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FULL PAPER

Hemodynamically self-corrected ΔADC analysis in idiopathic normal pressure hydrocephalus

[1]MARINA TAKATSUJI-NAGASO, MS, [2]TOSIAKI MIYATI, PhD, DMSc, [2]NAOKI OHNO, PhD, [3]MITSUHITO MASE, MD, PhD, [3]HARUMASA KASAI, PhD, [3]YUTA SHIBAMOTO, MD, PhD, [2,4]SATOSHI KOBAYASHI, MD, PhD, [4]TOSHIFUMI GABATA, MD, PhD, [1]KIYOHIDE KITAGAWA, MD, PhD and On behalf of

[1]Department of Radiology, Kouseiren Takaoka Hospital, Takaoka, Toyama, Japan
[2]Division of Health Sciences, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Ishikawa, Japan
[3]Department of Neurosurgery and Restorative Neuroscience, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Aich, Japan
[4]Department of Radiology, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan

Address correspondence to: Tosiaki Miyati
E-mail: *ramiyati@mhs.mp.kanazawa-u.ac.jp*

Objective: To clarify the cause of higher water fluctuation of the brain in idiopathic normal pressure hydrocephalus (iNPH), we assessed change in hemodynamic-independent apparent diffusion coefficient during the cardiac cycle (ΔADC) in iNPH.
Methods: Electrocardiographically synchronized single-shot diffusion echo-planer imaging (b = 0, 500, and 1000 s/mm^2) was performed in healthy volunteers, atrophic ventricular dilation group, and iNPH group, respectively. The ΔADC (b = 0 and 1000 s/mm^2) and maximum ADC (b = 0 and 500 s/mm^2) in the cardiac cycles were measured at the frontal white matter in the brain. Then, self-corrected ΔADC was obtained from the ΔADC divided by the maximum ADC (ADC_{peak}: perfusion-related diffusion) to correct the blood flow effect.
Results: The ΔADC after correction was significantly higher in the iNPH group than in the other two groups. However, there was no significant difference in ADC_{peak} values among the groups.
Conclusion: Self-corrected ΔADC in iNPH increased because of changes in the biomechanical properties of the brain. Self-corrected ΔADC analysis makes it possible to obtain information on hemodynamically independent water fluctuation as well as perfusion in iNPH.
Advances in knowledge: Analysis self-corrected ΔADC provides simultaneously information on biomechanical properties, perfusion, and water fluctuation in iNPH.

INTRODUCTION

First reported by Hakim and Adams[1] in 1965, normal pressure hydrocephalus (NPH) is characterized by a clinical triad of ataxia, urinary incontinence, and dementia; dilated ventricles on CT or MRI; normal cerebrospinal fluid (CSF) pressure; and improvement after CSF shunt surgery. In particular, the pathogenesis of idiopathic NPH (iNPH) remains poorly understood. Differential diagnosis is challenging, requiring careful consideration of diagnostic criteria and selection of appropriate patients for shunt surgery.[2] Moreover, iNPH can occur in combination with other neurodegenerative disorders, cerebrovascular disease, primary urological disorders, spinal stenosis, and other conditions.[3] Because a single standard for the diagnosis and prognosis of iNPH is insufficient, many supplemental tests including functional MRI have been suggested to improve the diagnostic and prognostic accuracy.[2,4–7]

Diffusion-weighted imaging (DWI)[8] is used generally in the diagnosis and treatment of various neurodegenerative disorders. The apparent diffusion coefficient (ADC) of the brain, calculated from DWI data, is overestimated because of the effect of bulk motion (rigid body motion caused by the brain pulsation).[9] Brockstedt et al[10] reported that the bulk motion effect could be reduced by using single-shot echo-planar imaging (EPI). However, Nakamura et al[11] clarified that EPI-obtained ADC values changed significantly over the cardiac cycle and were synchronized with intracranial volume changes even when the bulk motion effect was minimized. Moreover, Ohno et al[6] reported that the maximum change in the ADC (ΔADC) reflected the degree of the fluctuation of water molecules and the ΔADC was significantly higher in iNPH (mentioned above). Subsequently, it has been suggested that the ΔADC makes it possible to obtain brain biomechanics information such as intracranial compliance.[2,6] Kitanaka et al[12] normalized the ΔADC by using regional cerebral blood flow (rCBF), because the

ΔADC was affected by the rCBF, which was a driving force for water molecule fluctuation.[13] However, to acquire the rCBF values, an additional scan or examination must be performed, such as arterial spin labeling, dynamic contrast-enhanced study, or nuclear medicine examination. Thus, we speculated that the peak ADC in the cardiac cycle obtained with low *b*-value data sets (*e.g.* $b = 0$ and $b \leq 500$ s/mm^2) was sensitive to microcapillary perfusion.[14–16] This perfusion-related diffusion could be simultaneously obtained during a ΔADC scan, and we normalized the blood flow effect of ΔADC by using the perfusion-related diffusion.[16] This hemodynamic-independent method, *i.e.* self-corrected ΔADC, was thought to be useful for obtaining more detailed information on iNPH, because iNPH potentially changed the CBF as well as the intracranial compliance.[2,6]

Therefore, in this study, we applied this method to evaluate the hemodynamic-independent water fluctuation and perfusion-related diffusion in iNPH and we compared that with asymptomatic ventricular dilation or brain atrophy (atrophic VD) to characterize the iNPH.

METHODS AND MATERIALS

Procedure for calculation of ADC

Using a 1.5-T MRI unit (Gyroscan Intera; Philips Medical Systems, Best, Netherlands), electrocardiographically synchronized single-shot diffusion EPI imaging was performed to acquire transverse DWI at the basal ganglion level. The trigger delay was set at regular intervals depending on the heart rate (approximately 20 cardiac phases). DWI scanning included the following parameters: echo time, 70 ms; repetition time, two R–R intervals; field of view, 256 mm; imaging matrix, 64 × 64; section of thickness, 4 mm; *b*-values, 0, 500, and 1000 s/mm^2. Moreover, half-scan factors and parallel imaging were used to minimize the bulk motion effect. ADC maps were calculated on a pixel-by-pixel basis from the following equation (1):

$$\mathrm{ADC} = \ln\left(S_0/S_n\right) / \left(b_n\right) \quad (1)$$

where b_n represented diffusion gradient parameters, and S_0 and S_n represented signal intensities of DWI at each b-value.

Calculation of self-corrected ΔADC

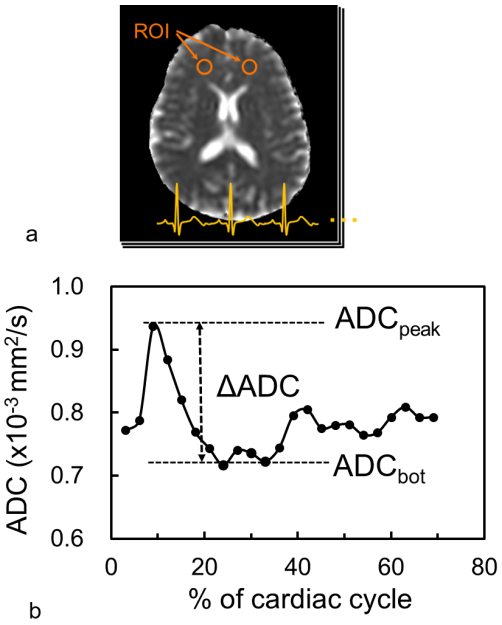
Regions of interest were set in the frontal white matter on ADC maps calculated from *b*-values of 0 and 1000 s/mm^2 over the cardiac cycle (Figure 1), and the maximum ADC ($ADC_{1000\ peak}$) and the minimum ADC ($ADC_{1000\ bot}$) were acquired. Next, the maximum change in ADC (ΔADC_{1000}) was calculated from the following equation (2):

$$\Delta ADC_{1000} = ADC_{1000\ peak} - ADC_{1000\ bot} \quad (2)$$

Then, to obtain hemodynamically independent ΔADC (self-corrected ΔADC), ΔADC_{1000} was normalized by the peak ADC in the cardiac cycle using *b*-values of 0 and 500 s/mm^2 ($ADC_{500\ peak}$, i.e. perfusion related diffusion), which showed a linear relationship with CBF from the following equation (3)[16]:

$$Self-corrected\ \Delta ADC = \Delta ADC_{1000} / ADC_{500\ peak} \quad (3)$$

Figure 1. (a) Regions of interest (ROI) in the frontal white matter on apparent diffusion coefficient (ADC) maps, and (b) ΔADC and ADC_{peak} obtained from the ADC curve in the cardiac cycle.



Participants and statistical analyses

The purpose and protocol of our investigation were explained to all the patients, and the studies were performed only after informed consent was obtained from each patient. The studies were performed in 17 patients with iNPH diagnosed by clinical examinations, brain imaging, and CSF tap test according to the Japanese guidelines[17] (13 males and 4 females; mean age, 77 ± 5 years), 9 patients with atrophic VD with an Evans index > 0.3 (6 males and 3 females; mean age, 72 ± 10 years), and 8 healthy volunteers (control; 4 males and 4 females; mean age, 71 ± 7 years).

SPSS ver. 19.0 for Windows (IBM, Chicago, IL, USA) was used to perform all analyses. We used Kruskal–Wallis tests followed by Dunn's *post-hoc* test to determine the correlation between groups. A *p*-value of < .05 was considered a statistically significant difference.

RESULTS

Figure 2 shows the self-corrected ΔADC and the representative images for the control, VD, and iNPH groups. The self-corrected ΔADC was significantly higher in the iNPH group (0.20 ± 0.05) than in the control (0.14 ± 0.03; $p = 0.021$) and atrophic VD groups (0.16 ± 0.07; $p = 0.035$) (Figure 2a). The non-corrected ΔADC was also significantly higher in the iNPH group (0.20 ± 0.06) than in the control (0.14 ± 0.03; $p = 0.006$) and atrophic VD groups (0.15 ± 0.06; $p = 0.018$) (Figure 3). There was no significant difference in the ADC_{peak} among the three groups (control, 0.83 ± 0.04; atrophic VD, 0.84 ± 0.07; iNPH, 0.90 ± 0.05; $p > 0.05$ for all) (Figure 4).

Figure 2. (a) Self-corrected ΔADC values for the control, asymptomatic ventricular dilation or brain atrophy (atrophic VD), and iNPH groups. Representative images of self-corrected ΔADC maps for the (b) control, (c) atrophic VD, and (d) iNPH groups. ΔADC, maximum change in apparent diffusion coefficient during the cardiac cycle; AU, arbitrary units; iNPH, idiopathic normal pressure hydrocephalus; NS, not significant.

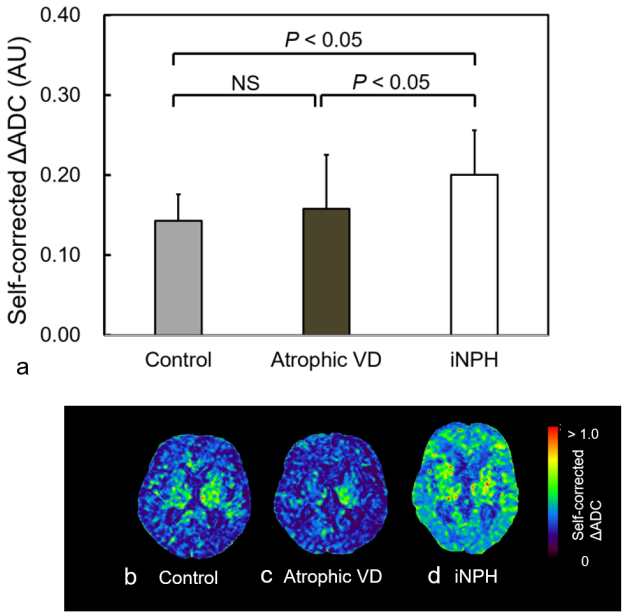
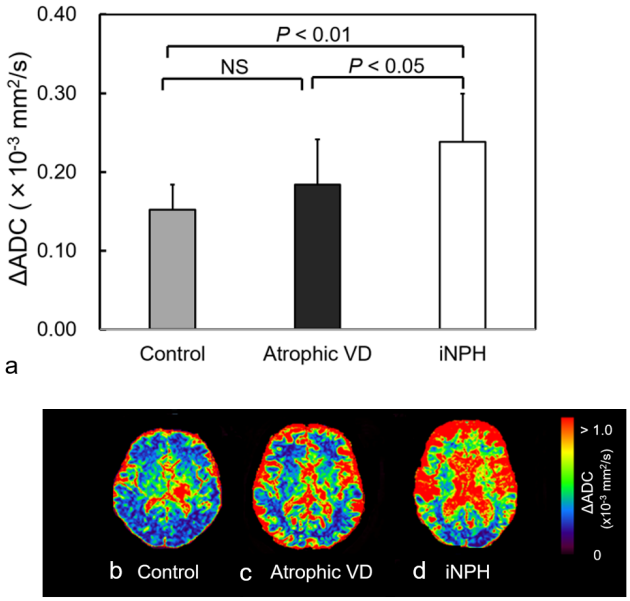


Figure 3. Non-corrected (ΔADC) values for the control, asymptomatic ventricular dilation or brain atrophy (atrophic VD), and iNPH groups. Representative images of non-corrected ΔADC maps for the (b) control, (c) atrophic VD, and (d) iNPH groups. ΔADC, maximum change in apparent diffusion coefficient during the cardiac cycle; iNPH, idiopathic normal pressure hydrocephalus; NS, not significant.



DISCUSSION

We applied the self-corrected ΔADC analysis method to participants with iNPH to assess the degree of hemodynamically-independent fluctuation of water molecules in the brain and to specify the primary factor of increase in the ΔADC. After the normalization of the ΔADC by using perfusion-related diffusion, the self-corrected ΔADC was found to be significantly higher in the iNPH group than in the atrophic VD group, although the imaging findings were sometimes similar. These results indicate that the reason for the increase in ΔADC (non-corrected ΔADC) in iNPH,[6] as the water fluctuation in the brain (output), is the change in biomechanical properties, such as intracranial compliance,[2] not CBF change as the driving force (input) (Figure 5). This view is supported by the fact that there is no significant difference in perfusion-related diffusion (peak ADC in the cardiac cycle with low *b*-value, which is in proportion to CBF[12,16]) among the groups. In fact, although some studies have reported that CBF of frontal white matter did not change or decreased in iNPH,[18–20] there are no reports of increases in CBF of frontal white matter in iNPH, which increases ΔADC. Thus, we considered that the increase in ΔADC, as an output in iNPH, reflected biomechanical properties rather than the change in CBF.

As described above, this novel analysis method makes it possible to simultaneously obtain information on hemodynamic-independent and biomechanical properties (self-corrected ΔADC), as well as CBF (perfusion-related diffusion) and water fluctuation (ΔADC: non-corrected ΔADC) in iNPH (Figure 5). If this method (within 10 min) is added during the standard MRI examination of iNPH, the acquired information may improve the diagnosis and prognosis of iNPH, because supplemental tests can increase the predictive accuracy of the prognosis, as mentioned in the iNPH guideline.[4] Other MRI methods for

Figure 4. $ADC_{500\ peak}$ values for the control, asymptomatic ventricular dilation or brain atrophy (atrophic VD), and iNPH groups. $ADC_{500\ peak}$, peak apparent diffusion coefficient in the cardiac cycle using *b*-values of 0 and 500 s/mm^2; iNPH, idiopathic normal pressure hydrocephalus; NS, not significant.

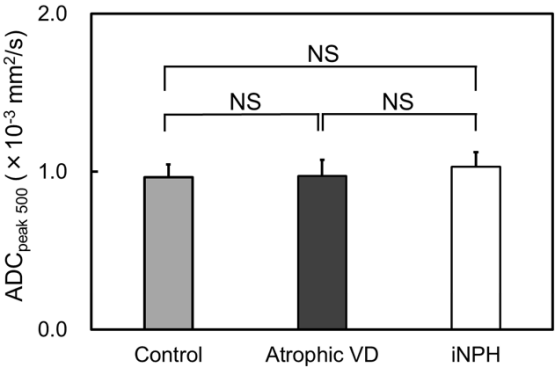
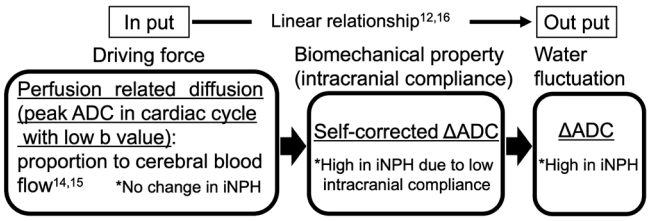


Figure 5. Overview of the self-corrected ΔADC analysis. ΔADC (output), which reflects degree of water fluctuation in brain tissue[6,13] is caused by cerebral blood flow (perfusion-related diffusion, *i.e.* peak ADC in the cardiac cycle with low *b*-value; input) as the driving force. Self-corrected ΔADC, which corresponds to the biomechanical properties, such as intracranial compliance, is calculated from ΔADC normalized by perfusion-related diffusion. ΔADC, maximum change in apparent diffusion coefficient during the cardiac cycle; iNPH, idiopathic normal pressure hydrocephalus; *, Results of this study.



evaluating iNPH were reported, including aqueductal CSF flow analysis[5] and multiexponential fitting to DWI data.[15] The aqueductal CSF flow analysis does not always show changes in intracranial compliance, because CSF flow is modulated by the hemodynamics of the brain.[2] Multiexponential fitting to DWI data can simultaneously obtain perfusion and diffusion information, but it cannot obtain biomechanical information as in this self-corrected ΔADC analysis.

A limitation of this study is the *b*-value for assessing perfusion-related diffusion ($ADC_{500\ peak}$) is not optimized, because we analyzed existing data sets obtained previously for conventional ΔADC analysis in iNPH. However, because the use of higher *b*-values ($ADC_{600\ peak}$) resulted in a linear relationship between $ADC_{600\ peak}$ and CBF obtained with arterial spin labeling,[16] we suggest that this is not a critical problem in this study. We plan to optimize combinations of *b*-values such as 0 and 200 s/mm^2 (*i.e.* $ADC_{200\ peak}$) to obtain accurate perfusion-related diffusion, and we plan to apply this method to iNPH, the other neurodegenerative disorders (*e.g.* Alzheimer's disease and Parkinson's disease), and vascular dementia. The other limitations of this study are related to the age and gender-composition differences between groups and the small number of samples. Although there was no significant difference in the age among the three groups, further study should be undertaken to clarify age and gender dependence in each group with a wider age range and larger sample size. Additionally, the sensitivity and specificity of our method for iNPH diagnosis should be evaluated.

CONCLUSION

We applied our original method of self-corrected ΔADC analysis to iNPH and found that self-corrected ΔADC in iNPH increased because of changes in the biomechanical properties of the brain. Self-corrected ΔADC analysis makes it possible to simultaneously obtain information on biomechanical properties, perfusion, and water fluctuation in iNPH.

FUNDING

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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* 1965; **273**: 117–26. doi: https://doi.org/10.1056/NEJM196507152730301
2. Miyati T, Mase M, Kasai H, Hara M, Yamada K, Shibamoto Y, et al. Noninvasive MRI assessment of intracranial compliance in Idiopathic normal pressure hydrocephalus. *J Magn Reson Imaging* 2007; **26**: 274–8. doi: https://doi.org/10.1002/jmri.20999
3. Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM. Diagnosing idiopathic normal-pressure hydrocephalus. *Neurosurgery* 2005; **57**(suppl_3): S2-4–S2-16. doi: https://doi.org/10.1227/01.NEU.0000168185.29659.C5
4. Marmarou A, Bergsneider M, Klinge P, Relkin N, Black PM. The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus. *Neurosurgery* 2005; **57**(suppl_3): S2-17–S2-28discussion ii–v.. doi: https://doi.org/10.1227/01.NEU.0000168184.01002.60
5. Miyati T, Mase M, Banno T, Kasuga T, Yamada K, Fujita H, et al. Frequency analyses of CSF flow on cine MRI in normal pressure hydrocephalus. *Eur Radiol* 2003; **13**: 1019–24. doi: https://doi.org/10.1007/s00330-002-1697-3
6. Ohno N, Miyati T, Mase M, Osawa T, Kan H, Kasai H, et al. Idiopathic normal-pressure hydrocephalus: temporal changes in ADC during cardiac cycle. *Radiology* 2011; **261**: 560–5. doi: https://doi.org/10.1148/radiol.11101860
7. Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD, Gronseth G, Gloss D. Practice Guideline: Idiopathic normal pressure hydrocephalus: Response to shunting and predictors of response: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2015; **85**: 2063–71. doi: https://doi.org/10.1212/WNL.0000000000002193
8. Moseley ME, Cohen Y, Mintorovitch J, Chileuitt L, Shimizu H, Kucharczyk J, et al. Early detection of regional cerebral ischemia in cats: comparison of diffusion- and T2-weighted MRI and spectroscopy. *Magn Reson Med* 1990; **14**: 330–46. doi: https://doi.org/10.1002/mrm.1910140218
9. Norris DG. Implications of bulk motion for diffusion-weighted imaging experiments: effects, mechanisms, and solutions. *J Magn Reson Imaging* 2001; **13**: 486–95. doi: https://doi.org/10.1002/jmri.1072
10. Brockstedt S, Borg M, Geijer B, Wirestam R, Thomsen C, Holtås S, et al. Triggering in quantitative diffusion imaging with single-shot EPI. *Acta Radiol* 1999; **40**: 263–9. doi: https://doi.org/10.3109/02841859909175552
11. Nakamura T, Miyati T, Kasai H, Ohno N, Yamada M, Mase M, et al. Bulk motion-independent analyses of water diffusion changes in the brain during the cardiac cycle. *Radiol Phys Technol* 2009; **2**: 133–7. doi: https://doi.org/10.1007/s12194-009-0056-3
12. Kitanaka A, Miyati T, Ohno N, Kan H, Kobayashi S, Gabata T. Hemodynamic

analysis of cerebral water fluctuation in brain using diffusion and perfusion MRI. *Med Imag & Infor Sci* 2016; **33**: 7–11.

13. Kan H, Miyati T, Kasai H, Arai N, Ohno N, Mase M, et al. Transfer characteristics of arterial pulsatile force in regional intracranial tissue using dynamic diffusion MRI: a phantom study. *Magn Reson Imaging* 2014; **32**: 1284–9. doi: https://doi.org/10.1016/j.mri.2014.08.026
14. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology* 1986; **161**: 401–7. doi: https://doi.org/10.1148/radiology.161.2.3763909
15. Ohno N, Miyati T, Kobayashi S, Gabata T. Modified triexponential analysis of intravoxel incoherent motion for brain perfusion and diffusion. *J Magn Reson Imaging* 2016; **43**: 818–23. doi: https://doi.org/10.1002/jmri.25048
16. Takatsuji M, Miyati T, Ohno N, Noda T, Mase M, Gabata T. Correction of blood flow effect using perfusion-related diffusion for brain-fluctuation MRI in healthy volunteers: a preliminary study. *Med Imag & Infor Sci* 2017; **34**: 132–5.
17. Mori E, Ishikawa M, Kato T, Kazui H, Miyake H, Miyajima M, et al. Japanese Society of normal pressure hydrocephalus. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. *Neurol Med Chir* 2012; **52**: 775–809.
18. Graff R, Rezai K, Godersky JC, Eslinger P, Damasio H, Kirchner PT. Regional cerebral blood flow in normal pressure hydrocephalus. *J Neurol* 1987; **50**: 1589–96.
19. Owler BK, Momjian S, Czosnyka Z, Czosnyka M, Péna A, Harris NG, et al. Normal pressure hydrocephalus and cerebral blood flow: a PET study of baseline values. *J Cereb Blood Flow Metab* 2004; **24**: 17–23. doi: https://doi.org/10.1097/01.WCB.0000093326.88757.49
20. Virhammar J, Laurell K, Ahlgren A, Larsson E-M. Arterial spin-labeling perfusion MR imaging demonstrates regional CBF decrease in Idiopathic normal pressure hydrocephalus. *AJNR Am J Neuroradiol* 2017; **38**: 2081–8. doi: https://doi.org/10.3174/ajnr.A5347