NMC Case Report Journal 10, 9-14, 2023

Ventriculoperitoneal Shunt Failure 3-year after Shunt Surgery Caused by Migration of Detached Ventricular Catheter into the Cranium: A Case Study of Idiopathic Normal-pressure Hydrocephalus

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Abstract

Idiopathic normal-pressure hydrocephalus (iNPH) is a neurological disorder that typically presents with gait disturbance, cognitive impairment, and urinary incontinence. Although most patients respond to cerebrospinal-fluid shunting, some do not react well because of shunt failure. A 77-year-old female with iNPH underwent ventriculoperitoneal shunt implantation, and her gait impairment, cognitive dysfunction, and urge urinary incontinence improved. However, 3 years after shunting (at the age of 80), her symptoms gradually recurred for 3 months and she did not respond to shunt valve adjustment. Imaging studies revealed that the ventricular catheter detached from the shunt valve and migrated into the cranium. With immediate revision of the ventriculoperitoneal shunt, her gait disturbance, cognitive dysfunction, and urinary incontinence improved. When a patient whose symptoms have been relieved by cerebrospinal-fluid shunting experiences an exacerbation, it is important to suspect shunt failure, even if many years have passed since the surgery. Identifying the position of the catheter is crucial to determine the cause of shunt failure. Prompt shunt surgery for iNPH can be beneficial, even in elderly patients.

Keywords: hydrocephalus, idiopathic normal-pressure hydrocephalus, cerebrospinal-fluid shunt, ventriculoperitoneal shunt, management

Introduction

Idiopathic normal-pressure hydrocephalus (iNPH) is a neurosurgical disease characterized by ventriculomegaly on imaging and clinical presentation of gait disturbance, cognitive impairment, and dysuria.[1,2] One Japanese community-based study estimated the prevalence of hydrocephalus to be 0.6%-2.9% in the elderly population.[3] A study in Sweden with a larger population also provided estimates within this range.[4] Cerebrospinal-fluid (CSF) shunt has been shown to improve the symptoms of iNPH at a high rate.[5-7] However, shunt failures, such as shunt tube blockage, may occur in some patients. Herein, we report a case of shunt failure in which the proximal catheter of a ventriculoperitoneal shunt (VPS) entered the cranium. This case is a type of shunt failure that has not been previously reported, and we hope that this report will be helpful in similar cases.

Case Report

An 80-year-old female was referred to our hospital. The

Received May 11, 2022; Accepted November 28, 2022

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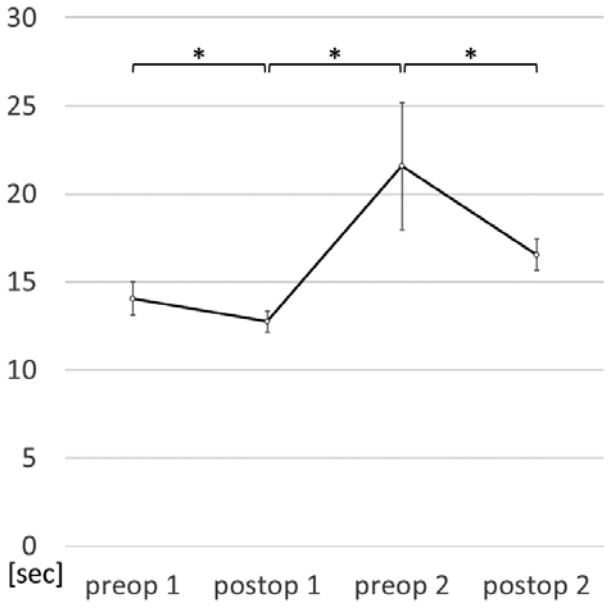

Fig. 1 Time score of 3 m Timed Up and Go test in each period (average ± standard deviation). Preop 1, postop 1, preop 2, and postop 2 refer to before the first shunt surgery (age 77), 1 year after the first shunt surgery (age 78), before the shunt revision (age 80), and 2-3 weeks after shunt revision, respectively. The asterisks indicate statistical significance in the independent *t*-test ($p < 0.01$).

patient presented with hypertension and osteoporosis. She had suffered from progressive cognitive dysfunction and gait disturbance for 9 years and had started experiencing urge urinary incontinence 4 years earlier. Based on the improvement in gait on the tap test[8] and imaging findings, including a disproportionately enlarged subarachnoid space,[6] the patient was diagnosed with probable iNPH[9] at the age of 77 years; in the same year, she underwent VPS surgery with the Codman Hakim programmable valve (Integra LifeSciences, Princeton, NJ, USA). Her cognitive function, gait symptoms, and urinary incontinence improved after the surgery, and a follow-up examination 1 year after the surgery confirmed no problems with the shunt condition and her postoperative course. Correspondingly, head computed tomography (CT) revealed shrinkage of the ventricular volume. She fell 1 year after the surgery, broke her right distal radius, fell again 1 year later, and broke her left distal radius, both of which were treated with orthopedic surgery and healed without significant sequelae. Her family doctor referred her to our department because she had developed gait, cognitive impairment, and urinary incontinence again over the last 3 months. When admitted to the hospital, she exhibited a broad-based, unsteady, and magnetic gait. The average time of the Timed Up and Go tests[8] showed deterioration from 12.7 sec (1 year after VPS) to 21.6 sec. The longitudinal changes in this test are illustrated in Fig. 1. The reservoir of her shunt valve did not collapse, and the adjustment of the valve-opening pressure did not improve her symptoms. Fig. 2 shows X-ray photographs (A, B) and parasagittal CT (C, D) 1 year after the first surgery and at the time of admission, respectively. These images suggest that the ventricular catheter had disconnected from the shunt valve and migrated into the cranium. Imaging studies also showed that the ventricles were enlarged.

Since shunt failure was believed to have caused deterioration in cognitive function and gait disturbance, a reoperation was performed. Upon removal of the shunt system, it was found that the ligature thread holding the proximal catheter in place ruptured. As the distal end of the proximal catheter was facing the burr hole (Fig. 3), it could be carefully pulled and removed. The shunt system implanted in the first surgery was entirely removed, including the peripheral catheter, and the VPS was reconstructed using new equipment. The postoperative course was favorable, with improvements in gait and cognition. Two years after the surgery, she could still walk on her own and live independently.

Discussion

CSF shunt efficacy and risk of failure in iNPH

The importance of proper diagnosis and management of iNPH has been emphasized in recent decades[6,9,10] as the reversibility of iNPH symptoms after CSF shunt surgery has been recognized. The outcomes of CSF shunts for iNPH have improved over time[11] through advances in both diagnosis[6,8,12-17] and treatment.[18-23] For example, a study reported in 1978 involving 37 cases of iNPH with CSF shunts showed up to 19 complications and a limited improvement rate of 33%, and the authors suggested that the expected benefits of CSF shunt were not reasonable compared to the risks involved in the shunt surgery in many cases,[24] while a recent review concluded that more than 75% of patients experienced improvement with shunt surgery.[5] Hung et al. reported that 28.9% of iNPH cases treated with VPS and 10.7% of ventriculoatrial shunts required revision surgery.[25] The authors reported that the most frequent complication was over-drainage. Recent studies have shown that programmable valves significantly reduce this complication.[22,23] Considering these advances, it is advisable to discuss the surgical outcomes of iNPH based on recent data.

Although the rate of shunt failure has decreased over time, some patients who undergo shunt surgery have experienced it. A recent meta-analysis reported a rate of reoperation after VPS of approximately 18%,[15] while studies employing programmable valves reported rates of 8.2%[26] and 15%.[27] Recent Japanese prospective cohort studies of iNPH showed more favorable outcomes; the response rates 1 year after surgery were 77% for VPS and 75% for lumboperitoneal shunt, while the reoperation rates were 1%

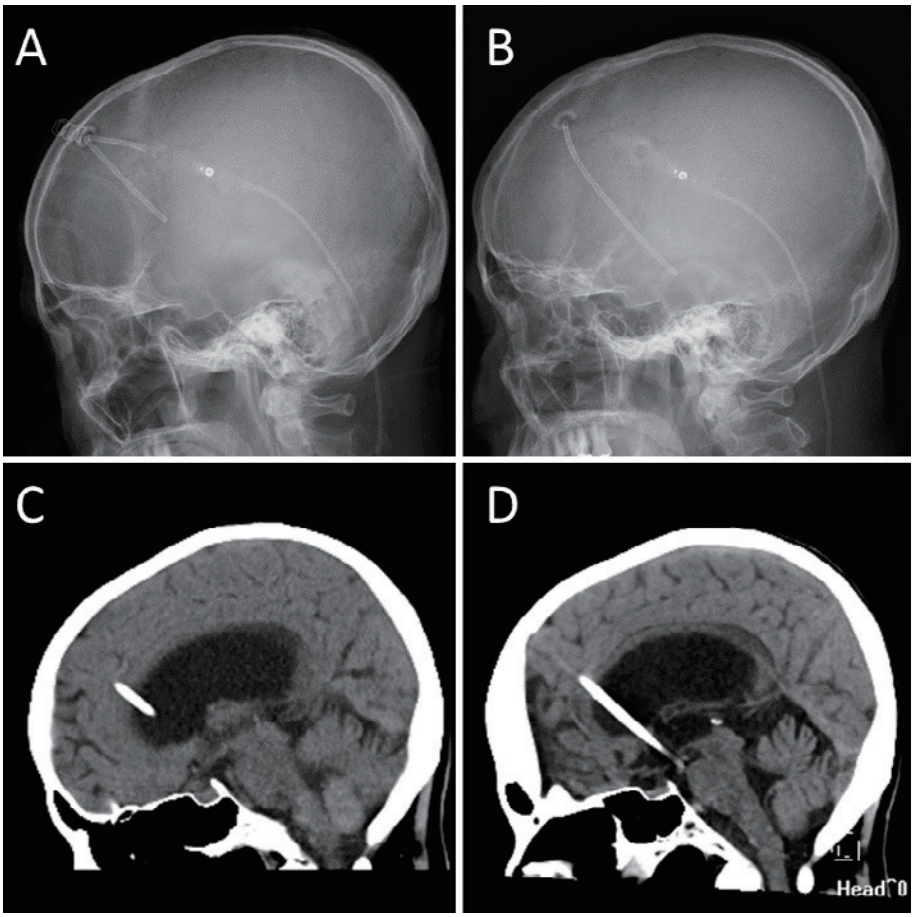

Fig. 2 Lateral view of the head X-ray 1 year after the first surgery (A) and at the time of the present admission (B). Computed tomography of the right paramedian sagittal section 1 year after the first surgery (C) and at present admission (D).

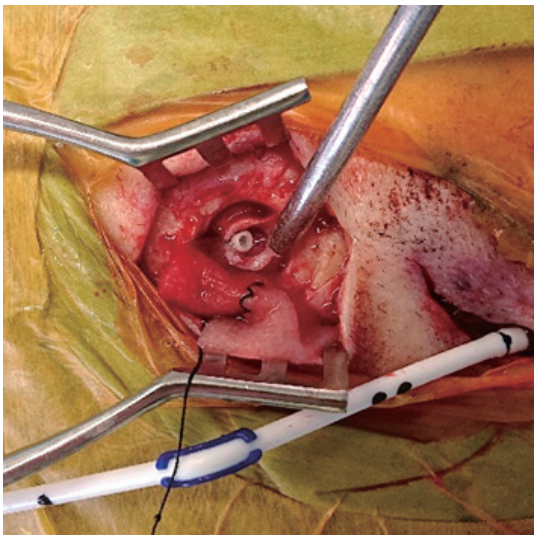

Fig. 3 The distal end of the ventricular catheter was found just below the skin incision, coinciding with the burr hole.

for VPS and 6% for lumboperitoneal shunt.[6,19] Most shunt failures occur within 1 month after surgery, and failures occurring more than 1 year after surgery are quite exceptional.[27]

Although programmable valves and antibiotic administration protocols have effectively reduced the complications of inappropriate drainage and infections,[20,28] there are mechanical shunt problems. The incidences of proximal occlusion, distal occlusion, and distal catheter dislocation have been reported to be 1.7%-12%, 1%-5.2%, and 1.4%-8%, respectively.[6,22,26,29] None of these mass studies reported proximal tube migration as a cause for shunt revision. In this sense, shunt failures in iNPH differ from those in pediatric hydrocephalus.

Proximal catheter migration is a relatively frequent complication in pediatric hydrocephalus cases,[30] and there are some case reports of proximal tubes and shunt systems migrating into the cranium[31-34] or into the subgaleal space.[35,36] As Shimizu et al. pointed out, proximal shunt failure is more likely to occur in infants with an occipital burr hole due to excessive head movements leading to shunt tube dislocation and use of valveless shunt sys-

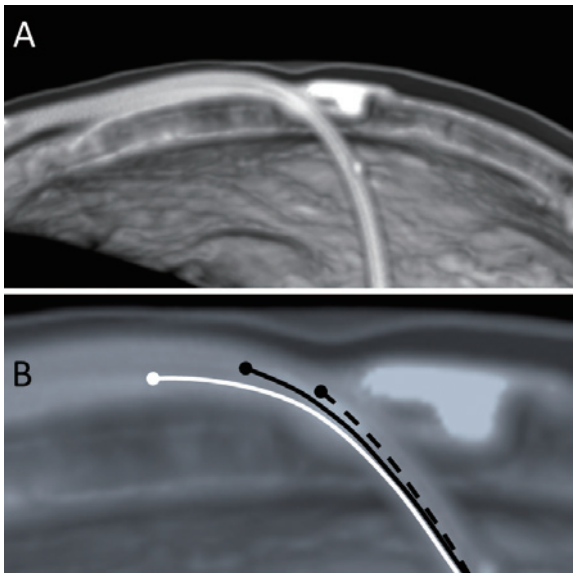

Fig. 4 A: A cross-section including the shunt tube and skull of a 3D reconstructed image made from CT images taken 1 year after the first VPS surgery. B: Model of the process of shunt slipping in. The elasticity of the shunt tube exerts a force from the white line toward the black line, then from the black line toward the dashed black line.

tems.[37] In addition, the skull of the infant is large relative to the body and the skull is flexible. This makes it relatively easy for the shunt system to migrate intracranially. Reported cases of migration of proximal tubes in adult VPS are exceptional, such as a case in which the head was repeatedly subjected to strong mechanical impacts[37] or a case with a valveless shunt system.[38]

Possible mechanism for shunt failure

In this case, 3 years following VPS surgery, the proximal catheter detached from the shunt valve and entered the cranium. The shunt system required a manual connection between the proximal tube and valve, and herein lies the potential for an accident to occur. The absence of abnormal findings on imaging studies at the 1-year postoperative follow-up examination ruled out the possibility that the proximal tube and valve were not connected during the initial surgery. Therefore, subsequent events should be considered the cause of this failure.

The first hypothetical factor is the tractive force from the distal tube, which can be caused by a patient's body movements. Although the shunt valve was unlikely to have been subjected to a large force at one time as no noticeable change was evident in its position, it is possible that repeated minor traction may have caused the peripheral tube to slowly and gradually separate from the shunt valve. The second hypothetical factor is that after the proximal shunt tube detached from the shunt valve and intruded the cranial cavity to some degree, the elasticity of the proximal tube might have induced further intrusion. Fig. 4A shows a cross-section of the shunt tube and skull in a 3D reconstructed image made from CT images taken 1 year after the first VPS surgery. Once the distal end of the proximal tube approaches the burr hole (white line in Fig. 4B), the elasticity of the tube exerts a force, which acts toward maneuvering the tube from the position of the white line to that of the black line. Subsequently, the force required for its transposition from the position of the black line to that of the dashed black line acts next. The finding that the distal end of the proximal tube was located just at the burr hole may be explained by this hypothesis.

There are several possible approaches to prevent shunt-related problems, as has been outlined here. A fundamental approach is to adopt a shunt system in which the proximal catheter is not separated from the shunt valve. However, shunt devices are usually selected based on several other factors. When using a separate shunt system, the connection of the proximal tube to the shunt valve is important. Regarding the connection, we have standardized double ligation with a single nylon thread at our hospital. Alternative threads may be less likely to slip than nylon threads; however, silk threads are inappropriate in terms of infection risk. Moreover, fixation of the shunt valve to the skull may be effective, which could prevent our first hypothetical factor from occurring. However, a disadvantage is that it hinders subsequent reoperations. Another approach to improve the fixation of the shunt valve is to make a skin incision on the cephalic side, create a subcutaneous pocket toward the body side, and insert the shunt valve into this pocket. This technique may reduce the room for the shunt valve to move distally when pulled by the distal tube. Finally, our second hypothetical factor was related to the bending angle of the proximal tube near the burr hole. Thus, it would be better to make the angle obtuse.

All prevention approaches listed here are hypothetical; however, some may be worth considering in clinical practice.

Impacts of prompt operation on functional prognosis

The importance of prompt CSF shunt reconstruction must also be discussed. Some neurosurgeons hesitate to reoperate on elderly patients, not only because of the high risk of complications but also because they anticipate less favorable outcomes. Although nationwide surveys in the United States indicate that older age is a risk factor for non-routine discharge[39] and readmission[40] after shunt surgery for iNPH, these results reflect the confounding effects of various background factors. Some controlled studies have shown that age does not predict postoperative improvement in iNPH.[25,41] Kobayashi et al. noted that the duration of untreated iNPH, but not age, predicts unfavorable postoperative improvement.[42]

Recent studies suggest that shunt therapy for iNPH can

benefit patients over 5 years if properly managed.[26,29,43] Although no group studies focusing on improvement after shunt revision have been conducted so far, Rinaldo et al. showed that of 18 patients who underwent shunt revision, 7 (38.9%) improved, 6 (33.3%) remained the same, and 5 (27.8%) worsened in symptoms.[22] In the management of iNPH, prompt treatment may be desirable regardless of age.

In this case, the patient and her family doctor noticed the recurrence of cognitive dysfunction, gait disturbance, and urinary incontinence, which led to relatively early detection of shunt failure and reoperation. After the shunt revision, the patient showed significant improvement compared with the preoperative levels (Fig. 1), although the levels observed 1 year after the first shunt surgery were not reached. If a patient with iNPH whose symptoms improve after surgery experiences another exacerbation and shows no improvement even after lowering the set pressure, shunt failure should be suspected, and a thorough examination should be performed. The cause of failure can only be identified by imaging studies, especially in cases of failure, such as in this case. Since the site of failure, in this case, was between the burr hole and shunt valve, the site of failure could have been overlooked if attention was paid only to the intracranial region on the head CT.

Conclusion

It is important to note that shunt failure can occur anywhere from the ventricles to the intraperitoneal cavity; all these areas should be covered with imaging studies in cases of suspected shunt failure. Since this patient was able to undergo re-examination and reoperation relatively early (3 months after the exacerbation), she showed good postoperative recovery in gait and cognitive function. It is worth noting that there are cases in which significant improvement in gait can be achieved even after shunt revision surgery at an elderly age.

Acknowledgments

This work was supported by the Health Labor Sciences Research (grant nos. 20GB1002 and 20GC1008), Grant-in-Aid for Transformative Research Areas (grant no. 20H 05956), and Grant-in-Aid for Scientific Research (B) (grant no. 21H03779) to KS. This study was conducted following the 1964 Declaration of Helsinki and its amendments. We obtained the patient's permission and informed consent to publish her information and images.

Conflicts of Interest Disclosure

The authors declare no conflict of interest.

References

1) Adams RD, Fisher CM, Hakim S, Ojemann RG, Sweet WH: Symptomatic occult hydrocephalus with normal cerebrospinal-fluid pressure: A treatable syndrome. *N Engl J Med* 273: 117-126, 1965
2) Hakim S, Adams RD: The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. *J Neurol Sci* 2: 307-327, 1965
3) Tanaka N, Yamaguchi S, Ishikawa H, Ishii H, Meguro K: Prevalence of possible idiopathic normal-pressure hydrocephalus in Japan: the Osaki-Tajiri project. *Neuroepidemiology* 32: 171-175, 2009
4) Jaraj D, Rabiei K, Marlow T, Jensen C, Skoog I, Wikkelsø C: Prevalence of idiopathic normal-pressure hydrocephalus. *Neurology* 82: 1449-1454, 2014
5) Giordan E, Palandri G, Lanzino G, Murad MH, Elder BD: Outcomes and complications of different surgical treatments for idiopathic normal pressure hydrocephalus: a systematic review and meta-analysis. *J Neurosurg* 131: 1-13, 2018
6) Hashimoto M, Ishikawa M, Mori E, Kuwana N, Study of INPH on neurological improvement (SINPHONI): Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: A prospective cohort study. *Cerebrospinal Fluid Res* 7: 18, 2010
7) Kazui H, Miyajima M, Mori E, Ishikawa M, SINPHONI-2 Investigators: Lumboperitoneal shunt surgery for idiopathic normal pressure hydrocephalus (SINPHONI-2): an open-label randomised trial. *Lancet Neurol* 14: 585-594, 2015
8) Yamada S, Ishikawa M, Miyajima M, et al.: Timed UP and Go test at tap test and shunt surgery in idiopathic normal pressure hydrocephalus. *Neurol Clin Pract* 7: 98-108, 2017
9) Mori E, Ishikawa M, Kato T, et al.: Guidelines for management of idiopathic normal pressure hydrocephalus: Second edition. *Neurol Med Chir (Tokyo). 2nd ed* 52: 775-809, 2012
10) Nakajima M, Yamada S, Miyajima M, et al.: Guidelines for Management of Idiopathic Normal Pressure Hydrocephalus (Third Edition): Endorsed by the Japanese Society of Normal Pressure Hydrocephalus. *Neurol Med Chir (Tokyo). 3rd ed* 61: 63-97, 2021
11) Toma AK, Papadopoulos MC, Stapleton S, Kitchen ND, Watkins LD: Systematic review of the outcome of shunt surgery in idiopathic normal-pressure hydrocephalus. *Acta Neurochir (Wien)* 155: 1977-1980, 2013
12) Ishii K, Kanda T, Harada A, et al.: Clinical impact of the callosal angle in the diagnosis of idiopathic normal pressure hydrocephalus. *Eur Radiol* 18: 2678-2683, 2008
13) Ishikawa M, Oowaki H, Matsumoto A, Suzuki T, Furuse M, Nishida N: Clinical significance of cerebrospinal fluid tap test and magnetic resonance imaging/computed tomography findings of tight high convexity in patients with possible idiopathic normal pressure hydrocephalus. *Neurol Med Chir (Tokyo)* 50: 119-123; disucussion 123, 2010
14) Sasaki M, Honda S, Yuasa T, Iwamura A, Shibata E, Ohba H: Narrow CSF space at high convexity and high midline areas in idiopathic normal pressure hydrocephalus detected by axial and coronal MRI. *Neuroradiology* 50: 117-122, 2008
15) Virhammar J, Laurell K, Cesarini KG, Larsson EM: Preoperative prognostic value of MRI findings in 108 patients with idiopathic normal pressure hydrocephalus. *AJNR Am J Neuroradiol* 35: 2311-2318, 2014
16) Wikkelsø C, Hellström P, Klinge PM, Tans JT, European iNPH Multicentre Study Group: The European iNPH multicentre study on the predictive values of resistance to CSF outflow and the

CSF tap test in patients with idiopathic normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatry* 84: 562-568, 2013
17) Yamada S, Ishikawa M, Yamamoto K: Fluid distribution pattern in adult-onset congenital, idiopathic, and secondary normal-pressure hydrocephalus: implications for clinical care. *Front Neurol* 8: 583, 2017
18) Aghayev K, Iqbal SM, Asghar W, Shahmurzada B, Vrionis FD: Advances in CSF shunt devices and their assessment for the treatment of hydrocephalus. *Expert Rev Med Devices* 18: 865-873, 2021
19) Miyajima M, Kazui H, Mori E, Ishikawa M, on behalf of the SINPHONI-2 Investigators: One-year outcome in patients with idiopathic normal-pressure hydrocephalus: comparison of lumboperitoneal shunt to ventriculoperitoneal shunt. *J Neurosurg* 125: 1483-1492, 2016
20) Okamura Y, Maruyama K, Fukuda S, et al.: Detailed standardized protocol to prevent cerebrospinal fluid shunt infection. *J Neurosurg* 132: 755-759, 2019
21) Pollack IF, Albright AL, Adelson PD: A randomized, controlled study of a programmable shunt valve versus a conventional valve for patients with hydrocephalus. Hakim-medos investigator group. *Neurosurgery* 45: 1399-1408; discussion 1408, 1999 [discussion] 1408-1311
22) Rinaldo L, Bhargav AG, Nesvick CL, Lanzino G, Elder BD: Effect of fixed-setting versus programmable valve on incidence of shunt revision after ventricular shunting for idiopathic normal pressure hydrocephalus. *J Neurosurg* 133: 1-9, 2019
23) Serarslan Y, Yilmaz A, Çakır M, et al.: Use of programmable versus nonprogrammable shunts in the management of normal pressure hydrocephalus: A multicenter retrospective study with cost-benefit analysis in Turkey. *Med (Baltim)* 96: e8185, 2017
24) Hughes CP, Siegel BA, Coxe WS, et al.: Adult idiopathic communicating hydrocephalus with and without shunting. *J Neurol Neurosurg Psychiatry* 41: 961-971, 1978
25) Hung AL, Vivas-Buitrago T, Adam A, et al.: Ventriculoatrial versus ventriculoperitoneal shunt complications in idiopathic normal pressure hydrocephalus. *Clin Neurol Neurosurg* 157: 1-6, 2017
26) Gölz L, Ruppert FH, Meier U, Lemcke J: Outcome of modern shunt therapy in patients with idiopathic normal pressure hydrocephalus 6 years postoperatively. *J Neurosurg* 121: 771-775, 2014
27) Feletti A, d'Avella D, Wikkelsø C, et al.: Ventriculoperitoneal shunt complications in the European idiopathic normal pressure hydrocephalus multicenter study. *Oper Neurosurg (Hagerstown)* 17: 97-102, 2019
28) Sundström N, Lagebrant M, Eklund A, Koskinen LD, Malm J: Subdural hematomas in 1846 patients with shunted idiopathic normal pressure hydrocephalus: treatment and long-term survival. *J Neurosurg* 129: 797-804, 2018
29) Grasso G, Torregrossa F, Leone L, Frisella A, Landi A: Long-term efficacy of shunt therapy in idiopathic normal pressure hydrocephalus. *World Neurosurg* 129: e458-e463, 2019
30) Kast J, Duong D, Nowzari F, Chadduck WM, Schiff SJ: Time-related patterns of ventricular shunt failure. *Childs Nerv Syst* 10: 524-528, 1994
31) Ammar A, Nasser M: Intraventricular migration of VP shunt. *Neurosurg Rev* 18: 293-295, 1995
32) Mazza CA, Bricolo A: Upward dislocation of peritoneal catheter into the ventricular cavity. A rare complication of the ventriculoperitoneal shunt. Report of a case. *Neuropädiatrie* 6: 313-316, 1975
33) Mori K, Yamashita J, Handa H: "Missing tube" of peritoneal shunt: migration of the whole system into ventricle. *Surg Neurol* 4: 57-59, 1975
34) Young HA, Robb PJ, Hardy DG: Complete migration of ventriculoperitoneal shunt into the ventricle: report of two cases. *Neurosurgery* 12: 469-471, 1983
35) Dominguez CJ, Tyagi A, Hall G, Timothy J, Chumas PD: Subgaleal coiling of the proximal and distal components of a ventriculo-peritoneal shunt. An unusual complication and proposed mechanism. *Childs Nerv Syst* 16: 493-495, 2000
36) Yılmaz M, Kalemci O, Ur K, Yüksel ZK, Yücesoy K: Extrusion of the ventricular component of a ventriculo-peritoneal shunt into the subgaleal space: case report of an unusual complication. *J Nerv Syst Surg* 4: 20-23, 2014
37) Shimizu S, Mochizuki T, Nakayama K, Fujii K: Visual field defects due to a shunt valve migrating into the cranium. *Acta Neurochir (Wien)* 144: 1055-1056, 2002
38) Garijo JA, Pecourt JC, de la Resurrección M: Migration of ventriculo-peritoneal shunt into lateral ventricle of an adult. *Surg Neurol* 11: 399-400, 1979
39) Alvi MA, Brown D, Yolcu YU, et al.: Predictors of adverse outcomes and cost after surgical management for idiopathic normal pressure hydrocephalus: analyses from a national database. *Clin Neurol Neurosurg* 197: 106178, 2020
40) Koo AB, Elsamadicy AA, Lin IH, et al.: Patient risk factors associated with 30- and 90-day readmission after ventriculoperitoneal shunt placement for idiopathic normal pressure hydrocephalus in elderly patients: A nationwide readmission study. *World Neurosurg* 152: e23-e31, 2021
41) Popal AM, Zhu Z, Guo X, et al.: Outcomes of ventriculoperitoneal shunt in patients with idiopathic normal-pressure hydrocephalus 2 years after surgery. *Front Surg* 8: 641561, 2021
42) Kobayashi E, Kanno S, Kawakami N, et al.: Risk factors for unfavourable outcomes after shunt surgery in patients with idiopathic normal-pressure hydrocephalus. *Sci Rep* 12: 13921, 2022
43) Mirzayan MJ, Luetjens G, Borremans JJ, Regel JP, Krauss JK: Extended long-term (> 5 years) outcome of cerebrospinal fluid shunting in idiopathic normal pressure hydrocephalus. *Neurosurgery* 67: 295-301, 2010

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