and normal CSF content.
   (3) One of the following three investigational features:
      (a) Neuroimaging features of narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface (DESH) under the presence of gait disturbance.
      (b) Improvement of symptoms after CSF tap test.
      (c) Improvement of symptoms after CSF drainage test.

3. Definite iNPH
   Improvement of symptoms after the shunt procedure.

CBF: cerebral blood flow, CSF: cerebrospinal fluid, DESH: disproportionately enlarged subarachnoid space hydrocephalus, MRI: magnetic resonance imaging.

tance of Alzheimer's pathology and the magnitude of shunt effects is controversial.[13,14,38,42,119] Comorbidity of cerebrovascular diseases is also common and may limit shunt effects.[14,20] A diagnosis of iNPH should not be excluded even in patients with other comorbid conditions (Recommendation grade C1).

5. Diagnostic Criteria

In the present Guidelines, iNPH is classified into 3 diagnostic levels: preoperatively ''possible'' and ''probable,'' and postoperatively ''definite.'' Probable iNPH must meet the diagnostic criteria of possible iNPH. A shunt procedure is indicated for probable iNPH, but not for possible iNPH. Definite iNPH is defined as cases in which the symptoms are improved after a shunt procedure.

Although the MRI sign of narrowing of the high convexity/midline sulci and subarachnoid spaces was a supplementary feature in the previous edition of the Guidelines, SINPHONI,[29] which aimed to validate the role of this sign in the diagnosis of iNPH, indicated that 80% of patients who fulfilled both the criteria for possible iNPH and the MRI criteria responded to ventriculoperitoneal shunting, so the criteria have been revised in this edition. The MRI sign of narrowing of the high convexity/midline sulci and subarachnoid spaces is now included in the criteria for probable iNPH as a feature of diagnostic value as well as a positive tap test and a positive drainage test. However, since 91% of the subjects in SINPHONI had gait disturbance, this item should be limited to those presenting with this feature. Furthermore, although normal CSF, including pressure, had been a mandatory feature of possible iNPH in the previous edition of the Guidelines, this item is now included in the criteria for probable iNPH in the revised Guidelines because CSF examination is not usually carried out in primary care clinics, so as to fit the practical flow and to be applicable to epidemiological studies. As MRI, but not CSF examination, would be available in epidemiological studies, those cases that fulfill both the possible iNPH criteria and the MRI criteria are classified into a new category, ''iNPH with MRI support.'' The diagnostic criteria for iNPH are tabulated in Table 5.

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CHAPTER IV: TREATMENT

1. Shunt Procedure for iNPH

Surgical intervention is the only treatment supported by high quality evidence. Although some cases exhibit improvements in their symptoms with repeated CSF removal by lumbar puncture, there is no long-term effectiveness in cases where surgical intervention is not possible.

1-A. Surgical procedures for iNPH

The surgical procedures for iNPH are the same as those for other types of communicating hydrocephalus: ventriculo-peritoneal shunt,[9,11,18,25,32,45,46,66] ventriculo-atrial shunt,[9,25,46] and lumbo-peritoneal shunt.[45,47,53] As for the historical view in the treatment of hydrocephalus, a ventriculo-atrial shunt was often performed on patients with iNPH in the past, whereas a ventriculo-peritoneal shunt is currently preferred. No studies have directly compared these surgical procedures in terms of efficacy for the treatment of iNPH. Approximately 50–90%[9,11,18,25,32,45–47,66] of cases reportedly improve after these shunting operations, and little difference between them is apparent in the management of iNPH (Recommendation grade B).

1-A-i. Ventriculo-peritoneal shunt, ventriculo-atrial shunt

Ventriculo-atrial shunt has reportedly been associated with specific complications, including sepsis, endocarditis, cardiac wall perforation due to distal tube-derived bacterial embolism, cardiac tamponade, accumulation of pleural fluid, kidney damage, pulmonary embolism, and pulmonary hypertension, some of which can be occasionally fatal.[63] From the perspective of having to treat a large number of elderly subjects, ventriculo-atrial shunt is not indicated in such patient groups with a high prevalence of cardiovascular disease.

1-A-ii. Lumbo-peritoneal shunt

If a tap test shows an improvement in symptoms, a logical choice of treatment in many cases is a lumbo-peritoneal shunt, which is similar to the tap test and is not invasive to the brain (requiring penetration of a ventricle).[4] To date, no trial has investigated directly whether lumbo-peritoneal shunting provides an equivalent or better outcome compared with other types of CSF shunts. A lumbo-peritoneal shunt is regarded as having a lower infection rate than a ventriculo-peritoneal shunt,[1] but shunt dysfunction has been identified as an issue, and occlusion or leg pain (spinal radiculopathy) may be induced by displacement of the lumbar catheter,[64] particularly in elderly patients who frequently suffer from degenerative lumbar spine disease. In addition, a lumbo-peritoneal shunt is not recommendable for patients with severe lumbar spondylosis or decubitus in the lumbosacral area.

1-A-iii. Endoscopic third ventriculostomy (ETV)

A few recent reports have described improved symptoms when ETV has been used to treat iNPH,[16,17,29,41,59] but imaging findings from individual cases are inconclusive. They include cases of so-called ''functional aqueductal stenosis'' in which the cerebral aqueduct is patent, but inferior displacement of the floor of the third ventricle is evident. Although such cases may have been described as iNPH, they may not actually represent the same condition defined in these Guidelines. ETV treatment is not currently regarded as beneficial for iNPH (Recommendation grade C2).

1-B. Types of shunt systems

The shunt systems for iNPH patients can be categorized by the following structural features: A) adjustable or programmable valves; B) fixed differential pressure valves; C) gravity-assisted valves; and D) flow-regulated valves. In addition, E) anti-siphon devices have been developed and employed to prevent excessive CSF drainage, which can occur when the patient is in a sitting or standing position. An anti-siphon device is either an auxiliary device for the above-mentioned valves or a built-in part.[19,54] Table 6 summarizes current models available in Japan.

1-B-i. Adjustable or programmable valves

The major advantage of this type of valve is that it is possible to adjust the pressure setting non-invasively, even after it is installed. Since the compliance of the brain is low in iNPH patients, readjustment of the pressure setting is very likely to be required multiple times.[51,57,67] A method to adjust the pressure setting based on the body size of the patient in a sitting position has been suggested.[43,44] Furthermore, there have been reports that the risk of postoperative complications can be minimized by gradually decreasing the pressure setting from high to lower values.[6,45] Adjustable or programmable valves are currently recommended for iNPH patients[18,57] (Recommendation grade B). Valves with built-in anti-siphon devices are also available, as will be mentioned below. The pressure setting must be

Table 6 Types of shunt system and current models available in Japan

Type of device	Current model	Recommendation grade
i. Programmable valve	Codman-Hakim Programmable Valve® (Codman), Codman-Hakim Programmable Valve Inline with SIPHONGUARD®* (Codman), StrataII®* (Medtronic), Strata NSC® (Medtronic), Polaris valve® (Sophysa), Sophy Valve® (Sophysa), proGAV®* (Aesculap), etc	B
ii. Fixed differential pressure valve	Hakim valve® (Codman), CSF-Flow Control valve® (Medtronic), Delta valve®* (Medtronic), LPVIIvalve® (Integra), SILASCON V-P Shunt A type® (Kaneka), etc.	C1
iii. Gravity-assisted valve	MIETHKE GAV® (Aesculap), MIETHKE DualSwitch® Valve (Aesculap)	C1
iv. Flow regulated valve	Orbis Sigme® (W. L. Gore & Associates)	C1
v. Anti-siphon device	SIPHONGUARD® (Codman), Shunt Assistant® (Aesculap), Delta Shunt Assemblies® (Medtronic), etc	C1

*Inline with anti-siphon device. Aesculap: Aesculap, Inc., Center Valley, Pennsylvania, USA; Codman: Codman, a Johnson & Johnson Company, Raynham, Massachusetts, USA; Integra: Integra NeuroSciences, Sophia Antipolis, France; Kaneka: Kaneka Medix Corp., Osaka, Japan; Medtronic: Medtronic, Inc., Minneapolis, Minnesota, USA; Sophysa: Sophysa, Crown Point, Indiana, USA; W. L. Gore & Associates: W. L. Gore & Associates, Inc., Newark, Delaware, USA.

checked after MRI examinations because the setting may change in strong magnetic fields[67] (Recommendation grade B). Laboratory experiments have shown that some valves are not affected in magnetic fields of up to 3 tesla.[27] However, close attention is needed at all times, considering possible mechanical malfunctions and/or the risk of subdural effusion, which cannot be prevented by changing the pressure setting.[51]

1-B-ii. Fixed differential pressure valves

The flow of the fluid is determined by a pressure gradient between the inlet and the outlet of the valve. The main features of fixed differential pressure valves are their simple structure, stable function, and low cost. Low- (5–50 mmH_2O) or medium-pressure (51–110 mmH_2O) valves have been recommended and used for iNPH patients. A low-pressure valve is probably more superior to a medium-pressure valve in terms of the improvement rate of dementia and gait disturbance.[11] However, medium- or high-pressure valves are preferable considering that the risk of overdrainage, such as subdural effusion, increases with low-pressure valves, and that the pressure setting of adjustable valves finally settles in the region of 150 mmH_2O.[43] The installed differential pressure valve should be replaced with another differential pressure valve of a different pressure level if overdrainage happens when using a low-pressure valve or if medium- or high-pressure valves do not produce the anticipated results. In either of these cases, another operation is necessary. Unlike for the programmable valves, it is not possible to change the pressure setting of this valve non-invasively. Differential pressure valves are inferior to programmable valves in terms of effectiveness and probability of postoperative complications[13,57] (Recommendation grade C1).

1-B-iii. Gravity-assisted valves

This type of valve is position-sensitive. Using a gravity-assisted valve provides CSF flow paths and resistance in two different ways, depending upon whether the patient is in a dorsal/supine or standing position. This type of valve is used for the prevention of overdrainage in a standing position. It is important to note that if the direction of the valve is not appropriate, it may not function as it should. This type of valve has been used for ventriculo-peritoneal shunt in iNPH patients. The valve's anti-siphon mechanism does not operate in a lumbo-peritoneal shunt if the axis of the valve is perpendicular to that of the patient's body[37] (Recommendation grade C1).

1-B-iv. Flow-regulated valves

According to the pressure on flow-regulated valves, their internal resistance varies automatically. The flow stabilizes as the pressure difference is settled. This type of valve has a theoretically important structural advantage for the treatment of iNPH patients, i.e., there is no artifact on MRI.[54,66] However, there is no significant difference between this type of valve and differential pressure valves in terms of improvement rate, infection rate, functional failure rate of the shunt procedure, and the incidence of subdural effusion.[31,66] Therefore, flow-regulated valves are not particularly preferable as the first choice for treatment (Recommendation grade C1).

1-B-v. Anti-siphon devices

With the CSF shunt systems A) to D) described above, excessive flow may occur when the patient is in a sitting or standing position. Anti-siphon devices have been developed and used to prevent this. These devices are either built into the valves A) through D) or used with them as auxiliary devices. Using programmable valves with anti-siphon devices in iNPH patients reduced the incidence of subdural effusion to 3%, but the probability of mechanical malfunctioning was 6%.[28] Overdrainage can happen when using programmable valves without a built-in anti-siphon device. If adjusting the pressure setting does not resolve overdrainage problems, an anti-siphon device should be considered (Recommendation grade C1).

2. Postoperative Management, Complications, and Long-term Management

2-A. Postoperative management

The initiation of gait training from postoperative day 1 is recommended. However, due to the siphon effect, the upright (sitting or standing) position can lead to excess shunt flow, and in order to avoid CSF overdrainage complications, which account for the majority of postoperative complications, it is important to maintain appropriate postoperative valve pressure settings. There is no established method for determining the initial postoperative valve pressure setting. The generally accepted method is to start with a high pressure setting and gradually lower the setting according to the clinical condition in order to prevent CSF overdrainage complications[7,8,18,26,51] (Recommendation grade B).

To date, several studies have used CSF dynamic tests (e.g., CSF outflow resistance) or ICP monitoring designed to develop a method for setting the initial postoperative valve pressure[55,60,67]; however, in all of these studies, there was a high readjustment rate, raising the question as to the validity of these strategies. Only one study, which was based on measurements in the upright position, has demonstrated satisfactory outcomes using a quantitative strategy for determining the initial pressure settings.[44] This method uses a higher initial pressure setting in order to compensate for the excessive decrease of ICP in the upright position. Other evidence in support of this algorithm include a study that showed symptomatic improvement in all subjects after setting a Sophy Valve® (Sophysa,

Table 7 Quick reference table for determining initial postoperative pressure settings of programmable pressure valves

Female:

Height (cm)	Body weight (kg)															
	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
140	16	12	9	6	3											
145	19	16	13	10	7	4										
150		19	16	13	10	7	4									
155			20	17	14	12	9	6	3							
160				20	18	16	13	11	8	5	3					
165					20	18	16	14	12	9	6	4				
170							20	18	15	13	11	9	6	4		
175								20	18	16	14	12	10	8	5	
180										20	18	16	14	12	10	8

Male:

Height (cm)	Body weight (kg)															
	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
145	20	18	15	12	9	6	3									
150		20	18	15	12	9	6	4								
155				19	16	14	11	8	5	3						
160					19	17	14	12	9	6	4					
165						20	18	16	14	11	8	6	4			
170							20	19	16	14	12	10	7	5		
175									20	18	16	14	12	10	7	5
180										20	19	17	15	13	11	9

Crown Point, Indiana, USA) at a high pressure,[26] and another study found that the final setting in more than 80% of patients using a Codman-Hakim Programmable Valve® (Codman, a Johnson & Johnson Company, Raynham, Massachusetts, USA) was approximately 150 mmH_2O.[51] These studies, however, employed methods that are relatively invasive and difficult to use. In recent years, however, a quick and easy algorithm based on the patient's height and weight has been developed (Table 7).[43] This algorithm is considered to be superior to other methods based on results showing reductions in overdrainage complications and no associated complications requiring evacuative operations for subdural hygroma or hematoma.[18,43] After making the initial valve pressure setting, subsequent readjustments should be made in relation to the patient's symptoms and radiological findings; however, a lack of ventricular narrowing should not be used as an indication for lowering the pressure setting. In the event of the development of a large subdural hematoma, immediate readjustment to the highest pressure setting should be performed. In cases of asymptomatic thin subdural hygromas/hematomas or in cases where the symptoms do not resolve, a pressure readjustment by 30 mmH_2O is advisable[7,18,42,67] (Recommendation grade C1).

In the past, with the use of fixed-pressure valves, treatment of overdrainage complications included bed rest with gradual increases in bed-up levels; however, the effectiveness of this method is questionable in elderly patients with low brain compliance. Furthermore, this approach has additional drawbacks of long admission times with delayed recovery and accompanying increased medical costs.

Because anti-siphon valves are designed to prevent excess shunt drainage in the upright position, it is necessary to confirm adequate flow in the supine position at sufficiently low settings.[37,39,42] In addition, the pressure environment in a lumbo-peritoneal shunt can be considered to be equivalent to that in a ventriculo-peritoneal shunt. Although the spinal catheter is longer and narrower in diameter than the ventricular catheter, which in theory should lead to less shunt flow, there have been no comparative studies to date, and current settings are based on ventriculo-peritoneal shunt settings. Early postoperative complications in addition to CSF overdrainage include the possibility of CSF leaks from around the catheter insertion point.

In general, follow-up CT studies should be performed on postoperative day 0, at 1–2 weeks, and at 1, 3, 6, and 12 months; however, in the presence of clinical worsening, CT should be performed on an as-needed basis. Normally, improvements in gait are apparent during the early postoperative period; however, until full recovery of gait is achieved, there is a period of instability and a high risk for falls. Furthermore, patients who fall are also at a high risk for the formation of chronic subdural hematoma. MRI is not contraindicated in patients with shunts, although depending on the type of MRI sequence and the type of valve and its location, there is the possibility of imaging artifacts. In adjustable-pressure valves without lock capabilities, the valve settings must be checked after performing MRI because there is the possibility of alterations to the valve settings. Moreover, there have been reports of 3-tesla MRI causing damage to the cam located within adjustable-pressure valves.[65] MRI with a high magnetic field should be avoided (Recommendation grade C1).

2-B. Complications

Postoperative shunt complications include infection, shunt failure, headache, and subdural hygroma/hematoma due to CSF overdrainage. According to a 2001 nationwide Japanese study, there was a relatively high incidence of shunt-related complications (18.3%), perhaps partially reflecting treatment of a predominantly elderly patient population.[45] SINPHONI found a 3% incidence of serious adverse events (subdural hematoma, intestinal perforation, shunt obstruction), and a 20% incidence of less serious adverse events such as subdural hygroma and orthostatic headache.[18] There have been no studies comparing the Codman-Hakim Programmable Valve®, Sophy Valve®, and fixed-pressure valves, and superiority among the valves remains to be determined. However, reports have shown that there are no major differences between the valves in terms of complication rates of infection[30,51,55,68] or shunt occlusion.[32,55,56,67] However, the use of antibiotics during the perioperative period has been shown to reduce the incidence of infection.[67] Complications of non-traumatic subdural hygroma/hematoma were reported to improve by resetting to higher pressures in the Codman-Hakim Programmable Valve® and Sophy Valve®, and evacuative operations were only required in 2.7% of cases using the Codman-Hakim Programmable Valve®[51,68] and 1.4% using the Sophy Valve®.[55] Furthermore, one study using an anti-siphon device (the dual-switch valve) showed a 3% transient incidence of subdural hygroma and no cases needing operation.[56] In contrast, patency rates for Orbis-Sigma Valve® (Integra NeuroSciences, Sophia Antipolis, France) were lower than for the other tested valves and the rates of operation for

subdural hematoma were higher than for the other valves.[66] Other reports of infrequent complications include gastrointestinal and bladder perforations from peritoneal catheters,[34] hearing deficits,[61] and tension pneumocephalus.[3]

2-C. Long-term management

Although there are no long-term studies on postoperative shunt management, postoperative changes in patient body weight frequently necessitate concomitant valve pressure readjustments because the pressure environment in shunted patients is affected by their physique.[23,44,58] In particular, accurate and appropriate pressure settings are especially important for iNPH patients who have low brain compliance and a narrow range of tolerable ICP. Currently, pressure-adjustable valves/pressure-adjustable anti-siphon valves are the only effective devices recommended for long-term management (Recommendation grade C1). In addition, conditions that raise the intra-abdominal pressure, such as constipation,[58] can result in transient worsening of symptoms and should be treated accordingly. Finally, in the case of bedridden patients, it is recommended that they spend as much time as possible in the sitting position so as to avoid complications of CSF underdrainage. If patients are unable to maintain an upright position, the pressure settings should be adjusted to a lower value.

2-D. Shunt occlusion: diagnosis and treatment

The possibility of shunt occlusion should be suspected if no improvement in symptoms is observed after 2 setting reductions (30 $mmH_2O \times 2 =$ 60 mmH_2O). Shunt contrast studies should be performed to confirm the presence of an occlusion (Recommendation grade C1). A minimum 2-week observation interval should follow each shunt readjustment period. When performing shunt contrast studies, a thin butterfly needle is inserted into the valve reservoir and the CSF pulsations of the butterfly tube should be checked first. If no pulsations are observed, obstruction of the ventricular (or lumbar) catheter should be suspected. Next, using a minimal amount of contrast medium, radiography confirmation of peritoneal catheter obstruction should be performed. In the case of anti-siphon devices, injection of contrast medium may be difficult, but with gentle injection, radiographic visualization of the peritoneal catheter can be accomplished. Mild shunt obstruction can be resolved by the mechanical disruption effect of injecting contrast medium, whereas partial resection of the obstructed portion or complete shunt revision may be needed in cases with persistent obstruction.

3. Outcome

The outcomes at 3 months and up to 5 years after surgery have been reported. The efficacy of shunt procedures maintained for the short term ranged from 3–6 months in 64–96% of patients,[2,5,15,21,22,24,32,35,36,48] and at 1 year in 41–95%[10,12,18,25,33,40,49,50,62,66]; while the efficacy of shunt procedures maintained for the long term ranged from 3–5 years in 28–91% of patients.[2,9,21,32,36,38,46,49,50,52]

The best improvement rate was for gait disturbance, between 58–90%.[2,5,14,21,32,35,36,45,49,50,52,66] The improvement rate for dementia differed with the evaluation scale used; however, the symptoms improved in 29–80% of patients. Urinary incontinence reportedly improved in 20–82.5% of patients.[2,14,32,46,66] A prospective study comparing 25 patients with and 26 patients without a shunt procedure showed that the rate of independence for the activities of daily living was higher in the former than in the latter until 5 years after the procedure.[52] As for the classical triad after a shunt procedure, gait disturbance showed an improvement in 90% of patients within 2 months after the procedure, and in 95% of patients at 1 year after the procedure. Urinary incontinence improved in 90% of patients within 1 week after the procedure. Conversely, dementia gradually improved, and an improvement rate of 67% was reported at 1 year after the procedure.[50]

There are many NPH-specific scales for outcome evaluation. The Stein-Langfitt grading scale or the modified Rankin scale for functional impairment as a non-specific test, one of the most popular scales for NPH, underestimates the effect of the shunt procedure.[10,18] There are several options of evaluation scale. A comparison between the modified Rankin scale as a non-specific scale and the NPH scale for the classical triad as a disease-specific scale showed that the improvement rate differed depending on the evaluation scale used. Various outcome measures were used in previous studies, so it is difficult to compare their results directly; therefore, standardized measures are awaited. At the present time, modified Rankin scale is recommended to assess functional impairment, and the iNPH grading scale should be used to assess each specific symptom (Recommendation grade C1).

4. Drug Treatment, Rehabilitation, and Care

4-A. Drug treatment

There is no definitive drug therapy for iNPH. There is no high level evidence showing the benefits

of anti-dementia and anti-Parkinson agents as symptomatic treatment. Anti-dementia and anti-Parkinson agents may be effective for the comorbidity of Alzheimer's disease and Parkinson's disease (Recommendation grade C1).

4-B. Rehabilitation

A rare report was found about the usefulness of rehabilitation for patients with iNPH.[20] However, rehabilitation is necessary in many patients with iNPH, especially in those with disuse syndrome in the preoperative stage (Recommendation grade C1).

4-C. Care and social services

The daily life of patients with iNPH and their families should be supported by the medical and care services. Although this section is very specific for the application of care and social services in Japan, it should be interpreted as they are provided according to each country's own health care system.

In Japan, a certification of required long-term care is necessary for individuals to use the long-term care insurance system. The object of the long-term care service is a person who is aged 65 years or older (primary insured person) or a person who has a condition that requires long-term care and is aged from 40 years to less than 65 years (secondary insured person), and the physical or mental problems that are the causes of said condition are a result of diseases that are caused by the physical and mental changes due to aging, which are specified by a cabinet order (specified diseases). Secondary insured persons must obtain a certification of long-term care for one of 16 specified diseases if patients with iNPH have dementia. To use the long-term care service, an insured person who intends to obtain a certification of required long-term care should submit an application to their municipality. A municipality will direct its personnel to interview an insured person named in an application and investigate their mental and physical conditions, and surroundings, and then conduct on-the-spot fact-finding for the 74 nationally common paragraphs from the patient or their family. A municipality shall provide the relevant certification according to the opinion of the attending physician on the presence of dementia and special medical care and shall certify and judge the categories of the condition requiring long-term care to the certification committee for required long-term care.

When a person is certified for one of the five categories requiring long-term care or for one of the two categories requiring support, a facility service plan, in-home long-term care service plan, or preventive long-term care service is necessary. If a person is certified for one of the five categories requiring long-term care, they can request an in-home service plan or facility service plan from a long-term care support specialist (care manager) in facilities designed for in-home long-term care support. If a person is certified for one of the two categories requiring support, they can request a preventive long-term care service plan from a community general support center. To use the long-term care service, the service is based on an in-home care service plan, preventive long-term care service plan, and facility service plan.

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CHAPTER V: FLOWCHARTS FOR MANAGEMENT

This section gives flowcharts to facilitate at-a-glance understanding of the measures to be taken for practical issues. Figure 7 illustrates the algorithm for the diagnosis of iNPH, Fig. 8 illustrates the decision-making process for shunt surgery and post-surgical assessment, and Fig. 9 illustrates the algorithm solving problems of overdrainage and underdrainage. The readers should refer each corresponding part of the Guidelines for further details.

1. Further Notes for Algorithm for the Diagnosis (Fig. 7)

1) Symptoms: Gait disturbance and cognitive impairment are the most prevalent. Apraxic/ataxic gait with a small-stepped, magnet, and broad-based nature is characteristic. Freezing is apparent on the initiation of walking, walking in a narrow space, and turning around. Cognitive impairment is demonstrable on neuropsychological tests. Loss of attention, spontaneity, and executive function are remarkable, and disorientation is usually preserved

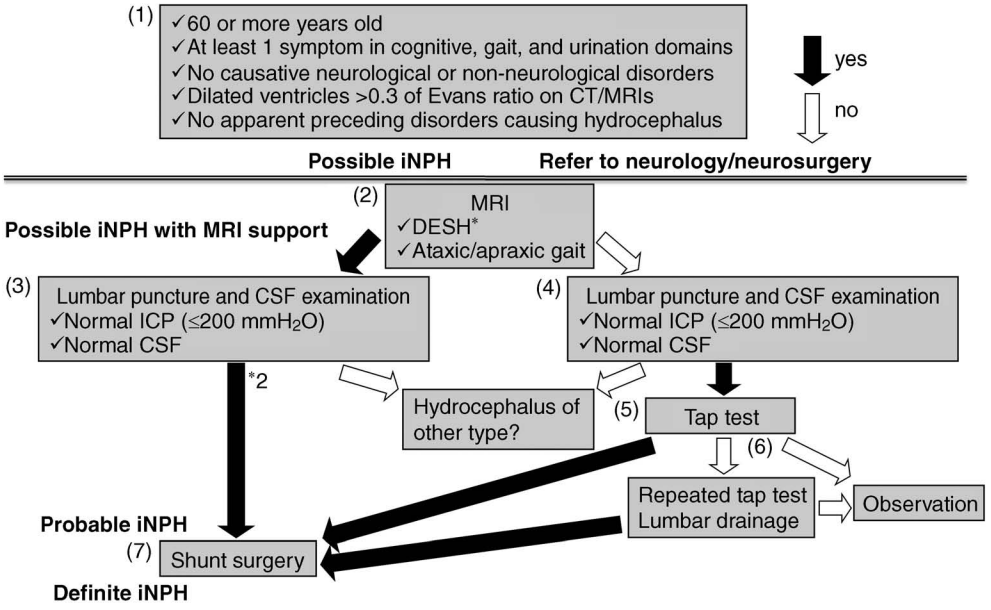

Fig. 7 Algorithm for diagnosis. *DESH: disproportionately enlarged subarachnoid space hydrocephalus. The features include tight high convexity and medial subarachnoid spaces and enlarged sylvian fissure associated with ventriculomegaly. CSF: cerebrospinal fluid, CT: computed tomography, ICP: intracranial pressure, iNPH: idiopathic normal pressure hydrocephalus, MRI: magnetic resonance imaging.

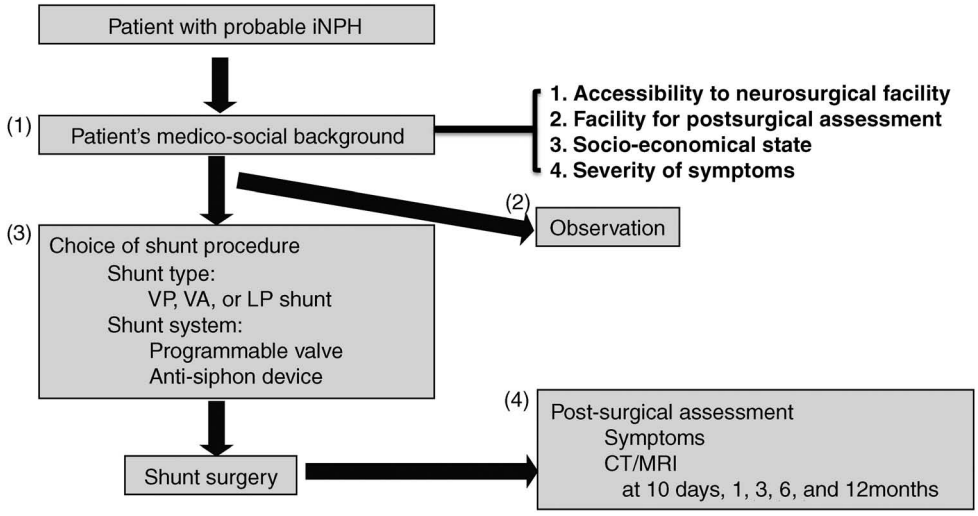

Fig. 8 Decision-making for shunt surgery and post-surgical assessment. CT: computed tomography, iNPH: idiopathic normal pressure hydrocephalus, LP: lumbo-peritoneal, MRI: magnetic resonance imaging, VA: ventriculo-atrial, VP: ventriculo-peritoneal.

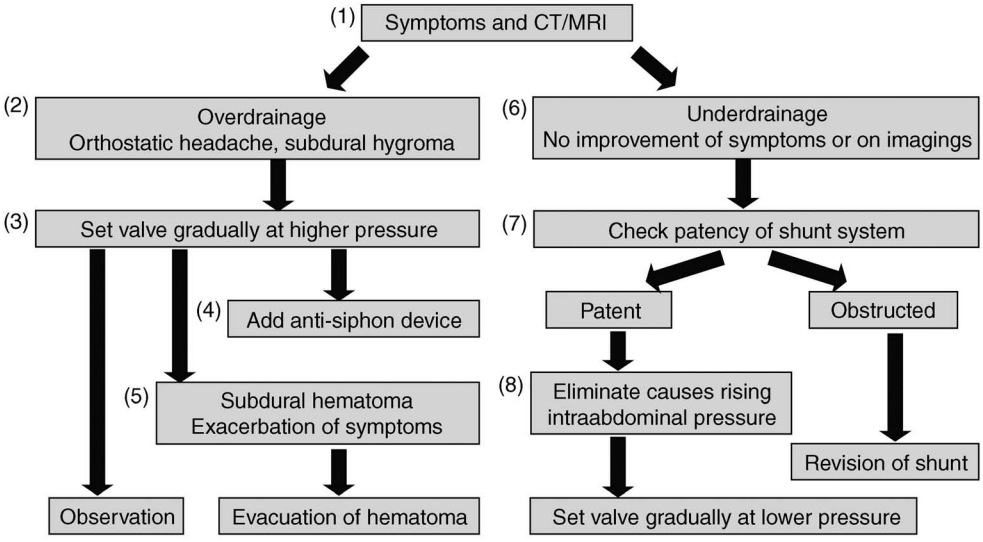

Fig. 9 Flowchart for solving shunt flow problems. CT: computed tomography, MRI: magnetic resonance imaging.

better than in Alzheimer's disease. Characteristics of the urinary symptoms include urgency and incontinence.

2) MRI and CT: MRI is recommended for diagnosis. CT may be used, when MRI is contraindicated. The diagnosis of iNPH should be suspected based on both symptomatic and imaging findings. It should not be diagnosed based only on imaging findings, if there is no characteristic symptom. The diagnostic class of possible iNPH with MRI support is applicable to those with both characteristic symptomatic and MRI findings but lacking CSF examination, for example, in epidemiological studies, where CSF examination is not available. A tap test may be performed, even if the patients have fulfilled both the symptomatic and neuroimaging criteria for probable iNPH. A positive tap test may help the patient's and family's understanding of the need for surgery.

3) If the diagnosis of iNPH is questionable because of suspected concomitant diseases or non-typical symptoms, a tap test is recommended.

4) A Queckenstedt test should be performed before removing CSF to assess the passage of the spinal

canal. A tap test should be avoided, if the result is abnormal.
5) Test tap: Remove 30 ml of CSF by lumbar puncture. Thick needle (19 gauge or higher) is recommended, as leakage of CSF after the puncture is also likely to contribute to the improvement of the symptoms. Symptomatic improvement is seen within a week. Although the improvement of gait is a convenient and secure indicator, improvement of other domains including cognitive function, spontaneity, and urinary incontinence may be seen in some cases, even if improvement of gait is not detected.
6) When a tap test is negative: A shunt may be effective in some patients with a negative tap test. When a tap test is negative, there are three options: a repeat tap test; a drainage test; and reconsider the diagnosis, or observe further. When repeating a tap test, use a thicker needle and remove a greater amount of CSF than during the first test. The effect may rather decrease in some cases, when a tap test is repeated. A drainage test removes 100–150 ml CSF per day for a few days.
7) Shunt surgery: Ventriculo-peritoneal, ventriculo-atrial, and lumbo-peritoneal shunt procedures. Attention must be paid to status of care-giving and consent of the family. Conduct rehabilitation before and after surgery, whenever necessary. Evaluation of the effects should be repeated until one year after surgery and on an as-needed basis thereafter.

2. Further Notes for Surgical Decision-Making and Post-surgical Assessment (Fig. 8)
1) Medico-social background: Review the general condition to consider if general anesthesia is available. Improvement is achieved in more than 80% of patients who receive shunt surgery, but the effect is generally modest in those with severe deficits. The decision should be made after obtaining informed consent from the patients and their family, taking this factor into account. As long-term regular follow-ups after the operation including pressure setting adjustment of programmable valves are necessary, access to a capable facility may be a factor for decision-making.
2) Observation: Patients who require a shunt but are ineligible because of their unsuitable background should be observed carefully, and their eligibility should be reconsidered depending on the situation.
3) Implementation of shunt surgery: Consider the following. a) Choose the standard and experienced shunt technique used in the facility. Although ventriculo-peritoneal and lumbo-peritoneal shunts are recommended, each has its own advantages and disadvantages. As there has been no evidence of superiority so far, the procedure should be selected according to the situation. b) Because there is a need to change the pressure setting depending on the symptomatic and imaging findings, in principle, a programmable valve shunt system should be selected. c) There are no views as to whether an anti-siphon device should be used from the beginning or added only when overdrainage symptoms are uncontrolled.

3. Further Notes for Algorithm for Overdrainage and Underdrainage (Fig. 9)
1) Symptoms and CT/MRI: When the expected effects are not observed in the assessment after shunt surgery, the symptoms and CT/MRI findings should be reevaluated to determine excess or absence of shunt flow. Then, ascertain the pressure setting of the programmable valve.
2) Overdrainage: Orthostatic headache and subdural hygroma on CT are typically seen. Subdural hematoma may develop after even minor head trauma, which requires surgical evacuation.
3) Change of pressure setting: If overdrainage is suspected, raise the pressure setting gradually (30 mmH_2O at a time), and observe the improvement. In most cases, the symptoms will be expected eliminated by this, however, CT should be used to check whether there is an increase of subdural hygroma or hematoma.
4) Addition of an anti-siphon device: If overdrainage symptoms do not improve even after raising the pressure setting to the maximum, consider adding an anti-siphon device.
5) Subdural hematoma: Observe the patient closely, and evacuation of the hematoma is indicated if the symptoms worsen.
6) Underdrainage: When there is no improvement of symptoms after shunt surgery, underdrainage may be suspected.
7) Verification of the patency of the shunt system: Determine patency or obstruction of the shunt system by a valve pumping maneuver, and shuntography if necessary.
8) If the system is patent: If there is a rise in intraabdominal pressure due to constipation and weight gain, resolve these causes. Immobility may reduce shunt flow. Increase the amount of time in the upright position. If an improvement is not seen following these measures, lower the pressure setting gradually (30 mmH_2O at a time).

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