Clinical Neurology and Neurosurgery 193 (2020) 105748

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

The efficacy and limitation of lumboperitoneal shunt in normal pressure hydrocephalus

Jung-Tung Liu[a,b,*], Pen-Hua Su[a,c,**]

[a] School of Medicine, Chung Shan Medical University, Taichung 40201, Taiwan
[b] Department of Neurosurgery, Chung Shan Medical University Hospital, Taichung 40201, Taiwan
[c] Department of Pediatrics and Genetics, Chung Shan Medical University Hospital, Taichung 40201, Taiwan

ARTICLE INFO

Keywords:
Alzheimer's disease
Cerebrospinal fluid
Idiopathic normal pressure hydrocephalus
lumbar–peritoneal shunt

ABSTRACT

Objective: To investigate whether the efficacy of the lumbar–peritoneal (LP) shunt is sustainable, we measured the outcomes of patients with idiopathic NPH (iNPH) preoperatively and postoperatively.
Patients and methods: We retrospective reviewed records of 58 patients with iNPH from 2013 to 2015. Exclusion of 7 patients expired, 1 patient shunt infection, and 8 patients was loss of follow-up. In the remaining 42 patients, the mood, talking response, movement, attention, recalling memory, and mini-mental state examination (MMSE), representing patient outcomes, were measured. All of whom were follow-up for 3 years.
Results: Mood (1.91 ± 0.30), talking response (1.98 ± 0.15), movement (1.71 ± 0.51), attention (1.95 ± 0.22), and recalling memory (1.86 ± 0.35) were significantly improved after surgery (1 week;$p < 0.0001$). However, the indicators significantly declined after 3 years (mood: 0.31 ± 0.52, talking response: 0.50 ± 0.59, movement: 0.17 ± 0.38, attention: 0.40 ± 0.59, recalling memory: 0.21 ± 0.42). The MMSE was also significantly improved after 3 months of surgery (17.9 5 ± 2.80 vs. 25.02 ± 3.36; $p < 0.0001$). However, it declined after 3 years (17.83 ± 3.66; $p = 0.83$).
Conclusion: The iNPH is considered potentially reversible. Our data supported that the LP shunt was efficient in the short term. However, the neurological degeneration was still progressive.

1. Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a reversible neurological disorder often seen in elderly populations. It is characterized by ventriculomegaly and major triad symptoms of gait disturbance, cognitive decline, and urinary incontinence [1–4]. The pathophysiology underlying iNPH has not been fully elucidated [5]. According to epidemiology surveys, the estimated prevalence and incidence of iNPH range from 10.2 to 21.9 and 1.08–5.5 individuals per 100,000 persons, respectively [6–9]. Such discrepancy among these epidemiological studies may result from the general age-related symptoms in elderly people that tend to not be recognized as symptoms of iNPH precisely [10].

Both ventriculoperitoneal (VP) and lumbar–peritoneal (LP) shunt implantations are efficient for alleviating the symptoms of iNPH with no evident differences in treatment outcomes between interventions [10]. Despite the association of LP shunt with high risk of surgical complications and frequent revisions [11,12], it can be recommended for the treatment of iNPH because of minimal invasiveness and non-lethal complications [13,14].

To date, the usefulness and complications of VP shunt for the treatment of iNPH patients have been established even in long-term studies in Western countries [15–18]. However, few studies have investigated the efficacy of LP shunt for the short-term treatment of iNPH [10,11,13,14]. No study has investigated its long-term effects. The long-term outcomes of LP shunt in iNPH patients remain to be determined. Therefore, we conducted a retrospective review of iNPH patients who received LP shunt followed for 3 years and assessed indicators of outcome to examine the improvements in iNPH patients.

2. Patients and methods

2.1. Patient demographics and procedures

From 2013–2015, 58 patients who were diagnosed with iNPH based on international consensus guidelines [3] and planned for LP shunt

* Corresponding author at: Department of Neurosurgery, No. 110 Sec 1 Chien-Kuo N.Road, Taichung City 40201, Taiwan.
** Corresponding author at: Department of Genetics, No. 110 Sec 1 Chien-Kuo N.Road, Taichung City 40201, Taiwan.
E-mail addresses: cshy654@csh.org.tw (J.-T. Liu), jen@csh.org.tw (P.-H. Su).

https://doi.org/10.1016/j.clineuro.2020.105748
Received 25 December 2019; Received in revised form 17 February 2020; Accepted 23 February 2020
Available online 24 February 2020
0303-8467/

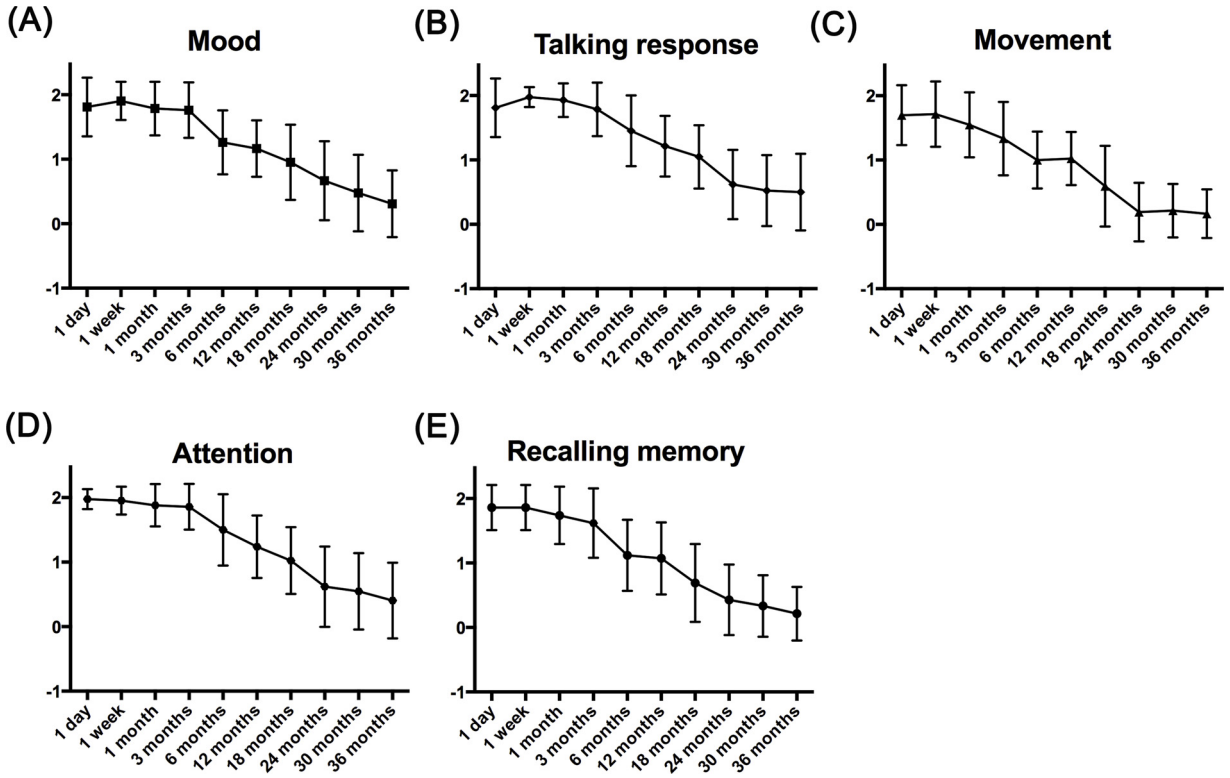

Fig. 1. (A) Mood, (B) talking response, (C) movement, (D) attention, and (E) recalling memory were measured pre- and postoperatively (3, 6, 12, 18, 24, 30, and 36 months).

surgery were included in this study. All patients had ventricular enlargement (Evan's ratio > 0.3), presenting one or more major triad symptoms, and received tap test for evaluation of shunt implantation. Seven patients expired (three had cardiac problems, two suffered from pneumonia, and two had a stroke), one patient were shunt infection and eight patients were lost to follow-up and excluded in this study. In the remaining 42 patients, the mood, talking response, movement, attention, recalling memory, and MMSE, representing patient outcomes, were measured. The male iNPH patients comprised 40.5 % (17 of 42) of the population. The mean age was 79.05 ± 6.55 years (male: 78.59 ± 5.79 years; female: 79.36 ± 7.12 years). The outcome follow-up duration was 3 years. The retrospective review without patient consent was performed at the Chung Shan Medical University Hospital after approval was obtained from the local institutional review board (CS18205).

2.2. Valve adjustment

The pressure of the LP shunt system was set to its highest level of 2.5 initially. After operation, we check the function, if no improvement in the patient's clinical symptoms were observed, we lowered the pressure setting by 1 step (0.5 level). While patients return and with clinical outcomes exacerbation, we lowered the pressure setting by 0.5 level until the level of 1. Every setting is with careful consideration of the patient's safety range. The pressure was setting back immediately if a symptomatic subdural hematoma related to overdrainage was found.

2.3. Clinical evaluation

Dr. Jung-Tung Liu successfully completed LP shunt ("Medtronic" PS Medical Strata NSC Lumboperitoneal Valve and Shunt System 44420, Cremona Drive, Goleta, CA 93117, U.S.A.) surgery in all patients with symptoms of typical iNPH, including gait disturbance with or without cognition decline or urinary incontinence, which were progressive during the time. The MMSE was measured preoperatively and postoperatively (3, 6, 12, 18, 24, 30, and 36 months) [19]. The patients and their families were also interviewed regarding observed cognitive and gait changes at home after interventions and, in particular, functional impairment resulting from dementia. The questionnaire for the recovery rate was divided into five domains, including mood, talking response, movement, attention, and recalling memory. The recovery rate of iNPH was scored as follows: improved; 2 points, better; 1 point, maintained; 0 points, and worse; -1 point. All recovery outcomes were collected and assessed at 1 day, 1 week, 1 month, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months.

2.4. Statistical analysis

Data plotting and statistics were processed using the GraphPad Prism software for Mac OS X. Values represent the mean ± SD. The mood, talking response, movement, attention, recalling memory, and MMSE were evaluated using the paired Student's *t*-test. Significance was set at $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

3. Results

All 58 patients were diagnosed with iNPH and received LP shunt implantation initially. However, seven patients expired (three had cardiac problems, two suffered from pneumonia, and two had a stroke), one patient shunt infection and eight patients were lost to follow-up. The remaining 42 patients were enrolled, and the mood, talking response, movement, attention, recalling memory, and MMSE, representing patient outcomes, were measured. The outcome follow-up duration was 3 years. Mood (1.91 ± 0.30), talking response (1.98 ± 0.15), movement (1.71 ± 0.51), attention (1.95 ± 0.22), and recalling memory (1.86 ± 0.35) were significantly improved 1 week after surgery (Figs. 1 and 2; $p < 0.0001$), suggesting that the recovery rates were efficient immediately. However, the recovery

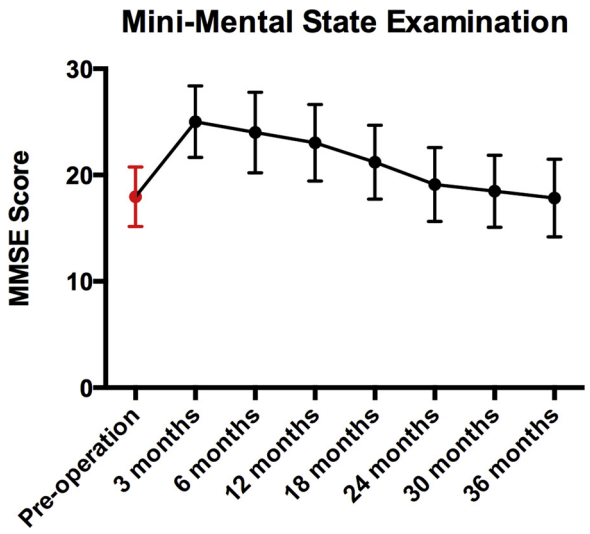

Fig. 2. MMSE was measured pre- and postoperatively (3, 6, 12, 18, 24, 30, and 36 months).

outcomes declined over time. The indicators significantly declined after 3 years (mood: 0.31 ± 0.52, talking response: 0.50 ± 0.59, movement: 0.17 ± 0.38, attention: 0.40 ± 0.59, recalling memory: 0.21 ± 0.42). Moreover, the MMSE (17.95 ± 2.80 vs. 25.02 ± 3.36) significantly improved after 3 months of surgery (Fig. 2; $p < 0.0001$). However, it also declined over time. The significant decline (17.83 ± 3.66) was observed after 3 years compared with the pre-operation (Fig. 2; $p = 0.83$), indicating that the recovery outcomes of LP shunt for the treatment of iNPH were not sustainable. The neurological degeneration was still progressive. Therefore, combining shunt interventions may be beneficial for sustaining their efficacy. Moreover, randomized controlled trials must be performed to determine the efficacy.

4. Discussions

To our knowledge, the length of response to LP shunt surgery is limited in duration. Only a few studies have reported the efficacy of LP shunt for the treatment of iNPH in short-term follow-up examination [10,11,13,14]. In the present study, we demonstrated the benefit of LP shunt for the treatment of iNPH. The recovery outcomes significantly improved immediately after 1 week. However, the recovery outcomes, including MMSE, declined over time. The outcomes deteriorated near pre-operation levels after 3 years, indicating that the recovery outcomes of LP shunt for the treatment of iNPH were not sustainable. Consistent with VP shunt surgery studies, a high percentage of patients (96 %) subjectively perceived improvements at the short-term follow-up examination; however, at long-term follow-up, only 57 % reported improvements [20]. Despite receiving shunt surgery, 80 % of iNPH patients had cognitive decline, and 46 % had clinical dementia.

Common complications affect the efficacy of the LP shunt include shunt infection; malfunction (including dislocation, disconnection, migration, and obstruction); Arnold–Chiari I malformation (ACM); subdural hematoma due to overdrainage; CSF leakage; and radicular pain [21–23]. Therefore, to avoid the higher occurred rate of complications (40.2 %), including three majors of shunt malfunction, infection, subdural hematoma due to overdrainage [24], we performed LP shunt implantation by using two-stage procedure [25]. The report indicated significant decline the rate of shunt revision (1% vs. 13.5 %; $p = 0.001$) in LP shunt group compared to VP shunt group. However, the decline the rate of shunt malfunction (0% vs. 7.3 %; N/A), and infection (1.0 % vs. 5.7 %; $p = 0.061$) was not considered significant different. Although the subdural hematoma was lower than Tracy et al. proposed (27.5 %) [24]. The occurred rate of subdural hematoma was not different significantly between two groups in the previous study [25].

Based on clinical experience, the poor prognosis of iNPH patients with shunts is associated with longstanding symptoms and old age at the time of shunt implantation [16]. This progressive cognitive impairment is related to coexisting degenerative brain disease [26]. Moreover, frontal lobe executive functions deteriorate early in iNPH patients, and irreversible pathological changes in the frontostriatal pathways may develop [6,27]. To differentiate iNPH and Alzheimer's disease (AD) in the workup preceding shunt placement, cerebrospinal fluid (CSF) levels of Ab42, total tau, and HPtau may serve as biomarkers. However, despite differentiating iNPH from AD by using CSF biopsy, AD-related neuropathological changes such as Aβ deposits, neurofibrillary tangles, and reduced CSF Aβ42 may be observed in iNPH patients. Therefore, the assessment of neurotoxic proteins can be considered in future studies.

Aβ levels should be analyzed in the circulating CSF as a small frontal brain biopsy sample may reflect only a limited brain region that may not be representative of the global tissue levels of Aβ. Carbon 11-labeled Pittsburgh compound B ([^{11}C]PiB) PET and its analog fluorine-18 [^{18}F]flutemetamol PET may quantify insoluble fibril Aβ deposits *in vivo* [28–30]. In iNPH patients, [^{11}C]PiB and [^{18}F]flutemetamol uptake seems to be correlated with immunohistochemical Aβ aggregates [31,32]. However, PET cannot estimate soluble Aβ species in brain tissues.

The relation between neurotoxic proteins in brain biopsy samples and CSF in response to shunt surgery has been previously documented and confirmed [33–35]. In the present study, the diversion of CSF by shunt surgery for the treatment of iNPH is effective. However, the symptoms are still progressive. Therefore, we think combining shunt interventions may be beneficial for sustaining their efficacy.

The study has a number of limitations. First, the cohort is small. The findings have to be confirmed in a larger cohort. Second, this is a retrospective study. Randomized controlled trials should be performed in the future. Third, the poor long-term outcomes possibly related to the upregulation of valve adjustment with uncovered overdrainage has to be validated. Finally, future studies should examine the levels of neurotoxic proteins in CSF and brain tissues to determine the progression of AD-related diseases in long-term follow-up.

5. Conclusion

The iNPH is considered potentially reversible. Our data supported that the LP shunt was efficient in the short term. The neurological degeneration was still progressive.

Disclosure of funding

None.

CRediT authorship contribution statement

Jung-Tung Liu: Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Pen-Hua Su:** Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

All authors have no potential conflicts of interest to disclose.

Acknowledgments

We thank Dr. Ryh-Shine Su who was our teacher in medical school for the encouragement that we can fulfill this study.

References

[1] R.D. Adams, C.M. Fisher, S. Hakim, R.G. Ojemann, W.H. Sweet, Symptomatic occult hydrocephalus with "Normal" cerebrospinal-fluid pressure. A treatable syndrome, N. Engl. J. Med. 273 (1965) 117–126.

[2] S. Hakim, R.D. Adams, The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics, J. Neurol. Sci. 2 (4) (1965) 307–327.

[3] N. Relkin, A. Marmarou, P. Klinge, M. Bergsneider, P.M. Black, Diagnosing idiopathic normal-pressure hydrocephalus, Neurosurgery 57 (Suppl. (3)) (2005) S4–16 discussion ii-v.

[4] A. Marmarou, M. Bergsneider, N. Relkin, P. Klinge, P.M. Black, Development of guidelines for idiopathic normal-pressure hydrocephalus: introduction, Neurosurgery 57 (Suppl. (3)) (2005) S1–3 discussion ii-v.

[5] C. Iseki, Y. Takahashi, M. Wada, T. Kawanami, M. Adachi, T. Kato, Incidence of idiopathic normal pressure hydrocephalus (iNPH): a 10-year follow-up study of a rural community in Japan, J. Neurol. Sci. 339 (1-2) (2014) 108–112.

[6] A. Brean, P.K. Eide, Prevalence of probable idiopathic normal pressure hydrocephalus in a Norwegian population, Acta Neurol. Scand. 118 (1) (2008) 48–53.

[7] N. Kuriyama, M. Miyajima, M. Nakajima, M. Kurosawa, W. Fukushima, Y. Watanabe, E. Ozaki, Y. Hirota, A. Tamakoshi, E. Mori, T. Kato, T. Tokuda, A. Urae, H. Arai, Nationwide hospital-based survey of idiopathic normal pressure hydrocephalus in Japan: epidemiological and clinical characteristics, Brain Behav. 7 (3) (2017) e00635.

[8] J. Lemcke, D. Stengel, F. Stockhammer, C. Guthoff, V. Rohde, U. Meier, Nationwide incidence of normal pressure hydrocephalus (NPH) assessed by insurance claim data in Germany, Open Neurol. J. 10 (2016) 15–24.

[9] R. Martin-Laez, H. Caballero-Arzapalo, N. Valle-San Roman, L.A. Lopez-Menendez, J.C. Arango-Lasprilla, A. Vazquez-Barquero, Incidence of idiopathic normal-pressure hydrocephalus in Northern Spain, World Neurosurg. 87 (2016) 298–310.

[10] M. Nakajima, M. Miyajima, I. Ogino, C. Akiba, K. Kawamura, M. Kurosawa, N. Kuriyama, Y. Watanabe, W. Fukushima, E. Mori, T. Kato, H. Sugano, K. Karagiozov, H. Arai, Shunt intervention for possible idiopathic normal pressure hydrocephalus improves patient outcomes: a nationwide hospital-based survey in Japan, Front. Neurol. 9 (2018) 421.

[11] M. Miyajima, H. Kazui, E. Mori, M. Ishikawa, o.b.o.t. Sinphoni-Investigators, One-year outcome in patients with idiopathic normal-pressure hydrocephalus: comparison of lumboperitoneal shunt to ventriculoperitoneal shunt, J. Neurosurg. 125 (6) (2016) 1483–1492.

[12] R.P. Menger, D.E. Connor Jr., J.D. Thakur, A. Sonig, E. Smith, B. Guthikonda, A. Nanda, A comparison of lumboperitoneal and ventriculoperitoneal shunting for idiopathic intracranial hypertension: an analysis of economic impact and complications using the Nationwide Inpatient Sample, Neurosurg. Focus 37 (5) (2014) E4.

[13] H. Kazui, M. Miyajima, E. Mori, M. Ishikawa, S.- Investigators, Lumboperitoneal shunt surgery for idiopathic normal pressure hydrocephalus (SINPHONI-2): an open-label randomised trial, Lancet Neurol. 14 (6) (2015) 585–594.

[14] M. Nakajima, M. Miyajima, I. Ogino, H. Sugano, C. Akiba, N. Domon, K.L. Karagiozov, H. Arai, Use of external lumbar cerebrospinal fluid drainage and lumboperitoneal shunts with Strata NSC valves in idiopathic normal pressure hydrocephalus: a single-center experience, World Neurosurg. 83 (3) (2015) 387–393.

[15] L. Golz, F.H. Ruppert, U. Meier, J. Lemcke, Outcome of modern shunt therapy in patients with idiopathic normal pressure hydrocephalus 6 years postoperatively, J. Neurosurg. 121 (4) (2014) 771–775.

[16] A.M. Koivisto, I. Alafuzoff, S. Savolainen, A. Sutela, J. Rummukainen, M. Kurki, J.E. Jaaskelainen, H. Soininen, J. Rinne, V. Leinonen, N.P.H.R. Kuopio, Poor cognitive outcome in shunt-responsive idiopathic normal pressure hydrocephalus, Neurosurgery 72 (1) (2013) 1–8 discussion 8.

[17] M.J. McGirt, G. Woodworth, A.L. Coon, G. Thomas, M.A. Williams, D. Rigamonti, Diagnosis, treatment, and analysis of long-term outcomes in idiopathic normal-pressure hydrocephalus, Neurosurgery 57 (4) (2005) 699–705 discussion 699-705.

[18] S. Pujari, S. Kharkar, P. Metellus, J. Shuck, M.A. Williams, D. Rigamonti, Normal pressure hydrocephalus: long-term outcome after shunt surgery, J. Neurol. Neurosurg. Psychiatry 79 (11) (2008) 1282–1286.

[19] M.F. Folstein, L.N. Robins, J.E. Helzer, The mini-mental state examination, Arch. Gen. Psychiatry 40 (7) (1983) 812.

[20] B. Kahlon, J. Sjunnesson, S. Rehncrona, Long-term outcome in patients with suspected normal pressure hydrocephalus, Neurosurgery 60 (2) (2007) 327–332 discussion 332.

[21] Y.R. Yadav, S. Pande, V.K. Raina, M. Singh, Lumboperitoneal shunts: review of 409 cases, Neurol. India 52 (2) (2004) 188–190.

[22] V.Y. Wang, N.M. Barbaro, M.T. Lawton, L. Pitts, S. Kunwar, A.T. Parsa, N. Gupta, M.W. McDermott, Complications of lumboperitoneal shunts, Neurosurgery 60 (6) (2007) 1045–1048 discussion 1049.

[23] Y.R. Yadav, V. Parihar, M. Sinha, Lumbar peritoneal shunt, Neurol. India 58 (2) (2010) 179–184.

[24] T.S. Ma, N. Sharma, M.S. Grady, A simplified pressure adjustment clinical pathway for programmable valves in NPH patients, Clin. Neurol. Neurosurg. 159 (2017) 83–86.

[25] T.H. Yang, C.S. Chang, W.W. Sung, J.T. Liu, Lumboperitoneal shunt: a new modified surgical technique and a comparison of the complications with ventriculoperitoneal shunt in a single center, Medicina (Kaunas) 55 (10) (2019).

[26] V. Leinonen, A.M. Koivisto, S. Savolainen, J. Rummukainen, J.N. Tamminen, T. Tillgren, S. Vainikka, O.T. Pyykko, J. Molsa, M. Fraunberg, T. Pirttila, J.E. Jaaskelainen, H. Soininen, J. Rinne, I. Alafuzoff, Amyloid and tau proteins in cortical brain biopsy and Alzheimer's disease, Ann. Neurol. 68 (4) (2010) 446–453.

[27] C. Raftopoulos, J. Deleval, C. Chaskis, A. Leonard, F. Cantraine, F. Desmyttere, S. Clarysse, J. Brotchi, Cognitive recovery in idiopathic normal pressure hydrocephalus: a prospective study, Neurosurgery 35 (3) (1994) 397–404 discussion 404-5.

[28] M.D. Ikonomovic, W.E. Klunk, E.E. Abrahamson, C.A. Mathis, J.C. Price, N.D. Tsopelas, B.J. Lopresti, S. Ziolko, W. Bi, W.R. Paljug, M.L. Debnath, C.E. Hope, B.A. Isanski, R.L. Hamilton, S.T. DeKosky, Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease, Brain 131 (Pt 6) (2008) 1630–1645.

[29] V. Leinonen, I. Alafuzoff, S. Aalto, T. Suotunen, S. Savolainen, K. Nagren, T. Tapiola, T. Pirttila, J. Rinne, J.E. Jaaskelainen, H. Soininen, J.O. Rinne, Assessment of beta-amyloid in a frontal cortical brain biopsy specimen and by positron emission tomography with carbon 11-labeled Pittsburgh Compound B, Arch. Neurol. 65 (10) (2008) 1304–1309.

[30] N. Nelissen, K. Van Laere, L. Thurfjell, R. Owenius, M. Vandenbulcke, M. Koole, G. Bormans, D.J. Brooks, R. Vandenberghe, Phase 1 study of the Pittsburgh compound B derivative 18F-flutemetamol in healthy volunteers and patients with probable Alzheimer disease, J. Nucl. Med. 50 (8) (2009) 1251–1259.

[31] V. Leinonen, J.O. Rinne, K.A. Virtanen, O. Eskola, J. Rummukainen, J. Huttunen, M. von Und Zu Fraunberg, O. Nerg, A.M. Koivisto, J. Rinne, J.E. Jaaskelainen, C. Buckley, A. Smith, P.A. Jones, P. Sherwin, G. Farrar, R. McLain, M. Kailajarvi, K. Heurling, I.D. Grachev, Positron emission tomography with [18F]flutemetamol and [11C]PiB for in vivo detection of cerebral cortical amyloid in normal pressure hydrocephalus patients, Eur. J. Neurol. 20 (7) (2013) 1043–1052.

[32] D.A. Wolk, I.D. Grachev, C. Buckley, H. Kazi, M.S. Grady, J.Q. Trojanowski, R.H. Hamilton, P. Sherwin, R. McLain, S.E. Arnold, Association between in vivo fluorine 18-labeled flutemetamol amyloid positron emission tomography imaging and in vivo cerebral cortical histopathology, Arch. Neurol. 68 (11) (2011) 1398–1403.

[33] M. Nakajima, M. Miyajima, I. Ogino, C. Akiba, H. Sugano, T. Hara, K. Fusegi, K. Karagiozov, H. Arai, Cerebrospinal fluid biomarkers for prognosis of long-term cognitive treatment outcomes in patients with idiopathic normal pressure hydrocephalus, J. Neurol. Sci. 357 (1-2) (2015) 88–95.

[34] S. Patel, E.B. Lee, S.X. Xie, A. Law, E.M. Jackson, S.E. Arnold, C.M. Clark, L.M. Shaw, M.S. Grady, J.Q. Trojanowski, R.H. Hamilton, Phosphorylated tau/amyloid beta 1-42 ratio in ventricular cerebrospinal fluid reflects outcome in idiopathic normal pressure hydrocephalus, Fluids Barriers CNS 9 (1) (2012) 7.

[35] I.J. Pomeraniec, A.E. Bond, M.B. Lopes, J.A. Jane Sr., Concurrent Alzheimer's pathology in patients with clinical normal pressure hydrocephalus: correlation of high-volume lumbar puncture results, cortical brain biopsies, and outcomes, J. Neurosurg. 124 (2) (2016) 382–388.