Effect of Cerebrospinal Fluid Area Mask Correction on ^{123}I -FP-CIT SPECT Images in Idiopathic Normal Pressure Hydrocephalus

Makoto Ohba (✉ m-ohba@med.id.yamagata-u.ac.jp)

Yamagata University Hospital

Ryota Kobayashi

Yamagata University School of Medicine

Chifumi Iseki

Yamagata University School of Medicine

Kazukuni Kiri

Yamagata University School of Medicine

Daichi Morioka

Yamagata University School of Medicine

Koichi Otani

Yamagata University School of Medicine

Yasuyuki Ohta

Yamagata University School of Medicine

Yukihiko Sonoda

Yamagata University School of Medicine

Koji Suzuki

Yamagata University Hospital

Masafumi Kanoto

Yamagata University School of Medicine

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Abstract

Cerebrospinal fluid (CSF) mask correction has been developed to reduce the influence by CSF area dilatation for ^{123}I -FP-CIT accumulation. In this study, we assessed the effect of CSF mask correction on the specific binding ratio (SBR) for 25 patients with idiopathic normal pressure hydrocephalus (iNPH). The SBRs with and without CSF mask correction were calculated, and changes in quantitative values were verified. Additionally, the volume removed from striatal and background (BG) volume of interest (VOI) by the CSF mask correction was calculated, the volumes removed were compared to verify their effect on SBR. Twenty and five patients had low and high SBRs, respectively, after CSF mask correction. The images of 20 and 5 patients with SBRs that were decreased and increased, respectively, by CSF mask correction showed that the volumes removed from the BG region VOI were higher and lower, respectively, than those in the striatal region. In conclusion, the SBR before and after CSF mask correction was associated with the ratio of the volume removed from the striatal and BG VOIs, and the SBR was high or low according to the ratio. The results may indicate that CSF mask correction is effective in patients with iNPH.

This study was registered in the UMIN Clinical Trials Registry (UMIN-CTR) as UMIN study ID: UMIN000044826.

Introduction

[^{123}I]-N-fluoropropyl-2b-carbomethoxy-3b-(4-iodophenyl) nortropane (^{123}I -FP-CIT) single-photon emission computed tomography (SPECT) visualizes the dopamine transporter (DAT) and is useful for diagnosing Parkinson's disease (PD) and dementia with Lewy bodies (DLB) [1, 2, 3]. The findings of ^{123}I -FP-CIT SPECT are mainly assessed visually [2, 4], but quantitative assessment is also used for ^{123}I -FP-CIT SPECT image interpretation [5]. The specific binding ratio (SBR) for ^{123}I -FP-CIT SPECT quantitation is calculated by subtracting the amount of ^{123}I -FP-CIT accumulation in the striatal region from that of the whole brain. The accumulation in the striatal region is calculated as the ratio of the background (BG) volume of interest (VOI) [6]. The Southampton method described by Tossici-Bolt et al. [6] is widely used to calculate SBR.

However, when the region of cerebrospinal fluid (CSF) has expanded due to cerebral atrophy or ventricular enlargement, a CSF region of low ^{123}I -FP-CIT accumulation can be mixed in the striatal VOI, which leads to underestimation of the accumulated amount in the striatal VOI when applying the Southampton method [7]. Therefore, the CSF area mask correction method for masking the CSF area and calculating the SBR was developed [7], and this method has improved the ability to differentially diagnose patients with parkinsonism such as PD and progressive supranuclear palsy (PSP) and those without parkinsonism, in cases with ventricular dilatation [8].

Idiopathic normal pressure hydrocephalus (iNPH) is characterized by cognitive dysfunction, gait disturbance, and urinary incontinence [9]. Furthermore, enlargement of the Sylvian fissures and ventricles

and disproportional narrowing of the subarachnoid space and sulci in the higher fornix are hallmarks for diagnosing iNPH radiologically [9]. To date, the DAT imaging findings of iNPH have been reported to be normal because iNPH does not involve the degeneration of the nigrostriatal neurons [10, 11]. However, it has recently been reported that DAT on DAT imaging was reduced in 30.8–62.0% of patients with iNPH [12, 13, 14]. Furthermore, different from PD showing DAT reduction in the putamen predominantly, iNPH may be characterized by DAT reduction in the caudate as much as the putamen [15]. Thus, DAT-SPECT imaging in iNPH might be clinically important for diagnosing and understanding its pathophysiology [15].

Idiopathic NPH presents with ventriculomegaly and is likely to include the CSF region in the VOI in the Southampton method. However, to the best of our knowledge, the effects of CSF area mask correction on SBR in iNPH have not been determined. We compared the SBR before and after CSF area mask correction in iNPH using ^{123}I -FP-CIT SPECT and investigated the effect of the correction on the SBR.

Materials And Methods

Patients

The subjects were iNPH patients who visited Yamagata University Hospital and were diagnosed based on the guideline diagnostic criteria [16] between March 2017 and April 2021. Of these, 25 patients with iNPH who were assessed using ^{123}I -FP-CIT SPECT before shunt surgery or the tap test were included in this study. Furthermore, to establish the diagnosis of iNPH more reliably, only patients with an Evans index greater than 0.3 were included. The iNPH stage composition consisted of four possible cases, six probable cases, and 15 definite cases. All subjects in this study underwent $^{99\text{m}}\text{Tc}$ -ethyl cysteinate dimer SPECT and ^{123}I -metaiodobenzylguanidine (MIBG) myocardial scintigraphy, eliminating as much as possible DLB and PD, which are characterized by decreased blood flow in the occipital lobe [17] and/or decreased cardiac sympathetic function [17, 18]. Demographic and clinical data of the subjects are shown in Table 1.

Single-photon emission computed tomography imaging

We acquired ^{123}I -FP-CIT SPECT/computed tomography (CT) images over 28 min using a Symbia T2 with a rotating, dual-detector gamma camera (Siemens Healthineers, Erlangen, Germany) and a low- to medium-energy general-purpose collimator (Siemens Healthineers), with 360° continuous rotation (7.0 min/rotation $\times$ 4 rotations). Supine patients at rest with their eyes closed were intravenously injected with ^{123}I -FP-CIT (167 MBq), and SPECT/CT images were acquired for 3 h under the following conditions: magnification, 1.45; matrix, 128 $\times$ 128 (3.3 mm/pixel); main window, 159 $\pm$ 12.0 keV; and sub-window, 8%.

A Gaussian post-processing filter with a full width half maximum of 6.6 mm, six subsets, and eight iterations was applied for ordered subset expectation maximization reconstruction with CT-based attenuation correction, a multi-energy window, and collimator aperture correction for scatter correction.

Specific binding ratio (SBR) calculation

Volumes of interest were placed on the striatum and BG regions determined using the Tossici-Bolt method [6] (Figure 1). We obtained a highly reproducible quantitative index using a 44-mm-thick tomographic image centered on the striatum along with a large region of interest.

SBR was calculated as follows:

$$\text{SBR} = \frac{\text{Striatum accumulation} - \text{BG accumulation}}{\text{BG accumulation}} \times \frac{\text{Striatum area volume}}{\text{Striatum actual volume}}$$

CSF area mask correction

The CSF area mask correction creates a standard normal distribution for each VOI in the striatal and BG regions and excludes the low accumulation of the set standard deviation (SD) from the SBR calculation. The SD threshold was set to an average of -1.0 SD [7].

Changes in SBR before and after CSF area mask correction

The SBR can be calculated using DaTView analysis (Nihon Medi-Physics, Tokyo, Japan), with differences between facilities corrected by applying the formula derived from the striatal phantom using SPECT/CT, $y = 0.9369x + 0.0404$ (19). The SBRs with and without CSF area mask correction were calculated, respectively, and changes in the quantitative values were verified.

Verification of striatum and background volume of interest (BG VOI) volumes before and after CSF area mask correction

Removing a larger volume via CSF area mask correction results in a higher VOI count. Therefore, we hypothesized that the change in SBR was dependent on whether the volume removed by CSF area mask correction was larger in the striatal VOI or BG VOI. In other words, it was estimated that the SBR decreased when the volume removed by the CSF area mask correction in the striatum VOI was larger than the volume removed by the CSF area mask correction in the BG VOI. Moreover, it was estimated that the SBR increased when the volume removed by the CSF area mask correction in the striatum VOI was smaller than the volume removed by the CSF area mask correction in the BG VOI. The number of voxels in each VOI before and after CSF area mask correction was extracted from DaTView (Nihon Medi-Physics, Tokyo, Japan). The number of voxels after was subtracted from that before CSF area mask correction, and the volume removed by the CSF area mask correction was calculated. The volumes removed from the VOIs were compared to verify their effect on the SBR.

Comparison of SBR before and after CSF area mask correction with a database of age-matched healthy controls

A database of Japanese healthy controls shows the upper and lower limits of the 95% prediction interval for each age [19]. We compared the SBR before and after CSF area mask correction with the normal SBR obtained from these controls.

Ethical statements

This study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethical Review Committee of Yamagata University Faculty of Medicine for epidemiological research (approval number: 2021-89), and the requirement for obtaining informed consent from the patients was waived because this study was retrospective design by the Ethical Review Committee of Yamagata University Faculty of Medicine (approval number: 2021-89).

Results

Changes in SBRs before and after CSF area mask correction

The SBRs before and after the CSF area mask correction are shown in Table 1. The averages ($\pm$ SD) were 5.49 ± 1.71 before correction and 5.18 ± 1.38 after correction. After CSF area mask correction, SBRs were low in 20 patients (cases 1~20) and high in 5 patients (cases 21~25).

Verification of the striatum and BG VOI volume before and after CSF area mask correction

The volumes of the striatum and BG region VOIs removed by CSF area mask correction are shown in Table 1. The images of 20 and 5 patients with SBRs that were decreased and increased, respectively, by CSF area mask correction showed that the volumes removed from the BG region VOI were higher and lower, respectively, than those in the striatal region.

Comparison of SBRs before and after CSF area mask correction with a database of healthy controls by age

We compared the SBRs before and after CSF area mask correction using the phantom formula and the database of healthy controls by age (Figure 2). The SBRs of one patient each were below and near the lower limit of the 95% prediction interval after the CSF area mask correction.

Discussion

This is the first study to evaluate the SBRs before and after CSF area mask correction in patients with iNPH characterized by Sylvian fissures and ventricular enlargement. Recently, a study assessing the effect of CSF mask correction in parkinsonian syndromes with ventriculomegaly, such as PD and PSP, has been reported [8]. In this prior study, CSF mask correction improved the ability to distinguish between patients with parkinsonism and those without parkinsonism in cases with moderate to severe ventricular dilatation [8]. This previous study has included a small number of iNPH in the group without parkinsonism. Recent studies have revealed that DAT availability decreases from 30.8–62.0% in patients with iNPH [12, 13, 14]. In other words, the results of discrimination in their study may vary depending on the proportion of iNPH with and without the pathophysiology of DAT reduction, if a large number of iNPH subjects were included.

Interestingly, changes in SBR with CSF mask correction in patients with iNPH were not constant in the present study. The SBR with CSF area mask correction was low in 20 patients and high in five patients compared with the uncorrected SBR. The changes in SBR were related to the ratios of the volumes removed by CSF mask correction from the striatal and BG regions. That is, individual differences in the enlargement of Sylvian fissures and the anterior horn of the lateral ventricle affected the SBR. The VOI analysis of the Southampton method is based on the premise that nonspecific accumulation in the BG regions is uniform. Therefore, CSF area mask correction might be particularly useful for diseases in which there are large individual differences in the enlargement of Sylvian fissures and cerebral ventricle.

It should be noted that the SBR after CSF area mask correction was below and near the lower limit of the 95% prediction interval of the normal database by age in one patient each. These findings suggest that CSF area mask correction might affect the visual and quantitative assessment of iNPH. The pathophysiology of DAT reduction, which was observed in approximately 30–60% of iNPH, has not been clarified [12, 13, 14]. Therefore, future studies of DAT availability in iNPH require more accurate visual and quantitative analyses. Consequently, we propose that CSF area mask correction should be applied when using the Southampton method in DAT imaging studies of iNPH.

This study had several limitations. First, we excluded patients with PD and DLB as much as possible based on cerebral blood flow SPECT/CT and MIBG myocardial scintigraphy, but other iNPH-like disorders might have been included. Second, complex pathologies, such as Alzheimer's disease, which can affect cerebral atrophy, were not considered. Third, the study cohort was small, and more patients with definite iNPH were not available. Finally, this study was a retrospective study at only one medical institution. Therefore, the results of this study should be validated in multicenter prospective studies.

In conclusion, the SBR before and after CSF area mask correction was associated with the ratio of the volume removed from the striatal and BG VOIs, and the SBR was high or low according to the ratio. The results may indicate that CSF area mask correction is effective, particularly in patients with iNPH characterized by ventriculomegaly.

Declarations

Acknowledgments

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Conflict of interest

The authors declare that they do not have anything to disclose regarding funding or conflicts of interest with respect to this manuscript.

Author's contributions

MO and RK conceptualized the study, analyzed neuroradiological examinations, analyzed the clinical data, and drafted the manuscript. CI, DM, KO, YO, and YS analyzed the clinical data, and revised the manuscript. KK and KS analyzed the neuroradiological examinations and revised the manuscript. MK encouraged the study and revised the manuscript accordingly. All authors have read and approved the final version of this manuscript.

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Tables

Table 1 Demographic, clinical data, and the SBRs before and after the CSF area mask correction of the subjects

Case	Age	Sex	Diagnosis	Visual assessment	Before- After voxel (pixels)		ncSBR	cSBR
					Striatum VOI	BG VOI		
1	66	M	definite iNPH	Abnormal	1572	3059	5.03	4.87
2	70	F	definite iNPH	Normal	1182	1947	6.21	5.58
3	71	F	definite iNPH	Normal	1712	2226	5.12	4.87
4	72	M	definite iNPH	Abnormal	946	2475	8.66	7.67
5	73	F	definite iNPH	Normal	1025	2221	7.07	6.13
6	77	M	definite iNPH	Normal	1314	2210	6.58	6.08
7	78	F	definite iNPH	Normal	1345	2122	7.25	6.67
8	81	F	definite iNPH	Normal	1372	1435	5.77	5.51
9	79	F	definite iNPH	Normal	1290	1813	6.13	5.64
10	79	F	definite iNPH	Normal	1733	1854	6.52	6.48
11	80	F	definite iNPH	Normal	1474	1739	5.70	5.64
12	81	M	definite iNPH	Normal	1636	2057	5.51	4.96
13	84	M	definite iNPH	Normal	1118	2376	6.07	5.27
14	72	M	probable iNPH	Abnormal	1445	2384	3.41	3.40
15	75	M	probable iNPH	Normal	1931	2253	8.46	7.78
16	76	M	probable iNPH	Normal	1148	2645	6.68	5.66
17	80	M	probable iNPH	Normal	1202	2042	4.79	4.45

Case	Age	Sex	Diagnosis	Visual assessment	Before- After voxel (pixels)		ncSBR	cSBR
					Striatum VOI	BG VOI		
18	83	M	probable iNPH	Abnormal	1410	2412	5.79	5.18
19	78	F	possible iNPH	Normal	1304	2029	6.04	5.80
20	84	F	possible iNPH	Normal	1547	1852	4.55	4.35
21	78	F	definite iNPH	Normal	2056	1763	4.45	4.87
22	83	F	definite iNPH	Normal	1933	1828	4.88	5.03
23	86	F	probable iNPH	Abnormal	1916	1426	2.41	2.88
24	80	M	possible iNPH	Abnormal	2197	1394	2.12	2.61
25	83	F	possible iNPH	Abnormal	2076	2140	2.08	2.20
Average (± SD)	78.0 ± 4.9	-	-	-	1515.4 ± 350.8	2068.1 ± 387.6	5.49 ± 1.71	5.18 ± 1.38

SBR: specific binding ratio, CSF: cerebrospinal fluid, F: female, M: male, iNPH: idiopathic normal pressure hydrocephalus, VOI: volume of interest, BG: background, ncSBR: the SBR without CSF area mask correction, cSBR: the SBR with CSF area mask correction, SD: standard deviation

Figures

S : Striatum region

B : BG region

Figure 1

VOI for SBR calculation using the Southampton method VOI (S): striatal region. VOI (B): BG region. VOI: volume of interest, SBR: specific binding ratio, BG: background

Figure 2

Comparison of SBR before and after CSF area mask correction with a database of healthy controls by age Scatterplot of SBR before and after CSF area mask correction. Filled dots and white dots represent the SBR before and after CSF area mask correction, respectively. The dotted line shows the 95% upper (purple), average (red), and lower (green) prediction intervals of the Japanese healthy adult database. The cases in which SBR was below and near the lower limit of the 95% prediction interval after the CSF area mask correction were indicated by arrow ($\nwarrow$) and double arrow ($\searrow$), respectively SBR: specific binding ratio, CSF: cerebrospinal fluid, ncSBR: the SBR without CSF area mask correction, cSBR: the SBR with CSF area mask correction, PI: prediction interval