Pathophysiology of Cerebral Circulatory Disorders in Idiopathic Normal Pressure Hydrocephalus

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Abstract

This study was conducted to elucidate the pathologic conditions of cerebral circulatory disorders in idiopathic normal pressure hydrocephalus (iNPH). Among 44 possible iNPH patients, 40 patients underwent shunt surgery based on diagnostic flow charts plotted by the Southern Tohoku method and were evaluated to be shunt-effective at the end of the first post-surgical month. The cerebral blood flow (CBF) was measured by N-isopropyl- ^{123}I -P-iodo-amphetamine single photon emission computed tomography (mean, mCBF; cortical region, cCBF; thalamus-basal ganglia region, tbCBF on autoradiography [ARG] method) and the perfusion patterns of the cerebral cortex were measured based on three-dimensional stereotactic surface projection (3D-SSP) Z-score images, before and 1 month after the surgery in all 40 subjects. The mCBF rose significantly from 32.1 ± 2.74 ml/100 g/min before surgery to 39.8 ± 3.02 ml/100 g/min after surgery ($p < 0.03$). Investigation of the change of CBF revealed reductions in the cCBF (3 cases), tbCBF (9 cases), and cCBF + tbCBF (28 cases), with the reduced-cCBF group totaling 31 cases and the reduced-tbCBF group totaling 37 cases. Investigation of cerebral cortex hypoperfusion by 3D-SSP Z-score revealed 31 cases with hypoperfusion (frontal lobe type [19 cases], occipitotemporal lobe type [5 cases], mixed type [7 cases]) and nine cases with cortical normoperfusion (N). The pattern of reduction of the cortical blood flow on ARG method was favorably correlated with the pattern of hypoperfusion of the cerebral cortex on 3D-SSP Z-score images before surgery. A reduction of blood flow was found in the thalamus-basal ganglia region of all N type cases. The blood flow improved in 19 of 31 (61.3%) cases of the reduced-cCBF group and in 32 of 37 (86.5%) cases of the reduced-tbCBF group. All of the cases without detectable improvement exhibited increased blood flow in non-reduction areas. Investigation of the hypoperfusion patterns of the cerebral cortex on 3D-SSP Z-score images, revealed a reduction or disappearance of the hypoperfusion site in 19 of 31 (61.3%) cases, either no-change or a shift of the hypoperfusion site in 12 of 31 (38.7%) cases, and a correlation between the pattern of cortical blood flow reduction on ARG method and the pattern of cerebral cortex hypoperfusion on 3D-SSP Z-score images after surgery. Cerebral circulatory disorders in iNPH manifest as either of two pathophysiological conditions: the “circulatory disorder of the cerebral cortical region” and the “circulatory disorder of the thalamus-basal ganglia region.” Various patterns develop according to the disease stage.

Key words: idiopathic normal pressure hydrocephalus, cerebral blood flow, N-isopropyl- ^{123}I -P-iodo-amphetamine, single photon emission computed tomography, three-dimensional stereotactic surface projection

Introduction

Most researchers, including this author, agree that cases of idiopathic normal pressure hydrocephalus (iNPH) with decreased cerebral blood flow (CBF) before surgery undergo postoperative increases in blood flow when the shunts are effective.^{9,12-14,17-22,24,26-29,31,32,34} The results from reports on preoperative ischemic sites and postoperative sites of increased blood flow have varied,^{13,17,19,20,22,24,26,27,31,32} however, and no firm consensus has been reached.

In this study we use N-isopropyl-¹²³I-P-iodoamphetamine single photon emission computed tomography (¹²³I-IMP SPECT) to compare the CBF and perfusion patterns of the cerebral cortex assessed by the three-dimensional stereotactic surface projection (3D-SSP) Z-score images at each site before and after surgery in iNPH cases effectively resolved by shunt intervention (shunt-effective cases). We also discuss the cerebral circulatory disorders induced by iNPH. The study is herein reported.

Materials and Methods

Forty of 44 patients with possible iNPH, 26 males and 14 females aged 61–81 years (mean 70.2 years), underwent lumboperitoneal (28 cases) or ventriculoperitoneal (12 cases) shunt surgery based on diagnostic flow charts of the Southern Tohoku method²⁷ (Fig. 1), and were considered to be responsive at the end of the first post-surgical month. The possible iNPH patients satisfied the Japanese clinical guidelines for iNPH, including one or more of the classical triad of symptoms, ventricular dilation with Evans index >0.3, clear cerebrospinal fluid with normal pressure, middle age or elderly, and absence of causative disorders.⁷ The patients were evaluated by the revised Japanese grading scale for iNPH⁷ (Table 1) at the end of the first postsurgical month. Patients manifesting improvement of one point or higher in any item were regarded as responsive.

Two SPECT methods were used to measure CBF. First, CBF (mean CBF, mCBF; whole cortex, cCBF; thalamus-basal ganglia, tbCBF) was measured at each region of interest (ROI) (Fig. 2) by autoradiography (ARG) (equipment, Toshiba e-cam, Toshiba Medical Systems Co., Ohtawara, Tochigi; nuclear species, 222 MBq intravenous injection of ¹²³I-IMP [Perfuzamine®, Nihon Medi-physics Co., Nishinomiya, Hyogo]).^{8,10} Second, the perfusion patterns of the cerebral cortex were depicted by 3D-SSP Z-score images (Fig. 3) and investigated to assess the follow-

Flow-chart indication for shunting of iNPH (Southern Tohoku method)

Fig. 1 The Southern Tohoku method flow-chart indication for shunting in patients with idiopathic normal pressure hydrocephalus (iNPH).³⁰ LP: lumboperitoneal, mCBF: mean cerebral blood flow, mIR: mean increasing ratio, MMSE: Mini-Mental State Examination, Ro: cerebrospinal fluid out-flow resistance value, SPECT: single photon emission computed tomography, VP: ventriculoperitoneal.

ing: 1) the mCBF before and after surgery; 2) cCBF, tbCBF, and perfusion patterns of the cerebral cortex before surgery; and 3) the cCBF, tbCBF, and perfusion patterns of the cerebral cortex after surgery.

In ARG method in which supplementary regulation didn't conducted, a postoperative change of CBF of greater than 10% in the same subjects was assessed as significant because the aberration range was $\pm 6\%$.^{8,10} The patterns of cCBF and tbCBF reduction before surgery were evaluated by comparing the reduction rates with the mean cerebral flows of normal adults at each ROI by ¹²³I-IMP SPECT.³⁰

Table 1 Revised Japanese grading scale for normal pressure hydrocephalus (JGSNPH-R) in the clinical guidelines for idiopathic normal pressure hydrocephalus⁷⁾

Gait disturbance (G):	
0	normal
1	unstable, only subjective gait disturbance
2	objective gait disturbance, but independent gait
3	walking with canes or walker frame
4	walking not possible, wheelchair-bound
Dementia (D):	
0	within normal range
1	only subjective attention, memory disturbance
2	objective attention, memory disturbance, but normal time, place orientation
3	objective attention, memory disturbance with time, place disorientation
4	total disorientation, conversation not possible
Urinary incontinence (U):	
0	absent
1	absent but pollakiuria or urinary urgency
2	sometimes, more than 1–3 times a week
3	frequent, more than 1 time a day
4	uncontrollable urinary incontinence

Fig. 2 Regions of interest on N-isopropyl-(¹²³I)-P-iodo-amphetamine single photon emission computed tomography by autoradiography method. cCBF: whole cortex blood flow, mCBF: mean cerebral blood flow, tbCBF: thalamus-basal ganglia blood flow.

Fig. 3 Three-dimensional stereotactic surface projection Z-score images on N-isopropyl-(¹²³I)-P-iodo-amphetamine single photon emission computed tomography (frontal hypoperfusion type).

Fig. 4 Preoperative cerebral blood flow reduction patterns on N-isopropyl-(¹²³I)-P-iodo-amphetamine single photon emission computed tomography by autoradiography method. Left: type A, a 76-year-old male; center: type B, a 70-year-old male; right: type C, a 68-year-old female. cCBF: whole cortex blood flow in ml/100 g/min, tbCBF: thalamus-basal ganglia blood flow in ml/100 g/min.

Results

I. mCBF before and after surgery

The mCBF rose significantly from 32.1 ± 2.74 ml/100 g/min before surgery to 39.8 ± 3.02 ml/100 g/min after surgery ($p < 0.03$).

II. Preoperative cCBF, tbCBF, and perfusion patterns of the cerebral cortex

The patterns of preoperative CBF reduction were classified into three groups: the reduced-cCBF group (type A: 3 cases), reduced-tbCBF group (type B: 9 cases), and reduced-cCBF + tbCBF group (type

Table 2 Preoperative cerebral blood flow reduction patterns on N-isopropyl-(¹²³I)-P-iodo-amphetamine single photon emission computed tomography by autoradiography method

Type	cCBF (ml/100 g/min)	tbCBF (ml/100 g/min)
A (n = 3)	27.5 ± 6.24	45.1 ± 7.9
B (n = 9)	47.7 ± 2.81	30.2 ± 4.42
C (n = 28)	29.2 ± 3.3	31.0 ± 5.3

cCBF: whole cortex blood flow, tbCBF: thalamus-basal ganglia blood flow.

Fig. 5 Preoperative whole cortex blood flow and thalamus-basal ganglia blood flow on N-isopropyl-(¹²³I)-P-iodo-amphetamine single photon emission computed tomography by autoradiography method. cCBF↓: group with decrease in whole cortex blood flow, tbCBF↓: group with decrease in thalamus-basal ganglia blood flow.

C: 28 cases) (Fig. 4, Table 2). The type C cases, the patients with reduced CBF in both the cortex and thalamus-basal ganglia region, were by far the most numerous. Among the three groups combined, the cortical blood flow decreased in 31 patients and the blood flow of the thalamus-basal ganglia region decreased in 37 (Fig. 5).

The assessment of perfusion patterns of the cerebral cortex by 3D-SSP Z-score images revealed a clear cortical hypoperfusion in 31 cases. Three hypoperfusion patterns were noted: the frontal lobe type (F: 19 cases), occipitotemporal lobe type (OT: 5 cases), and mixed type (M: 7 cases). As in our previous report,²⁷⁾ the frontal lobe type was by far the most frequent. At the same time, however, as many as nine cases were assessed as the normoperfusion type (N), exhibiting a pattern with no detectable hypoperfusion in the cortex (Fig. 6). The mean tbCBF was 41.5 ± 3.52 ml/100 g/min in the 31 cases with cortical hypoperfusion and 30.5 ± 4.01 ml/100

Fig. 6 Preoperative cortical perfusion patterns on N-isopropyl-(¹²³I)-P-iodo-amphetamine single photon emission computed tomography three-dimensional stereotactic surface projection Z-score images. F: frontal type, M: mixed type, N: normoperfusion type, OT: occipitotemporal type.

Fig. 7 Postoperative blood flow improvement of whole cortex and thalamus-basal ganglia on N-isopropyl-(¹²³I)-P-iodo-amphetamine single photon emission computed tomography by autoradiography method. cCBF↓: group with decrease of whole cortex blood flow, tbCBF↓: group with decrease of thalamus-basal ganglia blood flow.

g/min in the nine cases with normoperfusion. The blood flow in the thalamus-basal ganglia region was significantly reduced in the N type ($p < 0.005$).

III. Variations of cCBF, tbCBF, and perfusion patterns of the cerebral cortex after surgery

The blood flow patterns of preoperative CBF reduction improved in one of three type A cases, seven of nine type B cases, and 15 of 28 type C cases. All of the cases without detectable improvement exhibited increased blood flow in non-reduction

Fig. 8 Postoperative variations of cortical hypoperfusion patterns on N-isopropyl- (^{123}I) -P-iodo-amphetamine single photon emission computed tomography three-dimensional stereotactic surface projection Z-score images. R/D: reduction or disappearance of hypoperfusion, NC/S: no-change or shift of hypoperfusion site.

areas. The total improvement rates were 19/31 (61.3%) in the reduced-cCBF cases and 32/37 (86.5%) in reduced-tbCBF cases. The blood flow improvement was marked in cases with preoperatively reduced blood flow of the thalamus-basal ganglia region (Fig. 7).

The assessments of the hypoperfusion patterns of the cerebral cortex by 3D-SSP Z-score images in the 31 cases presenting with preoperative cortical hypoperfusion revealed a reduction or disappearance of hypoperfusion in 19 of 31 (61.3%) cases and no-change or a shift of the hypoperfusion site in 12 of 31 (38.7%) (Fig. 8). The mean tbCBF in the 12 cases of no-change or shift rose from 34.2 ± 4.63 ml/100 g/min before surgery to 46.7 ± 3.78 ml/100 g/min after surgery. The blood flow in the thalamus-basal ganglia region improved significantly after surgery ($p < 0.003$) in both the no-change and shift cases.

The reductions of cortical blood flow on ARG method and hypoperfusion of the cerebral cortex on 3D-SSP Z-score images had very favorably correlated patterns both before and after surgery in this study.

Discussion

In a paper from 2005 we reported two notable results from evaluations of the shunt effect on CBF in shunt-effective iNPH cases: first, that the mean CBF increases by at least 10% after the cerebrospinal fluid tap test and increases significantly after

surgery; second, that the hypoperfusion pattern of the cerebral cortex by 3D-SSP Z-score images is not localized to the parietal lobe.²⁷⁾ In other respects, however, the results were discrepant: while the symptoms were improved and the mean CBF increased after surgery, the 3D-SSP Z-score images revealed no improvement in the postoperative hypoperfusion pattern of CBF in 40% of the cases.²⁷⁾ We speculate that the hypoperfusion patterns of the cerebral cortex by 3D-SSP Z-score mainly reflect the cerebral cortical blood flow, while the blood flows in the other regions might increase. We carried out the present study to investigate pathophysiological conditions of cerebral circulatory disorders in iNPH.

The results of our investigation reconfirmed the significant increase of the postoperative mean CBF in the shunt-effective cases. Further, a comparison between the perfusion pattern of the cerebral cortex (assessed by 3D-SSP Z-score images²³⁾) and the local CBF in the whole cortical region and thalamus-basal ganglia region (measured by the ARG method^{8,10)}) before surgery revealed two distinct groups: one presenting a reduced blood flow localized in either the cortical region or the thalamus-basal ganglia region, and one with reduced blood flow in both regions. The normoperfusion type (N) was not reflected in the 3D-SSP Z-score images in the group with reduced blood flow localized in the thalamus-basal ganglia region, hence the N type was only presumed in the 3D-SSP Z-score images of these cases. The post-surgical improvement of CBF appeared in several patterns: in addition to the group with complete CBF improvement in both the whole cortical region and thalamus-basal ganglia region, there were also groups with improvement in only one or the other. Moreover, the significant post-surgical increase of the blood flow in the 3D-SSP Z-score images of the thalamus-basal ganglia regions of the no-change or shift cases indicated a compensatory increase of the blood flow at the preoperative normoperfusion sites.

The cerebral circulatory disorders in iNPH are difficult to explain one-dimensionally from the results of this study. We speculate that there are two pathophysiological conditions: “circulatory disorder in the cerebral cortex” and “circulatory disorder in the thalamus-basal ganglia region.” In discussing these two pathologic conditions we must mention the mechanism behind the occurrence of iNPH.

Adams et al.^{1,2)} proposed that iNPH arises as a result of arachnoiditis in the cerebral convexity caused by an unknown etiology. This is refuted, however, by a report³³⁾ arguing that circulatory disorders of the cerebrospinal fluid itself confer no

effects.⁶⁾ In any case, we can surmise that some disorder of the absorbance mechanism of cerebrospinal fluid may be present.^{11,25)} Intriguingly, Kondo¹⁵⁾ hypothesized that the shift of blood from the bridging vein to the sinus may be induced by the balance among the pressures of the bridging vein, sinus, cerebrospinal fluid in the subarachnoid cavity, and wash-out mechanism of expired and inspired respiration. If this hypothesis is correct, any variation in the pressure of the cerebrospinal fluid in the subarachnoid cavity resulting from the iNPH-induced disorder of cerebrospinal could disturb the pressure balance of the wash-out mechanism. This condition would presumably induce collapse and reduced compliance of the cortical veins, including the bridging vein,³⁻⁵⁾ and consequently change the disorder from a hypoperfusion of the cortical vein to a disorder of the cortical circulation. This is assumed to be the pathophysiological condition of the “circulatory disorder in the cerebral cortex.” On the other hand, the expansion of the lateral ventricle and third ventricle induced by the circulatory disorder of the cerebrospinal fluid leads to a pressure of the peripheral cerebral tissues, which thus changes the disorder to a circulatory disorder of the tissues around the ventricle due to the hypoperfusion caused by the compression and ensuing lesser pathway. This is assumed to be the pathophysiological condition of the “circulatory disorder in the thalamus-basal ganglia region.” The interstitial fluid bulk flow³⁾ accompanying the circulatory disorder in the cerebral cortex and the lesser pathway from the ventricle eventually induces the circulatory disorder of the white matter and the paraventricular watershed region,^{7,24,32)} leading to a circulatory disorder of the whole brain (Fig. 9).

Earlier studies on ischemic sites in iNPH before surgery^{16,17,19,20,22,24,26-32,34)} have reported various patterns of these two pathophysiological conditions according to the disease stage of iNPH. While one group reports only reductions in hypoperfusion,³⁴⁾ most authors agree that the CBF improves after surgery in shunt-effective cases, in light of the compensatory increase of the blood flow at normoperfusion sites in non-improved hypoperfusion cases after surgery.^{9,12,13,16-18,20,21,28-32,34)}

The mCBF, cCBF, and tbCBF were measured by the ARG method before and after surgery in 40 patients with possible iNPH who responded well to shunt treatment. And the results were compared with the perfusion patterns of the cerebral cortex by 3D-SSP Z-score images. The following conclusions were obtained: 1) In shunt effective cases, the postoperative mCBF increased in shunt-effective cases. 2) The pattern of blood flow reduction in the

Fig. 9 Mechanisms of cerebral blood flow disturbance in idiopathic normal pressure hydrocephalus (iNPH). CSF: cerebrospinal fluid, CV: cortical vein, SS: sagittal sinus.

cerebral cortex assessed by the ARG method correlated with the pattern of hypoperfusion of the cerebral cortex assessed by 3D-SSP Z-score images. 3) The blood flow was significantly reduced in the thalamus-basal ganglia of the cases exhibiting normoperfusion of the cerebral cortex on 3D-SSP Z-score images. 4) The CBF improved postoperatively in the thalamus-basal ganglia region, in the cerebral cortex region, or in both regions. 5) A compensatory increase of blood flow was found in other normoperfusion sites in cases without postoperative improvement of the hypoperfusion sites. 6) The blood flow in the thalamus-basal ganglia region increased significantly after surgery in all the cases manifesting either no-change or a shift of hypoperfusion sites on 3D-SSP Z-score images. 7) Cerebral circulatory disorders in iNPH manifest as either of two pathophysiological conditions: the “circulatory disorder of the cerebral cortical region” and the “circulatory disorder of the thalamus-basal ganglia region.” Various patterns develop according to the disease stage.

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Commentary

This article is an important contribution to the pathophysiology of NPH. We were fortunate enough to work in Boston during the time that Dr. Hakim and Professor Ray Adams described this new syndrome. The authors have elegantly confirmed that iNPH with

decreased CBF before surgery undergo postoperative increase in BF when shunts are effective, as has been shown in the extensive literature. They have divided the perfusion patterns into three groups, with discrepant results, reconfirming the significant increase of the postoperative mean CBF in the shunt-effective cases, demonstrating that there are two main pathophysiological conditions: a) circulatory disorders in the cerebral cortex, and b) in the thalamus-basal ganglia region, thus creating a unified standard for the diagnosis and treatment of iNPH.

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Takeuchi et al. present interesting results of a study on regional cerebral blood flow (CBF) before and after shunting procedure in 40 patients with idiopathic normal pressure hydrocephalus (iNPH). CBF study using ^{123}I -IMP SPECT showed a decrease in CBF in the cerebral cortex and/or thalamus-basal ganglia in all of the patients preoperatively. After surgery, an increase in CBF in 61.3% of the 31 patients with decreased cortical blood flow and in 86.5% of the 37 patients with decreased blood flow in the thalamus-basal ganglia was observed. Furthermore, 3D-SSP Z-score images revealed a decrease or disappearance of cortical hypoperfusion area in 61.3% of 31 patients with preoperative cortical hypoperfusion after surgery. The authors refer to the mechanism of CBF disturbance in patients with iNPH, based on their data that there are three patterns in decreased regional CBF, which are decreases in CBF at the cortex, thalamus-basal ganglia or both.

Idiopathic NPH is a treatable neurological disorder characterized by gait disturbance, incontinence, and dementia. However, although we have recently published elaborate guidelines for diagnosis and management of iNPH, the preoperative diagnosis of iNPH remains controversial without definite criteria. The correlation between clinical symptoms and hemispheric or regional CBF in iNPH has not been established. This article demonstrates that decreased regional CBF is not the consequence of neural dysfunction but is associated with a causative mechanism of clinical symptoms in iNPH, because regional CBF improved after surgery in most of the patients who were judged to show shunt effectiveness. The authors have made a valuable contribution to better understanding of the pathophysiology of iNPH.

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