I-123-FP-CIT SPECT in dementia with Lewy bodies, Parkinson's disease and Alzheimer's disease: a new quantitative analysis of autopsy confirmed cases

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[^{123}I]FP-CIT SPECT in dementia with Lewy bodies, Parkinson's disease and Alzheimer's disease: a new quantitative analysis of autopsy confirmed cases

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Abstract

Purpose: The aim of this study was to re-evaluate the differentiation of patients with dementia with Lewy bodies (DLB) from Alzheimer's disease (AD) and Parkinson's disease (PD) using a quantitative analysis of [^{123}I]FP-CIT SPECT scans.

Methods: Thirty-six patients with *in vivo* [^{123}I]FP-CIT SPECT and neuropathological diagnoses were included. Based on neuropathological criteria, patients were further subclassified into 9 AD, 8 DLB, 10 PD and 9 with other diagnoses. An additional 16 healthy controls (HC) scanned with [^{123}I]FP-CIT SPECT were also included. All images were visually assessed as normal versus abnormal uptake by consensus of 5 nuclear medicine physicians. Bihemispheric mean was calculated for caudate binding potential (CBP), putamen binding potential (PBP) and putamen to caudate binding potentials ratio (PCR).

Results: Patients with DLB had significantly lower CBP and PBP than AD patients and significantly higher PCR than PD patients. Qualitative visual analysis of the images gave an accuracy of 88% in the evaluation of the status of the nigrostriatal pathway considering all individuals, and 96% considering only the PD, AD and DLB patients. Quantitative analyses provided a balanced accuracy of 94%, 94% and 100% in binary classifications DLB versus AD, DLB versus PD and PD versus AD, respectively; and an accuracy of 93% in the differentiation between DLB, AD and PD patients simultaneously. No statistically significant differences were observed between the AD and HC.

Conclusions: This study demonstrates a very high diagnostic accuracy of the quantitative analysis of [^{123}I]FP-CIT SPECT data to differentiate between DLB, PD and AD patients.

Keywords: autopsy; dementia with Lewy bodies; Parkinson's disease; Alzheimer's disease; [^{123}I]FP-CIT; quantification; classification

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most frequent cause of degenerative dementia in elderly people (15 to 25% of cases at autopsy).[1] Differentiation from Alzheimer's disease (AD) (50 to 60% of the cases in elderly patients) is important regarding patients' prognosis, treatment and clinical management.[1]

Clinical diagnosis of DLB is currently based on the identification of fluctuating cognition with pronounced variations in attention and alertness, recurrent visual hallucinations,

rapid eye movement (REM) sleep behavior disorder and one or more spontaneous cardinal features of Parkinsonism in patients with dementia.[2]

Although the revised International Consensus Criteria of 2005 showed increased diagnostic sensitivity for DLB,[3] the detection rates in clinical practice (prevalence among dementia patients of 7.2%) are below the rates found at autopsy (15 to 25%).[4] This suboptimal sensitivity is attributed to cases being missed or misdiagnosed, usually as Alzheimer's disease.[2]

Previous studies have shown that there is a loss of nigrostriatal dopaminergic neurons in the majority of patients clinically diagnosed with DLB compared to patients diagnosed with AD.[5-8] There are relatively few published papers concerning [^{123}I]FP-CIT brain SPECT in DLB with subsequent neuropathology.[9-13] The majority of previous studies focused mainly on visual assessment of [^{123}I]FP-CIT. We found no single study with autopsy diagnoses including patients with DLB and PD to ascertain differences in the pattern of dopaminergic deficit between the two conditions *in vivo*. The aim of this study was to use a quantitative analysis of *in vivo* [^{123}I]FP-CIT brain SPECT to re-evaluate the differentiation between DLB, AD and PD patients based on neuropathology diagnoses.

MATERIALS AND METHODS

Patients

Thirty-six patients, who underwent [^{123}I]FP-CIT brain SPECT during life and subsequently had a histopathological diagnosis at autopsy, were studied. Sixteen healthy controls (spouses of patients) were included and undertook [^{123}I]FP-CIT brain SPECT examination during the same period of time and in identical conditions. Table 1 shows the demographic data.

The DLB, AD and PD cases were reported previously with less sensitive semi-quantitative indices of scans and without autopsy.[6] Most of the DLB and AD cases were reported in a previous publication comparing clinical, visually rated scans and autopsy results.[10] The DLB and AD cases were recruited from dementia Memory clinics of ZW. The PD cases were recruited from the general Neurology clinics of RW and were all new cases of

hitherto undiagnosed PD, so they did not have advanced disease but did all have early motor involvement. The autopsy confirmed diagnoses of the PD cases have not previously been reported. Besides the DLB, AD and PD, a group of patients with other diagnoses at autopsy was included (Table 1). It comprises 2 patients with frontotemporal dementia (FTD), 2 patients with AD and vascular disease (AD+VD), 2 patients with AD and Lewy body disease (LBD) (AD+LBD), 1 patient with corticobasal degeneration (CBD), 1 patient with LBD plus AD and vascular disease (LBD+AD+VD), and 1 patient with no identified pathology.

Table 1: Demographic data for all patients according to autopsy confirmed diagnosis compared to heathy controls.

Characteristics	**DLB** (8)	**AD** (9)	**PD** (10)	**Other diagnoses** (9)	**HC** (16)
Sex ratio (M:F)	4:4	6:3	9:1	6:3	10:6
Age at time of [^{123}I]FP-CIT scan (years)	76 ± 10	77 ± 8	65 ± 9	78 ± 8	67 ± 11
Time from [^{123}I]FP-CIT scan to death (years)	4.0 ± 2.5	3.8 ± 3.3	12.4 ± 3.5	5.0 ± 3.6	Not applicable

[^{123}I]FP-CIT SPECT acquisition and processing

All [^{123}I]FP-CIT brain SPECT acquisitions were performed at the Institute of Nuclear Medicine, University College London, UK. All subjects were scanned with a dedicated single slice brain scanner (SME 810, Strichman Medical System, MA, USA) 3.5 to 6 hours after intravenous injection of approximately 185 MBq of [^{123}I]FP-CIT. Multiple slices were acquired sequentially as a stack of 2D transaxial images. Slice thickness was 10 mm with an overlap of 2.5 mm between consecutive slices. The number of slices varied between 4 and 10, most frequently 6 or 8 slices. Image reconstruction was carried out using a filtered back projection algorithm (FBP) available in the SME 810 scanner and specifically designed by the manufacturer to obtain the best gain in resolution and sensitivity per slice. Before the [^{123}I]FP-CIT injection, subjects received potassium iodide orally to block radioactive iodine thyroid uptake.

Reconstructed image slices were transferred from the NEURO-900 (software available in the SME 810) to an external storage device and afterwards interpreted and converted into 3D images (volumes) using in-house developed software. Then the 3D images were converted to DICOM format. The transformation from the 2D stack of slices into a 3D volume is likely to have introduced some image artifacts with impact on image quality.

Qualitative visual evaluation

Qualitative evaluation, “normal” or “abnormal” uptake, was first done individually by five Nuclear Medicine physicians. Subsequently, readers met to reach an agreement on the cases where they were not unanimous in the individual classification, blind to their previous classification after which a consensus rating was achieved. Physicians were unaware of the clinical and autopsy diagnoses of the participants. The Xeleris workstation (GE Healthcare) was used for the qualitative visual evaluation by all five Nuclear Medicine physicians.

Quantitative evaluation

Computation of the caudate binding potential (CBP), putamen binding potential (PBP) and putamen to caudate ratio (PCR) was done separately in both hemispheres based on the DICOM images previously created. The binding potential was computed as [(Tg - Bk) / Bk], where Tg represents the mean counts per voxel in the target region and Bk the mean counts per voxel in the background reference region. PCR is simply the ratio PBP/CBP. Then, the bihemispheric means of CBP, PBP and PCR were computed for each individual. Asymmetry indices were also computed, but these averages were the only parameters used for the quantitative analysis. In this work, the reference region was defined as the whole brain visible in the 3D SPECT image after removal of a large central region containing the basal ganglia.[14]

The quantification was done using dedicated software previously developed.[14] Minor adaptations were done to the software to deal with transaxial section images of the brain only containing the striatum, instead of the whole-brain for which it was originally designed. These adaptations influence only the automated image registration process, not the quantification algorithm.

Statistical analysis

Comparison of the CBP, PBP and PCR across groups was made using the Kruskal-Wallis test followed by post hoc analyses using the 2-tailed Mann-Whitney U test. Correction for multiple comparisons was made using the Holm-Bonferroni method. Statistical analysis was done using the IBM SPSS 20 software, and a significance level of 5% was defined.

Quantitative-based image classification

To assess the discriminative power of CBP, PBP and PCR, receiver operating characteristic curve (ROC curve) analysis was used for binary classification (DLB versus AD, DLB versus PD and AD versus PD).

Multiclass classification (DLB versus AD versus PD) was done based on the optimal cut-off found in the ROC analysis.

RESULTS

Comparison of autopsy confirmed diagnosis and clinical diagnosis at baseline (inclusion criteria pre-SPECT)

Table 2 shows the cross tabulation between the autopsy confirmed diagnosis and the clinical diagnosis at inclusion (baseline). Of the 36 autopsy diagnoses, in 22 cases there was full agreement with baseline, and in 3 cases the agreement was partial: 2 cases of AD at baseline and AD+LBD at autopsy, and 1 case of DLB at baseline and LBD+AD+VD at autopsy.

Considering only the patients with Parkinsonism at baseline (DLB, PD and CBD), dopaminergic degeneration in the striatum was confirmed in 20 out of 27 cases. This represents an overall accuracy of 74% of the clinical baseline diagnosis of neurodegenerative Parkinsonism.

Table 2: Cross tabulation of the autopsy confirmed diagnosis versus initial clinical diagnosis at inclusion.

		Clinical diagnosis at inclusion				Total
		DLB	AD	PD	CBD	
Autopsy confirmed diagnosis	DLB	7	0	0	1	8
	AD	4	5	0	0	9
	PD	0	0	10	0	10
	FTD	1	1	0	0	2
	AD+VD	1	0	1	0	2
	AD+LBD	0	2	0	0	2
	LBD+AD+VD	1	0	0	0	1
	CBD	1	0	0	0	1
	No pathology	0	1	0	0	1
Total		15	9	11	1	36

Comparison of the visual evaluation of the [^{123}I]FP-CIT SPECT and autopsy confirmed diagnosis

Table 3 shows the comparison of the qualitative visual evaluation of [^{123}I]FP-CIT brain SPECT images and diagnoses at autopsy. Seven out of 8 DLB patients were classified as abnormal, all AD patients were classified as normal, and all PD patients were classified as abnormal. For these three groups of patients, the pre-synaptic dopaminergic neuronal status (nigro-striatal pathway) was correctly determined in 26 out of 27 cases (accuracy 96%, sensitivity 94% and specificity 100%). Considering all subjects included in this study, the visual evaluation correctly identified dopaminergic degeneration in 46 out of 52 subjects (accuracy 88%, sensitivity 86% and specificity 90%).

There was a good interrater visual classification agreement (Fleiss' kappa = 0.75). Readers totally agreed in 39 out of 52 cases (75%). In 10 out of 13 cases where there was disagreement, at least one reader considered the image was abnormal on one side while other(s) considered it normal. For each of the remaining three cases, one reader considered the images abnormal on both sides and the remaining four readers considered the images normal.

Table 3: Cross tabulation of the autopsy confirmed diagnosis versus SPECT visual qualitative evaluation.

		Visual qualitative evaluation		Total
		Normal	Abnormal	
Autopsy confirmed diagnosis	DLB	1	7	8
	AD	9	0	9
	PD	0	10	10
	FTD	2	0	2
	AD+VD	1	1	2
	AD+LBD	1	1	2
	LBD+AD+VD	0	1	1
	CBD	1	0	1
	No pathology	0	1	1
Clinical diagnosis (without autopsy)	HC	15	1	16
Total		30	22	52

[^{123}I]FP-CIT regional binding potential comparative assessment

The distributions of CBP, PBP and PCR for the different diagnoses at autopsy plus the HC are shown in Figures 1, 2 and 3. In these figures, the visual classification is also indicated to allow comparison with the uptake indices. *P*-values for the comparisons among the groups HC, AD, DLB and PD are shown in Table 4. For the three indices there was a statistically significant difference among the four groups of patients (Kruskal-Wallis test, $p < 0.001$).

CBP was significantly lower in DLB than in AD, PD and HC. CBP was significantly lower in PD than in HC individuals (Figure 1, Table 4). No statistically significant differences between PD and AD and between HC and AD were found (Table 4).

PBP was significantly lower in PD and DLB patients than in HC and AD (Figure 2, Table 4). There was no statistically significant difference between the PD and DLB and between the HC and AD.

Although both the CBP and PBP were not significantly different between AD and HC (Table 4), there was a trend for lower binding potential in AD (Figures 1 and 2) than in HC.

PCR was significantly lower in PD patients than in DLB, AD and HC individuals (Figure 3, Table 4). There was a clear trend for lower PCR in DLB than in AD and HC; however it

was not statistically significant after correction for multiple comparisons (Figure 3, Table 4).

Classification

ROC curve analysis showed that the CBP can separate with high accuracy DLB patients from AD patients. The area under the curve (AUC) was 0.944. For a CBP cut-off of 1.90, a sensitivity of 87.5% and a specificity of 100% were achieved. Identical AUC, sensitivity and specificity were obtained using PBP, with an optimal cut-off 1.35.

Considering PCR for the differentiation between PD and DLB, the ROC curve gave an AUC = 0.963. For a cut-off value of 0.403, a sensitivity of 100% and a specificity of 87.5% were achieved.

If a cut-off for PBP was defined between 0.95 and 1.39, all PD patients had a PBP lower than the cut-off, and all AD patients had a PBP higher than the cut-off. This gave an AUC = 1.0 and consequently an accuracy of 100% for this binary classification.

Considering simultaneously the three groups of patients (DLB, AD and PD), the classification can be done in two steps using the indices PBP and PCR. First, PBP separates the AD cases from the PD and DLB cases based on a cut-off of 1.35. Then, PCR enables a separation of the PD cases from the DLB cases based on a cut-off of 0.403. In the final analysis, only 2 out of 27 patients are misclassified, which gives a global accuracy of 93%.

Comparing visual classification and quantitative classification, for a PBP cut-off between 1.34 and 1.39, all except one DLB patient are classified as abnormal, all PD patients are classified as abnormal and all AD patients are classified as normal. This results in identical accuracy to the visual classification (accuracy 96%). However, visual classification did not discriminate between DLB and PD patients.

Table 4: *p*-values for the pairwise comparison of the DLB, PD, AD and HC groups based on the semi-quantitative indices using 2-tailed Mann-Whitney U test.

	CBP			PBP			PCR		
	PD	AD	HC	PD	AD	HC	PD	AD	HC

DLB	0.004*	0.001*	<0.001*	0.573	0.001*	<0.001*	<0.001*	0.011	0.009
PD		0.113	0.001*		<0.001*	<0.001*		<0.001*	<0.001*
AD			0.032			0.169			0.522

(* means *p*-values survive to Holm-Bonferroni corrections for multiple comparison, considering all 18 comparisons)

Cases analysis

There are 6 cases where the visual classification, uptake indices and autopsy confirmed diagnosis do not match completely. The data are summarized in Table 5. In addition to these cases, there is a HC subject (without autopsy) with normal semi-quantitative indices but whose consensus visual rating was classified as abnormal (two readers classified the image as normal and the other three readers classified the image as abnormal on one side).

DISCUSSION

We have shown that patients with autopsy confirmed diagnosis of DLB, AD and PD can be clearly differentiated *in vivo* from each other using [^{123}I]FP-CIT brain SPECT images.

In keeping with previous data from the literature using a visual assessment, joining together the DLB and the PD group (assuming they should have abnormal uptake) in comparison with the AD group (accepting they should have a normal uptake), the consensus observers' rate achieved an accuracy of 96%.

Our results for sensitivity and specificity obtained for the differentiation between DLB and AD are higher than the corresponding values reported for the differentiation between DLB and non-DLB dementia patients in a European multicenter study (sensitivity 77.7% and specificity 90.4%).[8] This European multicenter study was based on a clinical consensus diagnosis and was in keeping with previously published data with autopsy diagnoses.[10-13] Recently a new visual rating scale for Lewy body disease (LBD) was developed by the Newcastle group with improved sensitivity of 97% and specificity of 100% in the differentiation of LBD versus non-LBD.[9] However, the visual assessment could not distinguish the different Lewy bodies disorders, i.e., DLB vs PD vs PDD.

In the present study three semi-quantitative indices (CBP, PBP and PCR) were used to differentiate between groups of patients with AD, PD and DLB. Using these indices, we were able to achieve excellent results: 94% balanced accuracy (average of sensitivity and specificity) in the differentiation between DLB and AD patients using CBP or PBP; 94% balanced accuracy in the differentiation between DLB and PD using PCR; 100% balanced accuracy in the differentiation between AD and PD; and 93% accuracy in the differentiation among DLB, AD and PD simultaneously.

It is well known that there is an overall decrease of the [^{123}I]FP-CIT striatal uptake with age in heathy subjects. In the present study, on average the PD patients are younger than the DLB patients and have significantly greater caudate uptake than the DLB patients. Thus, if correction for age is applied to the caudate uptake, the difference between PD and DLB would decrease. However, our differentiation relies on the ratio between the putamen and caudate binding potentials of the same subject. In this regard, the correction for age would have no impact if the same correction for age is applied in the entire striatum. Thus, correction for age does not seem to be beneficial for the quantitative-based classification. Besides, and despite the strengths of our data that includes pathology confirmation, the numbers are still relatively small to address age dependency in our groups of patients (DLB n=8; AD n=9; PD n=10; other diseases n=9).

A recent study found an AUC between 0.715 and 0.797 in the differentiation between PD and DLB patients diagnosed according to clinical criteria.[15] Even though a fair comparison is not possible due to using different datasets, it is worth noting this value is much lower than what we found (0.963). We believe our better AUC is in part due to using PCR rather than simple uptake ratios (striatal to extrastriatal). Others have assessed the added value of semi-quantitative indices for DLB diagnosis against other pathologies (not PD) compared to visual evaluation.[16 17] They have found that adding semi-quantitative indices increases the agreement, confidence and accuracy, especially for readers with limited experience.

This is the first study showing that quantitative analysis of PCR clearly differentiates DLB from PD. This is relevant to classifying patients within the spectrum of Lewy body disease. At present, PD, PD dementia (PDD) and DLB are distinguished solely on clinical

grounds. An arbitrary cut-off of one year is used to differentiate DLB from PDD, i.e. patients developing dementia within 1 year of PD diagnosis are classified as DLB, whilst patients developing dementia later than 1 year are considered as PDD. The cut-off has been purely pragmatic without support from any biomarker or any objective measure. We have shown that using PCR could help the separation in gray cases. Nevertheless, further studies need to be done to prove our hypothesis and also to ascertain whether changes in PCR would be sensitive in predicting cognitive decline. The likelihood of patients with PD developing PDD may be better understood, by obtaining an "in vivo" SPECT biomarker with added value over the simple dichotomization of caudate uptake as normal or abnormal.[18]

In the present study only three indices related to uptake ratios were used. Our software also computes other indices that were, on purpose, left out of the analysis, except the asymmetry indices for specific cases analysis.[14] This was because the [^{123}I]FP-CIT brain SPECT images in the present work had much higher levels of noise and artifacts than those available with contemporary scanners. The optimal cut-offs herein reported should not be immediately translated to other studies since different equipment and reconstruction protocols may affect their values. This methodology is valid with widespread applicability. However, the cut-offs should be adapted for the in-house scanner characteristic and image reconstruction algorithms.

It is remarkable that in our series of PD patients, the [^{123}I]FP-CIT scans were so abnormal taking into account the very early disease status/presentation. Patients with clinically evident motor PD have little or no need to be submitted to [^{123}I]FP-CIT scans unless there are doubts about the presence of rigidity and/or bradykinesia or the nature of tremor. In such situations one might expect to find cases with less abnormal or even only borderline abnormal scans. A large clinicopathological series of patients with Parkinsonism with [^{123}I]FP-CIT scans, including progressive supranuclear palsy, multiple systems atrophy and CBD cases, ideally including premotor PD cases would provide further data and understanding of the usefulness of [^{123}I]FP-CIT in diagnosing PD.

In this study, bihemispheric mean CBP, PBP and PCR were used. Motor PD however is typically asymmetric (more so than DLB)[19] and higher sensitivity for detecting PD might be achieved by concentrating on the worse affected putamen and caudate. This was not

done here, except for the cases analysis, due to the low quality of the images used after manipulations to obtain 3D data. We may have lost some sensitivity but gained robustness to noise. Another limitation of this study is the age difference between DLB and PD. PD patients were on average 11 years younger than DLB patients and were imaged on average 12 years before autopsy compared to 4 years for the DLB cases. Thus, differences in uptake may not be only diseases related.

In conclusion, the results presented showed high diagnostic accuracy for the differentiation between DLB, PD and AD patients based on quantitative analysis of [^{123}I]FP-CIT brain SPECT. The main limitation of this study is the single site origin of the entire data SPECT imaging database. However, the necropsy diagnoses for all the patients included offers an advantage over many other studies reported in the literature on this subject. Our software would be available for any future multicentre studies with autopsy-based data. It would be particularly desirable to confirm the added value of the presynaptic dopamine transporter imaging to differentiate other types of Parkinsonism.[20]

Table 5: Cases where the visual classification, uptake indices and autopsy confirmed diagnosis do not match completely.

Sex	Age at scan; Time from scan to death (years)	Autopsy diagnosis	Clinical features at time of scan and last UPDRS prior to death	Consensus visual classification (individual readers "normal" : "abnormal")	Semi-quantitative indices
F	57; 2.5	**DLB** Neocortical category; Atypical distribution	Clinical diagnosis: corticobasal syndrome; Cognitive impairment; Difficulty using right arm; No hallucinations; No fluctuation; Jerking and twitching; UPDRS 28; MMSE 8/30. Last UPDRS 33.	Abnormal (1:4)	CBP and PBP in normal range although with a PBP left-right asymmetry of 28%
M	86; 6.4	**DLB** Limbic category; High probability that LB pathology accounts for clinical syndrome; Hippocampal sclerosis	Clinical diagnosis: DLB; Cognitive decline with relatively preserved memory but poor visuospatial ability; Marked fluctuation in cognition; Vivid visual hallucinations; Later falls but no worsening of EPS; UPDRS 15; MMSE 25/30. Last UPDRS 20.	Normal (3:2)	Reduced CBP
M	73; 10.7	**AD+DLB** AD – Severe pathology - Braak stage 6 LBD – Neocortical category; Moderate LB pathology in substantia nigra	Clinical diagnosis: AD; Memory decline; Some fluctuation in cognition; At time of scan only one episode of visual hallucinations but later more persistent hallucinations; UPDRS 0; MMSE 21/30. Last UPDRS 3.	Normal (5:0)	CBP and PBP in normal range.
M	78; 7.3	**AD+DLB** AD – Severe pathology -Braak stage 5 LBD – Neocortical category; Atypical distribution relatively spared substantia nigra	Clinical diagnosis: AD; Memory impairment; Vivid dreams; No hallucinations; No fluctuation; UPDRS 0; MMSE 26/30. Last UPDRS 24.	Abnormal (0:5)	CBP and PBP in normal range. CBP left-right asymmetry is 30% and PBP left-right asymmetry is 28%
M	85; 0.2	**CBD** Braak stage 2 for AD; No LB pathology	Clinical diagnosis: DLB; Cognitive impairment, relatively preserved memory; Severe kyphosis; One episode of visual hallucinations; Marked fluctuation; UPDRS 31; MMSE 19/30. Last UPDRS 31.	Normal (5:0)	CBP reduced
M	68; 2.0	**FTD** No distinctive histological features	Initial clinical diagnosis: DLB; Cognitive impairment; No hallucinations; No fluctuation; UPDRS 33; MMSE 9/30. Last UPDRS 48.	Normal (4:1)	CBP and PBP reduced

Asymmetry index was computed as $2\times|$left side uptake – right side uptake$|$ / (left side uptake + right side uptake); PBP asymmetry index maximum in healthy controls 24%, CBP asymmetry index maximum in healthy controls 12%.

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Competing interests ZW and DCC received consultancy fees from GE Healthcare (previously Amersham Health), who also provided the [^{123}I]FP-CIT ligand. ZW also received research support from GE Healthcare.

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Data availability statement Image data will be available on a reasonable request after Ethical approval.

Ethics approval Ethics approval was obtained for the imaging study from West Essex Local Research Ethics Committee (REF: EC986), and a separate ethics approval was obtained from West Essex Health Authority Ethics Committee for the autopsy follow-up (REF: 1217).

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Figures caption

Figure 1: Comparison of the bihemispheric mean CBP. Visual classification is also represented for cross evaluation. Note some patients' values overlap.

Figure 2: Comparison of the bihemispheric mean PBP. Visual classification is also represented for cross evaluation. Note some patients' values overlap.

Figure 3: Comparison of the bihemispheric mean PCR. Visual classification is also represented for cross evaluation. Note some patients' values overlap.