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Venous compression causes chronic cerebral ischaemia in normal pressure hydrocephalus patients

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Abstract

Background Cerebral autoregulation is a robust regulatory mechanism that stabilizes cerebral blood flow in response to reduced blood pressure, thereby preventing cerebral ischaemia. Scientists have long believed that cerebral autoregulation also stabilizes cerebral blood flow against increases in intracranial pressure, which is another component that determines cerebral perfusion pressure. However, this idea was inconsistent with the complex pathogenesis of normal pressure hydrocephalus, which includes components of chronic cerebral ischaemia due to mild increases in intracranial pressure.

Methods Twenty-one patients who underwent ventriculoperitoneal shunt surgery for normal pressure hydrocephalus were included in this study. To determine the pressure setting of the Codman-Hakim programmable valve, intracranial pressure was measured after shunt surgery by puncturing the Ommaya reservoir, which formed a closed circuit with the needle and the syringe. Then, intracranial pressure was continuously measured with intermittent infusion of cerebrospinal fluid from the same closed circuit. We also continuously measured oximetry data, such as regional cerebral oxygen saturation derived from near-infrared spectroscopy monitoring. These data were digitized, recorded, and used for calculating intracranial compliance and the relationship between cerebrospinal fluid volume loading and intracranial pressure.

Results This study demonstrates that in patients with normal pressure hydrocephalus, cerebral venous vascular bed compression induces mild cerebral ischaemia when intracranial pressure is slightly higher than physiological venous pressure. Cerebral venous compression impairs cerebral blood flow by quadratically increasing circulatory resistance according to Poiseuille's law. Furthermore, chronic cerebral ischaemia occurred even at low or normal intracranial pressures when deep and subcortical white matter hyperintensities (DSWMHs) were severe.

Conclusion The fact that cerebral blood flow impairment begins at very low intracranial pressures indicates that cerebral autoregulation to compensate for reduced venous blood flow is not functioning adequately in NPH. These processes provide a link between impaired cerebrospinal fluid circulation, cerebral autoregulation, and neurological dysfunction, which has been missing in patients with NPH involving small vessel arteriosclerosis. These findings may provide insight into similar conditions, such as normal-tension glaucoma and chronic kidney disease, in which a mild increase in local compartment pressure leads to chronic ischemia in organs protected by autoregulatory mechanisms.

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Introduction

Maintaining brain function is the highest priority for survival, as loss of brain function, even if temporary, can be fatal. Therefore, strict stabilization of cerebral blood flow (CBF), which is essential for the supply of oxygen and glucose to maintain brain function, is stabilized across a wide range of mean arterial pressure (MAP) via the mechanism of cerebral autoregulation (CA). CA robustly stabilizes CBF against arterial hypotension or hypertension, and strongly prevents cerebral ischaemia or functional hyperaemia [1, 2]. CA ensures stable cerebral circulation in the blood pressure range of 50 to 150 mmHg by regulating the diameter of the arterioles in response to fluctuations in blood pressure [1, 3, 4].

Cerebral perfusion pressure (CPP) is the difference between blood pressure and intracranial pressure (ICP). ICP is a determinant of CBF, as it influences CPP linearly. Many investigators have reported that CA also robustly stabilizes cerebral circulation for increases in ICP up to approximately 40 mmHg [5–7]. However, in patients with normal pressure hydrocephalus (NPH), CBF and neurological function are impaired regardless of a mild ICP increase of around 15 mmHg, resulting in a subcritical ischemic phase that causes functional impairment but not infarction in the anatomic distribution [8–10]. This finding suggests that CA is not fully functional in patients with NPH and that factors other than CPP are involved in CBF impairment.

Numerical simulations have demonstrated that compression of the venous vascular bed due to a slight increase in ICP reduces intracranial compliance, quadratically increasing CBF resistance and reducing CBF [11]. Furthermore, simulations have indicated that in the absence of functional CA, even a slight increase in ICP above physiological cerebral venous pressure leads to reduced CBF. These simulation results may help elucidate the pathogenesis of iNPH. However, there is currently no clinical evidence to support these simulation results.

NPH is a potentially reversible dementia, characterized clinically by a triad of cognitive impairment, gait disturbance, and urinary incontinence [8, 9]. NPH is named because the increase in ICP due to cerebrospinal fluid (CSF) retention does not exceed approximately 15 mmHg (20 cm H2O), the upper limit of the normal range [8, 9]. NPH has been considered a rare disease. However, recent epidemiological studies have shown that NPH is much more common than previously thought, as 2% of people over 65 years and 9% of people over 80 years have excessive CSF accumulation and are at risk of developing NPH [12]. The primary aetiology of NPH is excessive CSF accumulation due to impaired CSF circulation, as manifested by increased CSF outflow resistance (Ro). Neurosurgeons can treat NPH with CSF shunting, which involves the placement of a catheter that continuously releases excess CSF into the abdominal cavity [8]. Recent studies have shown that early intervention can improve cognitive and gait impairment to a level where social participation is possible and prevent the onset of dementia in the long term [13].

It is unclear why CBF and the nervous system are impaired in patients with NPH despite normal intracranial pressure [14]. In other words, this is the missing link between impaired CSF circulation and impaired CBF in the pathogenesis of NPH. To clarify this, we conducted a controlled CSF infusion study in patients with NPH. We calculated intracranial compliance and assessed the mechanical state of the cerebrovascular bed from changes in ICP with CSF volume loading. We also assessed CBF status from changes in intracranial haemoglobin (Hb) (such as total-Hb, oxy-Hb, and deoxy-Hb). Deoxy-Hb and regional cerebral oxygen saturation (rSO_2) provide information on changes in CBF and the occurrence of cerebral ischaemia, while total-Hb reflects intracranial blood volume. The analysis of these indices allows a comprehensive understanding of the mechanical state of the cerebrovascular system and CBF status associated with CSF volume loading in patients with NPH.

Material and methods

Patient population

We studied 21 patients with normal pressure hydrocephalus (NPH) (15 males and 6 females, mean age: 61.9 years) who underwent ventriculoperitoneal shunt (VPS) at Osaka Medical College Hospital between January 1999 and March 2003. After shunting, all patients had improved in NPH symptoms such as gait disturbance and dementia. The cases consisted of 10 idiopathic NPH (iNPH) and 11 secondary NPH (sNPH).

Ventriculoperitoneal shunt surgery involved the placement of a ventricular catheter in the anterior horn of the right lateral ventricle and a peritoneal catheter in the lower part of the abdominal cavity. We placed an Ommaya reservoir in the right frontal region and an on–off valve, a Codman-Hakim programmable valve, and a Foltz reservoir in series in the chest (Supp Fig. A).

We measured the ICP of each patient postoperatively for valve pressure setting based on their ICP [15]. During this ICP measurement, we performed an additional intermittent infusion test.

The study protocol was approved by the Ethics Committee of Osaka Medical College (No. 27,27–1,2788) and all patients gave informed consent.

Measurement of ICP and CSF intermittent infusion test

We performed ICP measurements in 21 patients after VP shunting. The primary purpose of the ICP measurements was ICP-based valve pressure setting, with the CSF intermittent infusion test as a secondary measure. The shunt valve was turned off 8 h before, the patient was placed in the supine position, the skin was thoroughly disinfected, and the reservoir was punctured with a 22G needle to measure ICP. The shunt valve was then turned on with the shunt set pressure to the maximum pressure (200 mmH_2O). The position was changed from supine to sitting, and the ICP was recorded. After approximately 15 min, the ICP reached a steady state, and the steady-state ICP value was recorded. The shunt set pressure was then sequentially lowered, and the shunt set pressure corresponding to a steady-state ICP of −11 mmHg in the sitting position was considered the optimal set pressure [16]. The ICP at the optimal set pressure was then measured in the supine position, followed by turning off the shunt valve and performing the infusion test. The needle was connected via two three-way stopcocks to a 5 mL syringe for intermittent infusion, a 50 mL syringe for CSF storage, and a pressure transducer for intracranial pressure (ICP) measurement. These formed a closed circuit to prevent infection. The reference point for ICP at this time was the external auditory canal and was designated as ICPeac.

To measure changes in intracranial haemoglobin concentration, we attached the probe of a near-infrared spectroscopy (NIRS) monitor (OM-200 Shimazu co. Ltd, Kyoto, Japan) to the patient's left forehead. We first turned off the on–off valve. We then slowly aspirated CSF from the Ommaya reservoir until the ICP reached −20 mmHg. We stored this excluded CSF in a 50 ml syringe.

We then manually infused 3 ml of autologous CSF infusion at a rate of 1 ml/s for 3 s into the ventricles via the Ommaya reservoir. We repeated similar injection manoeuvres at 20 s intervals until the ICP reached almost 30 mmHg. We used artificial CSF if the infusion volume was insufficient with autologous CSF. We measured ICP continuously while performing intermittent infusions; the reference point for ICP was the external auditory canal level. Changes in ICP were limited from −20 to 30 mmHg to ensure that patients did not experience headaches or other distress. As a result, no patients experienced headaches or other discomfort and none became infected after the test.

We also continuously measured intracranial haemoglobin (Hb), that is, total-Hb, oxy-Hb, deoxy-Hb, and regional cerebral oxygen saturation (rSO_2) calculated as oxy-Hb/(oxy-Hb + deoxy-Hb), by NIRS monitoring. Measurement data from all pressure transducers and NIRS monitors were digitised and recorded with data acquisition software created in the G-language of LabVIEW (National Instruments Co. ltd, Austin, TX).

ICP measurements with cerebral venous pressure as a reference

Many researchers use the external auditory meatus as a reference for ICP measurements. In studies of the intracranial environment involving the intracranial venous system, it is preferable to use cerebral venous pressure as a reference for ICP measurements. However, it has not been possible to measure cerebral venous pressure non-invasively. Theoretically, the venous transmural pressure is zero when intracranial compliance is maximal. Therefore, the ICP at maximum compliance equals the intracranial venous pressure, from which we can estimate the venous pressure [17]. In the present study, ICP was defined as ICPvein in relation to cerebral venous pressure measured from ICP at maximum compliance.

Calculation of intracranial compliance

We calculated intracranial compliance automatically using analysis software programmed in the G-language. The analysis algorithm was as follows. First, the software detected the infusion period triggered by the pressure increase in the infusion circuit associated with infusion in the ICP measurements. The software then averaged the ICP values at 2 s before and after the infusion period, respectively, which we defined as the pre-infusion ICP (ICPpre) and post-infusion ICP (ICPpost), respectively. We calculated the intracranial compliance (C) and ICP at each infusion using the following formula:$C = \Delta CSF\ (ml) / \Delta ICP\ (mmHg) = 3/(ICPpost - ICPpre)$

$ICP = (ICPpre + ICPpost) / 2$

From the relationship between ICP and C determined above, an ICP-intracranial compliance curve was created by fitting with a spline curve.

The compliance measurement has an infusion time of 3 s and a measurement time of 2 s before and after the injection; the average time difference before and after the CSF injection is 5 s, so the time constant for this intracranial compliance value is 5 s (Supp Fig. B). The short time constant of 5 s indicates that the effect of CSF absorption during that period is negligible.

The ICP was sampled at 200 Hz and then downsampled to 20 Hz to reduce fine noise. The measurement time before and after injection was set to 2 s, as the longer the time, the more affected by delayed compliance, and no averaging of respiratory variations was performed.

NIRS data analysis

The NIRS data exhibit high variability and numerous artefacts. Due to its noise and significant respiratory variability, in order to detect subtle peaks, time series data from NIRS were subjected to approximately eighth-order polynomial fitting for the intermittent injection period, removing the data from the injection period. The fitted curve was then visually inspected to ensure accurate peak detection (Supp Fig. C). The ICP and NIRS relationships were determined from this time series data.

The NIRS data, except for deoxyHb, decreased inversely with ICP. However, deoxyHb decreased steadily with increasing ICP until it reached a point where it began to rise again, representing the transition between the physiological phase and the mild ischaemic phase, i.e., the subcritical ischemic phase.

We determined the ICP and compliance values when the ICP-deoxyHb curve exhibited a peak from the descending to the ascending phase. To accurately determine the peak, the ICP at which the derivative of the ICP-deoxyHb curve is zero was identified. In the case of a plateau without forming a peak, the ICP was determined as the ICP where the tangent lines before and after the plateau form an intersection. The above analysis was carried out using dedicated analysis software created in the G-language of LabVIEW.

ICP during shunt valve off and shunt valve on

In 17 patients in this study, ICP was measured with the Codman® Hakim® Programmable Valve both off and on prior to the infusion test. The ICP measurement with the shunt valve off can be considered the preoperative ICP since the shunt valve had been off for more than 8 h prior to measurement. After determining the optimal set pressure, ICP was measured with the shunt valve on to set the optimal pressure. ICP was shown as the mean ± standard deviation.

Calculation of the relationship between CSF volume loading and ICPeac

The relationship between CSF volume loading and ICPeac was calculated as follows. First, from the ICPeac-intracranial compliance curve, the increase in ICPeac with 0.5 ml CSF loading was calculated and added to the original ICPeac. The calculation was then repeated for the added ICP and the relationship between CSF volume loading and ICP was calculated (Supp Fig. C).

Deep and subcortical white matter hyperintensities (DSWMHs) grading

DSWMHs were graded according to the classification of the Fazekas classification [18] (grade 0 = absence; grade 1 = punctate foci; grade 2 = beginning confluence of foci; grade 3 = large confluent areas). DSWMH grades 0 and 1 were regarded as low and DSWMH grades 2 and 3 as high. DSWMH grading was performed on patients with iNPH and sNPH respectively and divided into two groups: high and low.

Stratified analysis of patients

The intracranial pressure at which the transition from the physiological to the subcritical ischaemic phase begins was determined for the two groups, iNPH and sNPH. Similarly, it was determined separately for the two groups of DSWMH high grade and DSWMH low grade. We analysed whether there were statistical differences in the intracranial pressure at which the transition from the physiological ischaemic phase to the subcritical ischaemic phase began, depending on the type of hydrocephalus and the severity of DSWMH, using the Mann–Whitney U test. $p < 0.05$ was considered statistically significant.

Results

R1 Relationship between ICPvein, oximetry data by NIRS, and compliance (Fig. 1 & Supp Fig. D).

Six patients were excluded from the analysis due to poor measurement results. Because the oximetric data were analysed using NIRS data, the target of measurement is considered to be the cortex close to the skin, rather than the deep white matter or periventricular white matter.

As ICPvein increased, oxyHb and totalHb decreased. On the other hand, deoxyHb decreased and then increased after 2.5 mmHg as indicated by the asterisk (*) in Fig. 1. In general, the increase in deoxyHb is due to an increase in cerebral oxygen extraction fraction (OEF). Furthermore, the regional cerebral oxygen saturation (rSO_2) also decreased, indicating a subcritical ischemic phase.

Whereas the distribution of ICPvein during the valve-on period (−3.3 ± 4.6 mmHg [n = 21]) in shunted NPH patients is in a physiological phase, the distribution of ICPvein during the valve-off period is in a subcritical ischemic phase (7.1 ± 7.4 mmHg [n = 17]). Of the 17 participants whose ICP was measured during the valve-off period, two scaled out to a range higher than 15 mmHg. One was a clear outlier at −7.44 mmHg. Thus, during the valve-off period, 3 of the 17 participants were in the physiological phase, while the remaining 14 were in the subcritical ischaemic phase. This indicates that the intracranial pressure of untreated NPH patients is in the subcritical

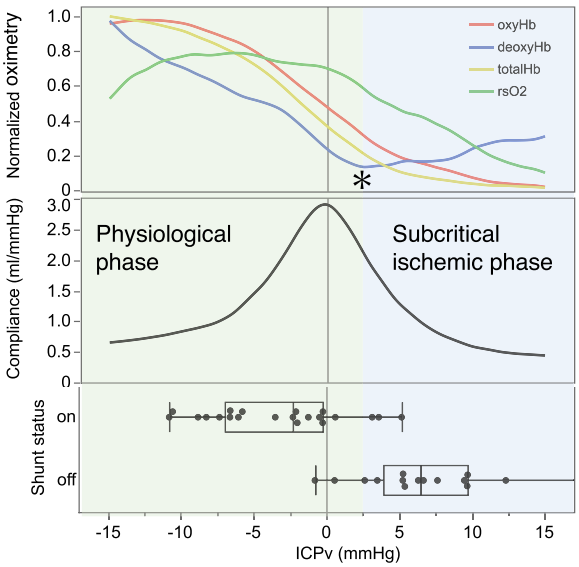

Fig. 1 Relationship between ICPvein, oximetry data by NIRS, and compliance: Compliance and oximetry curves were derived from the mean values of all patients measured. As ICPvein increased, oxyHb and totalHb decreased. On the other hand, deoxyHb decreased and then increased after 2.5 mmHg. The asterisk (*) in this figure indicates the trough where deoxyHb transitions from decreasing to increasing with increasing ICP. In general, the increase in deoxyHb is due to an increase in cerebral oxygen extraction fraction (OEF). Furthermore, the regional cerebral oxygen saturation (rSO2) also decreased, indicating a subcritical ischemic phase (blue background region in this figure). Whereas the distribution of ICPvein during the valve-on period (-3.3 ± 4.6 mmHg, n = 21) in shunted NPH patients is in a physiological phase, the distribution of ICPvein during the valve-off period is in a subcritical ischemic phase (7.1 ± 7.4 mmHg, n = 17). 3 of the 17 participants were in the physiological phase (green background), while the remaining 14 were in the subcritical ischaemic phase (blue background) dunring the valve-off period. (Note: Only 14 of the 17 patients are shown in the graph with valves off, as two were scaled to a range higher than 15 mmHg and one was a clear outlier at −7.44 mmHg). This indicates that the intracranial pressure of untreated NPH patients is in the subcritical ischemic phase, despite being in the normal range, and that shunt surgery allows them to move into the physiological phase. The ICPvein-compliance curve exhibited a symmetrical bell-shaped curve with a peak at 0 mmHg

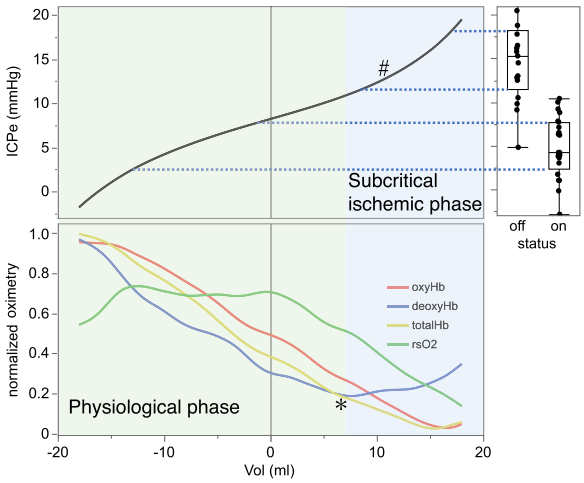

Fig. 2 Relationship between CSF volume loading and ICPeac: Relationship between CSF volume loading and ICPeac was simulated from the ICPvein-compliance curve. CSF volume loading increased ICPeac quadratically above approximately 10 ml (#). Surprisingly, the ICPeac that moved into the subcritical ischemic phase was only 10 mmHg (*). The right-hand graph illustrates that the distribution of ICPeac during the valve-on period (4.9 ± 3.6 mmHg) in shunted NPH patients is in the physiological phase, whereas the distribution of ICPeac during the valve-off period (15.4 ± 5.8 mmHg) is in the subcritical ischemic phase

ischemic phase, despite being within the normal range, and that shunt treatment allows them to transition into the physiological phase. The ICPvein value was 8.3 ± 3.4 mmHg when the ICP reference point was the external auditory canal.

As ICP in this study was defined as ICPvein in relation to cerebral venous pressure measured at maximum compliance, the ICPvein-compliance curve exhibited a symmetrical bell-shaped curve with a peak at 0 mmHg.

R2 Relationship between CSF volume loading and ICPeac (Fig. 2).

CSF volume loading increased ICPeac quadratically above approximately 12 ml. Surprisingly, the ICPeac that shifted the system into the subcritical ischemic phase was only 10 mmHg. The right-hand graph illustrates that the distribution of ICPeac during the valve-on period (4.9 ± 3.6 mmHg) in shunted NPH patients is in the physiological phase, whereas the distribution of ICPeac during the valve-off period (15.4 ± 5.8 mmHg) is in the subcritical ischemic phase.

R3 Patients with iNPH are exposed to a subcritical ischemic phase from lower intracranial pressure than patients with sNPH (Fig. 3).

ICPvein values at the beginning of the transition from the physiological phase to the subcritical ischaemic phase, which coincide with the timing of deoxy-Hb changing from a previous decrease to an increase, are lower in patients with iNPH compared to those with sNPH. Statistical analysis showed that ICPvein at the beginning of the transition from the physiological phase to the subcritical ischemic phase was 2.2 ± 1.6 mmHg for iNPH (n = 8) and 4.9 ± 2.5 mmHg for sNPH (n = 7), which was significantly lower in iNPH. Compliance at the beginning of the transition from the physiological phase to the subcritical ischemic phase tended to be higher in iNPH than in sNPH (2.7 ± 1.4 ml/mmHg, 1.3 ± 0.4 ml/mmHg, iNPH, sNPH, respectively).

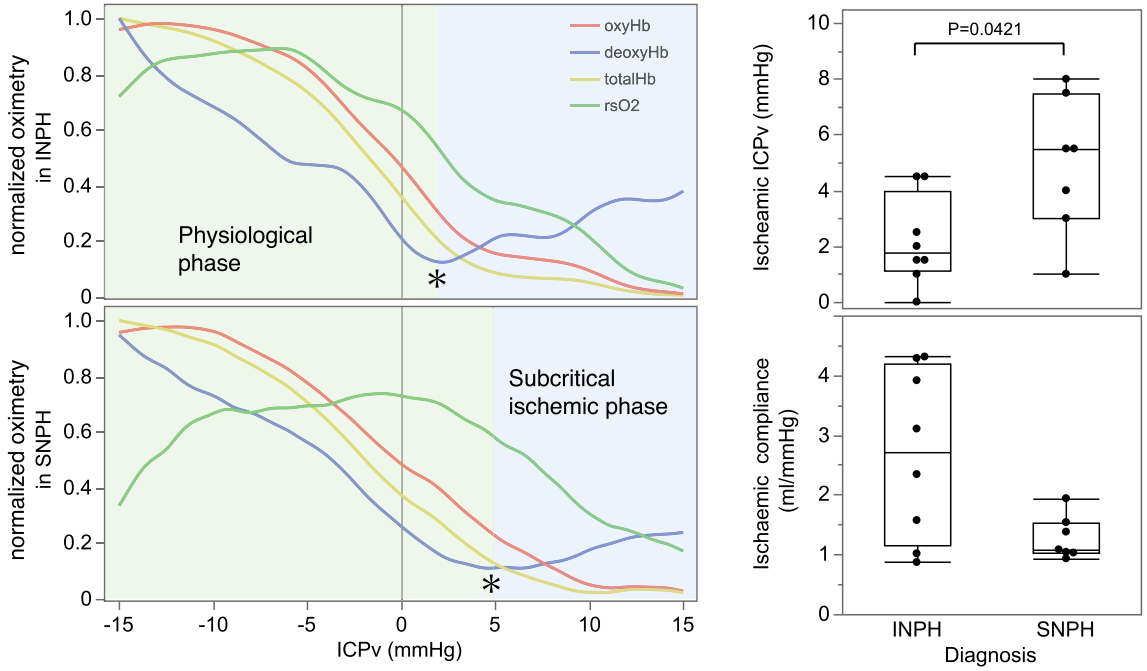

Fig. 3 Patients with iNPH are exposed to a subcritical ischemic phase from lower intracranial pressure than patients with sNPH: ICPvein values at the beginning of the transition from the physiological phase to the subcritical ischaemic phase, indicated by the timing of deoxy-Hb turning from the previous decrease to an increase, are lower in patients with iNPH (left top) than in those with sNPH (left bottom). Statistical analysis revealed that ICPvein at the beginning of the transition from the physiological phase to the subcritical ischemic phase was 2.2 ± 1.6 mmHg for iNPH and 4.9 ± 2.5 mmHg for sNPH, which was significantly lower in iNPH (right top). Compliance tended to be higher in iNPH than in sNPH (2.7 ± 1.4 ml/mmHg, 1.3 ± 0.4 ml/mmHg, iNPH, sNPH, respectively) (right bottom)

R4 The severity of DSWMH affects ICPvein and compliance at the start of the transition from the physiological ischaemic phase to the subcritical ischaemic phase (Fig. 4).

Of the eight patients with iNPH, all showed high-grade DSWMH; of the seven patients with sNPH, five showed low-grade DSWMH and two showed high-grade DSWMH. A statistical analysis was performed to determine whether the severity of DSWMH affected ICPvein and compliance at the beginning of the transition from the physiological ischaemic phase to the subcritical ischaemic phase. ICPvein at the beginning of the transition from the physiological ischaemic phase to the subcritical ischaemic phase was 2.4 ± 1.8 mmHg in the High group (n = 10) and 5.6 ± 2.2 mmHg in the Low group (n = 5), significantly lower in the High group. Compliance tended to be higher in the High group than in the Low group (2.5 ± 1.3 ml/mmHg in the High group and 1.1 ± 0.2 ml/mmHg in the Low group). The severity of DSWMH has been reported to be associated with a strong background of atherosclerotic changes. In the present study, the severity of DSWMH was high in all iNPH patients and they had a strong background of atherosclerotic changes.

Discussion

D1

In this study, total Hb and oxyHb consistently decreased with increasing ICP, but only deoxyHb displayed an increase. The fact that the rise in deoxyHb started from 2.5 mmHg, as well as the intracranial pressure data during shunt valve on and off, indicate that patients with NPH are in a subcritical ischaemic phase, suggest that shunt surgery can be expected to return ICP to a physiological stage. Patients with NPH exhibit rapid improvement of symptoms to some degree with shunting and tap testing. This suggests that NPH includes a component of the pathophysiology of immediately reversible ischemia [19].

Through numerical simulations, Cirovic et al. [11] have demonstrated that compression of the venous bed due to increased CSF induces cerebral ischaemia. They investigated the role of the cerebral venous bed in volume loading using a mathematical model based on a one-dimensional theory of flow in collapsible tubes. They showed that compression of the venous bed due to elevated ICP has an exponential effect on CBF. Furthermore, they showed that if brain autoregulation is impaired, compression of the venous vascular bed

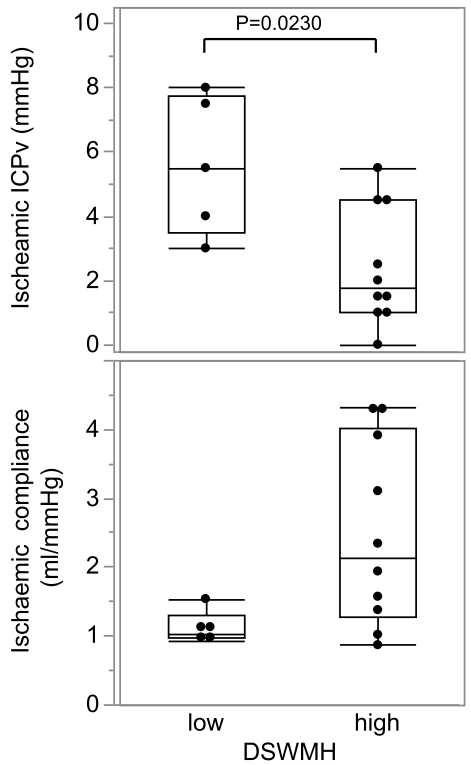

Fig. 4 Impact of severity of DSWMH: ICPvein at the beginning of the transition from the physiological phase to the subcritical ischemic phase was 2.4 ± 1.8 mmHg in the DSWMH grade High group and 5.6 ± 2.2 mmHg in the Low group, significantly lower in the High group. Compliance tended to be higher in the DSWMH grade High group than in the Low group (2.5 ± 1.3 ml/mmHg, 1.1 ± 0.2 ml/mmHg, DSWMH grade High and Low, respectively)

by very low ICP forces CBF to decrease. However, the clinical implication of their simulations has been unclear. Their simulations provide deeper insight into the pathogenesis of NPH.

D2 Vascular compression and circulatory resistance

Cirovic et al. state that venous collapse of the venous bed should begin at the most distal point, where venous pressure is lowest, and move toward the arterial end as ICP increases. A decrease in CBF requires proximal venous pressure to approach arterial pressure. They state that "when the proximal venous bed is compressed at a pressure of 110 mmHg, 10 mmHg higher than arterial pressure, it is almost completely emptied." On the other hand, we observed in this study that patients with NPH had a decrease in total Hb when the shunt valve was off, despite a low pressure of 15 mmHg, as shown in Fig. 2. We believe this may be due to inadequate autoregulation in addition to reduced blood flow caused by reduced vessel diameter from venous compression.

Cirovic et al. simulated veins as collapsible tubes with uniform wall properties for both distal and proximal veins. In this case, the vein collapses from distal to proximal [11]. However, in reality, the wall properties are not uniform between the proximal vein, which has just emerged from the capillary, and the distal vein, which is closer to the superior sagittal sinus. The proximal vein has thinner walls and is more susceptible to compression. Therefore, compression is likely to occur at the level of the thin-walled proximal veins. Poiseuille's law states that conductance is proportional to the fourth power of the vessel diameter, so if the vessel diameter is doubled, blood flow increases 16-fold. Conversely, 10% compression results in a 35% reduction in blood volume, and 50% compression results in a 94% reduction in blood volume. This reduction in vessel diameter due to venous compression and collapse results in a significant decrease in blood flow.

D3 Venous collapses and reduced compliance

As the vessels are elastic, they can be mechanically regarded as collapsible tubes. A positive pressure gradient across vessel walls makes them partially collapse. In the collapsed state, the bending stiffness of the tube wall supports the pressure difference between the inside and outside of the tube [20]. Vascular compliance corresponds to the inverse of this bending stiffness. In general, researchers can calculate compliance from changes in volume and pressure.

Cranial compliance consists of an intracranial component and a spinal component that is roughly equally distributed [21]. The intracranial component of cerebrospinal compliance is equivalent to vascular compliance because the intracranial space is a semi-closed cavity. Thus, we can consider changes in measured intracranial compliance to be approximately equivalent to changes in vascular compliance (Fig. 1) [11].

D4 Impaired cerebral autoregulation

Recently, Momjian et al. [14] also highlighted that disruption of CA contributes to the pathogenesis of cerebral ischaemia in iNPH. Our study confirms that an ICPeac of around 10 mmHg negatively affects CBF, indicating inadequate CA function in response to increased ICP in patients with NPH.

CA has long been thought to stabilize CBF against blood pressure fluctuations and to effectively mitigate ICP elevation. Therefore, it raises questions about the impairment of the autoregulatory function at ICPs as low as 10 mmHg, as observed in our study.

For a long time, it was assumed that CA maintains stable cerebral circulation within the blood pressure range of 50 to 150 mmHg by regulating the diameter of the arterioles

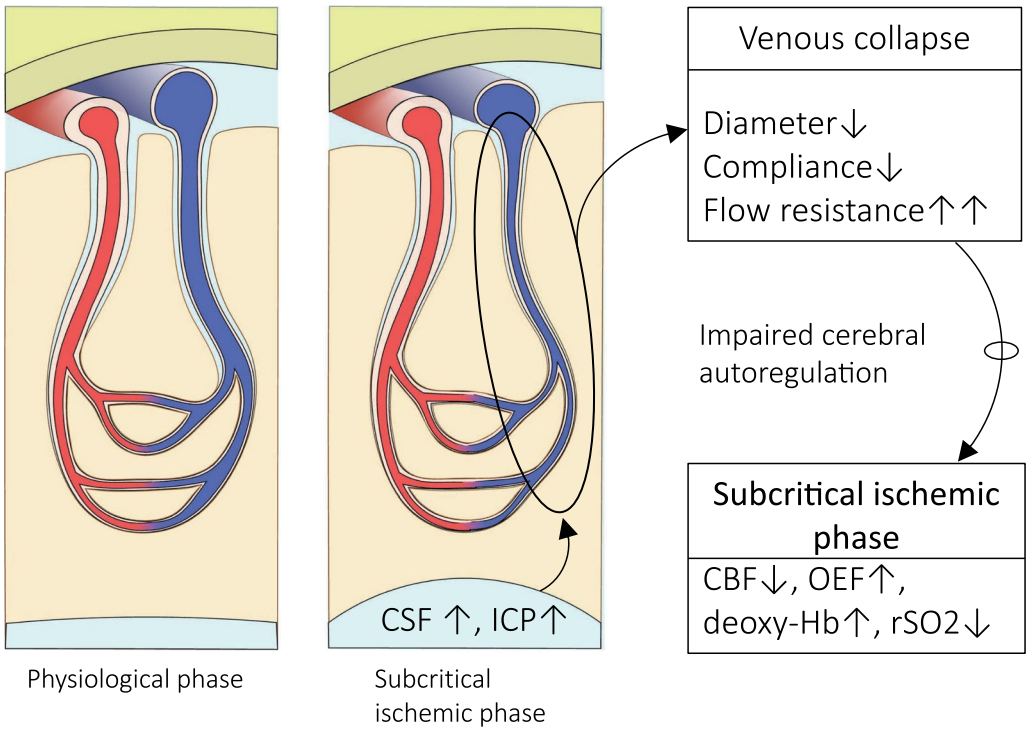

Fig. 5 The pathophysiology of NPH: Patients with NPH present with mild intracranial hypertension due to CSF accumulation caused by impaired CSF circulation. In addition, there is reduced compliance due to venous collapses, which, combined with ageing, arteriosclerosis, and brain atrophy, impairs CA, resulting in a subcritical ischemic phase with decreased CBF, increased OEF, increased deoxy-Hb, and decreased rSO2

in response to fluctuations in blood pressure [3, 4]. It has also been considered that that CBF remains constant for increases in ICP up to 40 mmHg [5–7]. However, these studies on CA had problems such as large measurement errors in cerebral blood flow and small sample sizes due to the fact that they were conducted in the 1950s. Upon review of the raw data from these pioneering studies, it appears that CBF may begin to decrease even with mild increases in intracranial pressure. Recent insights have illuminated the limitations of CA in responding to blood pressure fluctuations. For example, Tan et al. [22] reported that the regulatory range of CA in response to blood pressure variations is much narrower than previously thought. Arteriosclerosis, including ageing and vascular risk, tends to reduce CA function [23].

Czosnyka et al. [24] showed that CA was less functional in patients with NPH with brain atrophy. This suggests that in patients with non-functioning CA, even slight impairment of CSF circulation may lead to cerebral ischaemia. Patients with NPH have a number of factors, such as age, arteriosclerosis, and cerebral atrophy, which adversely affect the autoregulatory capacity of the brain and may be related to CA dysfunction associated with elevated ICP.

D5 Effects of cerebral arteriosclerosis

The study also showed that in patients with NPH with high cerebral arteriosclerosis, even very slight increases in intracranial pressure can injure cerebral circulation. This suggests that NPH symptoms can develop if cerebral arteriosclerosis is severe, even if there is little involvement of impaired CSF circulation. In addition, since all patients with iNPH have severe cerebral arteriosclerosis in this study, this indicates that patients with iNPH can also develop Hakim triad symptoms if they have severe cerebral arteriosclerosis, even if there is little involvement of CSF circulatory disturbance.

Binswanger disease presents similar symptoms and imaging findings as iNPH. We do not intend to claim that ischaemia is the sole cause of NPH, as previous literature has reported no correlation between CBF and white matter lesions in patients with dementia, suggesting that CBF pulsation is a major contributing factor [25, 26]. However, patients with Binswanger disease also often present deep white matter infarction, together with symptoms similar to those observed in patients with NPH [27]. Both diseases are similar in terms of subcortical cognitive dysfunction [28]. In addition, many symptoms of both conditions are similar, including frequent

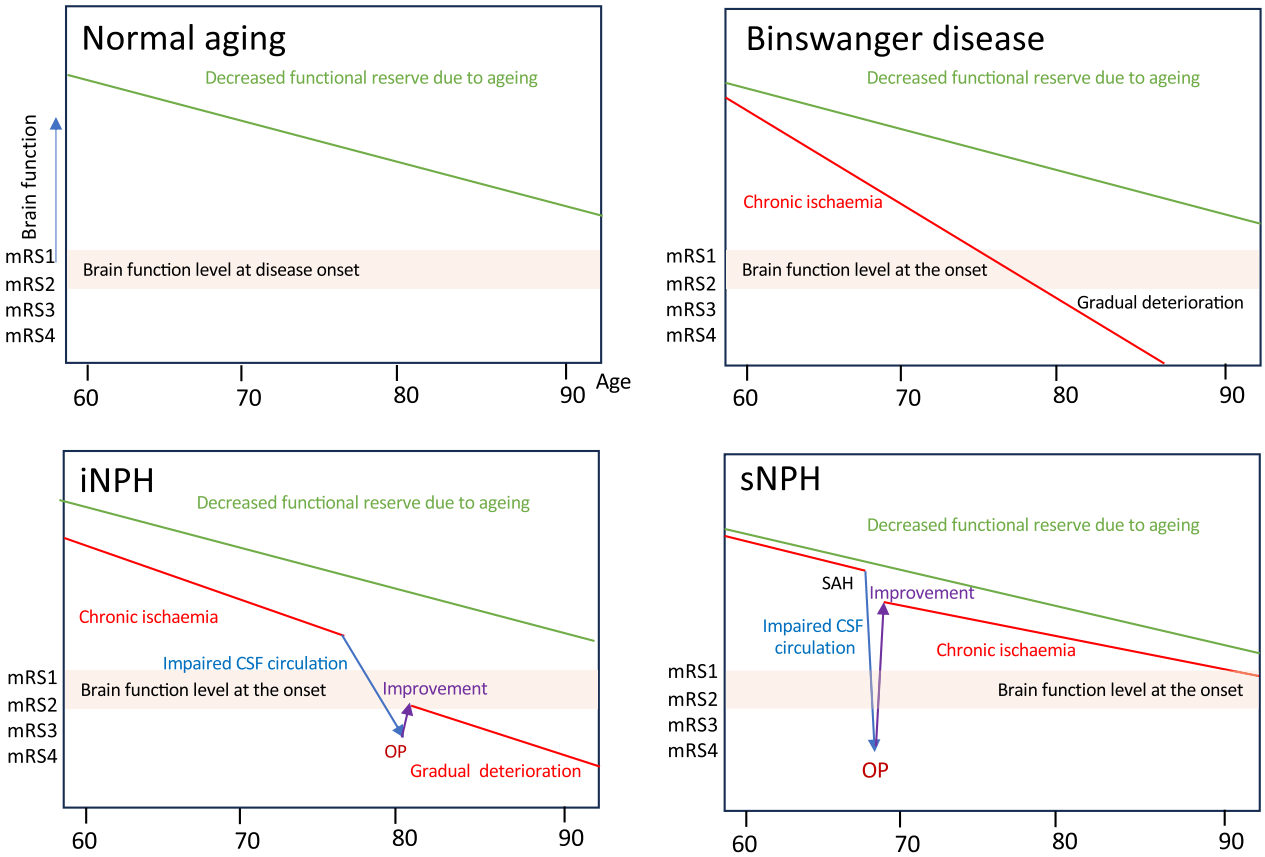

Fig. 6 General course of each disease: As people get older, it becomes progressively more difficult to maintain an active life. In addition, the reserve capacity of motor and cognitive functions declines. In the case of Binswanger disease, which develops after the mid-seventies due to chronic cerebral ischaemia in addition to the usual age-related functional decline, the symptoms of vascular dementia slowly worsen and the modified Rankin Scale (mRS) also worsens. Unlike pure Binswanger disease, iNPH is complicated by impaired CSF circulation. iNPH is a triad of additive effects of cerebral ischaemia due to chronic cerebral ischaemic damage from small artery arteriosclerosis and venous compression, in addition to low motor and cognitive reserve due to old age at onset. Patients are thus already in a subcritical ischemic phase at the onset of the disease. After onset, the mRS declines, but partial improvement is observed with shunt surgery (blue & purple line). However, the subsequent course of the disease is in deficit, with the mRS gradually worsening with age. sNPH is commonly associated with SAH, for example, and the onset of sNPH is usually at a younger age than iNPH. Unlike iNPH, sNPH is less likely to involve ischaemia derived from cerebral arteriosclerosis and more likely to involve purely CSF circulatory disturbance. Due to chronic cerebral ischaemia caused by impaired CSF circulation, the patient is already in a subcritical ischemic phase at the onset of the disease. With onset, the mRS deteriorates to a greater extent than in iNPH, but considerable improvement can be achieved by shunt surgery (blue & purple line). The course of the disease then follows a deficit course, with the mRS gradually worsening with age at the same rate as normal age-related functional decline

falls, gait changes, and urinary incontinence [29, 30], making it difficult to distinguish them symptomatically [31]. Tullberg et al. [32] also assessed DWMH and PVH on magnetic resonance imaging and reported no imaging differences between these diseases. Malm et al. [33] found that ventricular enlargement is not a criterion for Binswanger disease, but it is difficult or even impossible to distinguish the late stages of Binswanger disease from the advanced stages of iNPH, as the ventricles frequently enlarge in the late stages of Binswanger disease. Therefore, NPH and Binswanger disease are considered to be two diseases with similar pathophysiological mechanisms, or a pathophysiological continuum of increasing microangiopathy [32].

The present study highlights the pathophysiological similarities between the two diseases. Pathologically, sNPH is associated with a strong involvement of CSF circulatory disturbance, while iNPH is associated with ischaemia derived from cerebral arteriosclerosis. Those without involvement of CSF circulatory disturbance are categorized as pure Binswanger disease. These conditions form a spectrum of pathophysiological continua, with many patients with NPH falling along this continuum.

D6 Pathophysiology of iNPH

Based on the results of this study, we propose the following hypotheses regarding the pathogenesis of iNPH. The pathophysiology of iNPH is characterized by the additive effects of three factors: chronic cerebral ischaemic damage caused by small vessel arteriosclerosis, cerebral ischaemia due to venous compression, and low reserve capacity for motor and cognitive functions due to being elderly at the onset (Figs. 5 & 6). In particular, the subcritical ischemic phase, which is already present at the onset of the disease, is thought to be more likely to accumulate as cerebral ischaemic damage.

The irreversible progression reported by Andrén et al. [34] can be interpreted as the result of the long-term persistence of such an ischaemic phase, resulting in the irreversible accumulation of ischaemic damage derived from impaired CSF circulation.

We also consider that the reason why shunt surgery is effective for iNPH in the prodromal phase [13] is because the treatment is performed before the accumulation of irreversible ischaemic damage. On the other hand, the fact that age had a significant impact on the prognosis of cognitive function [35] may be attributed to the age-related depletion of the neurological functional reserve capacity for cognition, gait, and balance.

D7 Chronic ischaemic diseases due to increased mild compartmental pressure

Such a model of minor and chronic compression of the venous vascular bed may be adaptable to other compartmentalised, high-flow organs, such as the eye and kidney. That is, normal-tension glaucoma [36, 37] and chronic kidney disease [38, 39] may resemble the pathogenesis of NPH. There are many similarities between the blood circulation of the brain, retina, and kidneys. First, the brain, retina, and kidneys reside in compartmentalized spaces, namely, the cranial, ocular, and abdominal cavities, respectively. Second, they have high blood flow and autoregulatory mechanisms for blood flow in response to a drop in blood pressure. Third, they have a high tissue metabolic rate, which makes them less tolerant of ischaemia. In normal-tension glaucoma and chronic kidney disease, a reduction in tissue perfusion pressure due to minor venous collapses may also trigger chronic ischaemia.

Conclusion

Patients with normal pressure hydrocephalus are in a subcritical ischaemic phase, a minor ischaemic condition. Shunt surgery for patients with NPH can bring about a transition from this subcritical ischaemic phase to the physiological phase, resulting in recovery of neurological symptoms. This study provides the previously missing link between impaired CBF circulation and neurological dysfunction in patients with normal pressure hydrocephalus, which involves small vessel arteriosclerosis. The fact that a slight impairment of CSF circulation developed into a subcritical ischemic phase in patients with severe small vessel arteriosclerosis indicates that small vessel arteriosclerosis has a significant influence on the development of NPH and may be part of a continuum with Binswanger disease.

These findings provide insight into similar conditions, such as normal-tension glaucoma and chronic kidney disease, in which a mild increase in local compartment pressure leads to chronic ischemia in organs protected by autoregulatory mechanisms.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12987-024-00608-7.

Supp Fig. A: Intracranial pressure measurement in intermittent infusion test: The ventriculoperitoneal shunt system in patients with hydrocephalus includes an Ommaya reservoir in the head and an on-off valve in the chest. Puncture of the Ommaya reservoir with a 22G winged needle allows intraventricular pressure measurement and injection of CSF into the ventricles.

Supp Fig. B: This chart presents an example of ICP measurement during an intermittent infusion test. The overshoot of the ICP reflects the increase in pressure in the measurement circuit during the infusion, while the actual ICP does not overshoot. The overshoot of the ICP makes it easier to detect the infusion period. The exponential ICP increase associated with intermittent 3 ml CSF infusion is known as the Langfitt curve. The increased pulse pressure of ICP at low and high ICP reflects reduced intracranial compliance. An enlarged view of the area circled in red is shown on the right. CSF was injected at 20 s intervals, and compliance was calculated for 4 s (blue arrow), including a 3 s injection period and a dead zone of 0.5 s each before and after the injection. ICPpre and ICPpost were obtained for 2 s before and after the time of compliance calculation.

Supp Fig. C: 1) Compliance measurement: ICP extraction before and after CSF infusion (A). Calculate the averaged ICPpre and ICPpost 2 s before and after infusion. Calculate compliance (C) at infusion using the following equation: C = 3 ml / (ICPpost- ICPpre) mmHg. Calculate ICP at infusion using the following equation: ICP = (ICPpost - ICPpre) / 2. A median filter was applied to remove sudden large outliers and to select the median. 2) Data extraction in the no-infusion phase (B) Abbreviations: IAP: intra-abdominal pressure, HP: hydrostatic pressure, HPe: Hydrostatic pressure, The reference point for ICP at this time was the external auditory canal. 3) ICP domain analysis: Calculate the ICP-compliance curve using spline fitting (C). Plot the oximetric data at each ICP and fit a polynomial curve (D, E). 4) Volume domain analysis: Calculate the volume-compliance curve (F) and volume-pressure relationship (VPR) (G) from the ICP-compliance curve (C). Plot oximetric data at each ICP (D&E) on the VPR graph and fit polynomial curves (G)

Supp Fig. D: Normalised oximetry data corresponding to ICPv values are presented as mean ± SD.

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Author contributions

YK and HM made substantial contributions to the conception and design of the study. TO, YK and MKamo collected data regarding the participants. YK and MKameda analyzed the data. YK drafted the work, YK and MKameda and MC revised it. YK, TK, MC and MW supervised this project. All authors

contributed to patient management or other tasks as doctors and read and approved the submitted version.

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Availability of data and materials
The datasets generated for this study are available on request to the corresponding author.

Declarations

Consent for publication
I confirm the corresponding author has read the journal policies and submit this manuscript in accordance with those policies.

Competing interests
The authors declare no competing interests.

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