Pitfalls and Artifacts of ^{123}I-Ioflupane SPECT in Parkinsonian Syndromes: A Quality Improvement Teaching Tool

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The aim of the current article is to describe how to improve the quality of imaging with ^{123}I-ioflupane SPECT and to serve as a teaching tool on this topic. The radiopharmaceutical ^{123}I-ioflupane is used to visualize the nigrostriatal pathway. Parkinson disease and parkinsonian syndromes are movement disorders that exhibit nigrostriatal degeneration, with a decreased dopamine transporter level in the pathway and thus a decreased ^{123}I-ioflupane distribution. Other nonparkinsonian movement disorders, such as essential tremor, will have intact dopaminergic neurons and exhibit a normal distribution of the radiopharmaceutical throughout the striata. Parkinsonian disorders are usually diagnosed clinically. However, ^{123}I-ioflupane SPECT can be a valuable tool when the clinical features are not sufficiently clear. ^{123}I-ioflupane SPECT image interpretation is not always straightforward. Many pitfalls, including biologic factors, technical factors, medications, and factors such as age, race, ethnicity, and body habitus, can make the interpretation challenging. The technologist and nuclear radiologist must identify the expected imaging findings to avoid the most common mistakes related to artifacts. This article reviews the usual pitfalls and artifacts of ^{123}I-ioflupane SPECT that can compromise an accurate diagnosis and lead to misinterpretation of image findings.

Key Words: Parkinson disease; ioflupane; SPECT; artifacts; striatum; image quality

J Nucl Med Technol 2021; 49:114–119
DOI: 10.2967/jnmt.120.258491

Diagnosis of Parkinson disease and parkinsonian syndromes is based mainly on clinical signs, which include bradykinesia, rigidity, tremor, and postural instability (*1*). Clinical symptoms and the evaluation of response to levodopa are usually sufficient to diagnose Parkinson disease. However, some patients can present with incomplete signs and an unclear clinical picture, particularly in the early stages of the disease. Other patients may present with a mixed pattern that includes overlap between different concurrent conditions. Clinical diagnosis alone fails to recognize these patients fully. Conventional imaging is not sensitive in these disorders and is not used to differentiate among them. Functional imaging with the dopamine transporter analog comes into play under these circumstances, being remarkably useful in diagnosing Parkinson disease and other parkinsonian syndromes with equivocal signs and symptoms and debatable responses to treatment (*2*).

^{123}I-ioflupane is a radioiodinated cocaine analog used to visualize the dopamine transporters in the presynaptic membrane. A decreased amount of dopamine transporter in the dopaminergic nigrostriatal pathway is seen with presynaptic parkinsonian syndromes. Patients with essential tremor have an intact nigrostriatal pathway. As a result, ^{123}I-ioflupane SPECT (DaTscan; GE Healthcare) can differentiate a patient with essential tremor from a patient with presynaptic parkinsonian syndrome, as evidenced by nigrostriatal pathway degeneration (*3*). ^{123}I-ioflupane SPECT can also help differentiate Alzheimer disease from Lewy body dementia, with normal uptake in Alzheimer disease and decreased uptake in Lewy body dementia. ^{123}I-ioflupane SPECT image interpretation, however, is not always straightforward. Many pitfalls that make the interpretation challenging have been identified. Among these pitfalls are technical artifacts, interference from certain medications, and several patient biologic factors. This article reviews the most common pitfalls related to ^{123}I-ioflupane SPECT and how they affect the quality of imaging and interpretation.

TECHNICAL ARTIFACTS

Strict adhesion to imaging protocols is fundamental to avoid technical errors. ^{123}I-ioflupane SPECT should be performed with a 10% energy window centered on 159 keV, using a dual-head camera, a detector head with an 11- to 15-cm radius, low-energy high-resolution/low-energy ultra-high-resolution parallel-hole or fan-beam collimators, full

Received Oct. 14, 2020; revision accepted Dec. 17, 2020.
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Published online Dec. 24, 2020.

TABLE 1
Pitfalls in ^{123}I-Ioflupane SPECT

Pitfall type	Description
Biologic	Dopamine transporter density
	Age
	Sex
	Body habitus
	Ethnicity
	Allelic variants
	Medications competing with dopamine transporter
	Striatal infarct
	Brain tumors
	Trauma
	Surgery
Technical	Patient motion
	Patient position
	Patient orientation
	Equipment resolution
	Collimator
	Dose extravasation
	Time after injection
	Photopeak
	Oversmoothing on filtration
	Attenuation correction
	Size and placement of regions of interest

Adapted from Morbelli et al. (13).

360° sampling, 120 projections in total, and a 128 × 128 matrix. It is essential to block the thyroid gland with potassium iodide (Lugol solution) using approximately 100 mg of iodine or 400 mg of potassium perchlorate. Within 3–6 h after intravenous administration of 111–185 MBq (3–5 mCi) of ^{123}I-ioflupane, a SPECT scan of approximately 30–45 min should be performed (*4*).

Technical artifacts relate mainly to issues during acquisition (*1*), such as when a technologist does not follow standard practice parameters. These so-called inconsistency errors can result from a change in acquisition parameters, reconstruction parameters, or display normalization or from use of an inconsistent color scale (Table 1). These errors can easily be avoided by ensuring that there is a specific procedure to which technologists can consistently adhere. The Society of Nuclear Medicine practice guidelines are an invaluable resource that sets parameters for dopamine transporter imaging (*3*). Although the guidelines are not a fixed rule, they serve as an educational tool to assist health-care professionals in providing high-quality patient care. Also, the guidelines can be tailored to an individual to ensure the most accurate results. The most common technical artifacts, however, are related to patient positioning (*1*). ^{123}I-ioflupane SPECT relies on visualizing tiny anatomic structures, the caudate nucleus and putamen, known as the striatum. The caudate nucleus measures 3.4 cm^3 and the putamen 4.3 cm^3, making ^{123}I-ioflupane SPECT images particularly susceptible to significant position and motion artifacts (*4*).

Patient preparation and positioning are cornerstones of optimal ^{123}I-ioflupane brain SPECT images. Improper positioning of the head causes a forward tilt and the well-known semicolon sign (*4*), which causes the caudate nucleus and putamen to be seen on separate axial slices and gives the impression that dopamine transporter activity in the putamen is decreased or absent. To avoid false interpretation of this head-tilt artifact, the interpreting physician can scroll through the full dataset of images to ensure that there is, in fact, normal activity in the putamen. Confirmation with age-matched quantitative data analysis using any of several available software tools is helpful. Technologists should strictly follow the imaging protocol to correctly position each patient's head and not exceed the SPECT field-of-view diameter to minimize the head-tilt artifact on ^{123}I-ioflupane SPECT images. Orientation artifacts can be avoided or at least minimized by proper head positioning.

Correctly positioning each patient's head before acquisition of ^{123}I-ioflupane SPECT images is part of the quality control process. If the artifact is recognized after image acquisition, while the patient is still on the table, the technologist can potentially rescan the patient in a more optimal position (*4*). A head-and-neck holder should be used to ensure proper positioning. The head should rest entirely within the holder, with the vertex of the head reaching the superior edge of the holder. Identification of the canthomeatal line provides an additional aid. This imaginary line coursing from the lateral canthus to the corner of the eye to the external auditory canal should be oriented as vertically as possible. The technologist should also verify that the position of the chin is neutral, neither up nor down in relation to the head (Fig. 1).

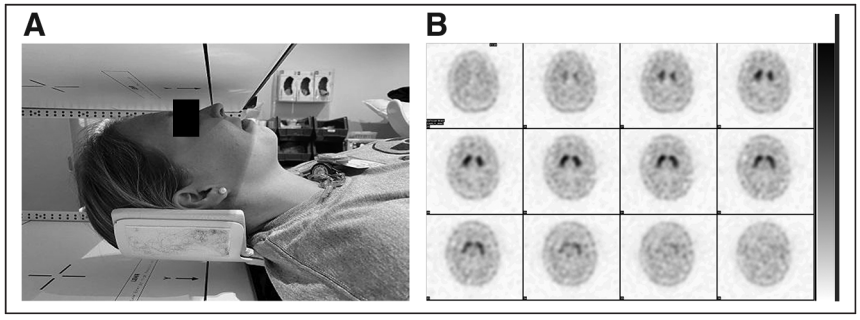

FIGURE 1. (Left) Correct positioning for brain SPECT scan, with head resting in head-and-neck holder and chin in neutral position. (Right) Axial brain SPECT images showing normal findings and no head tilt.

A lateral head tilt can give a false impression of asymmetry. An apparent lack of activity on only one side of the caudate nucleus and putamen can just be a result of an incorrect head position (Fig. 2).

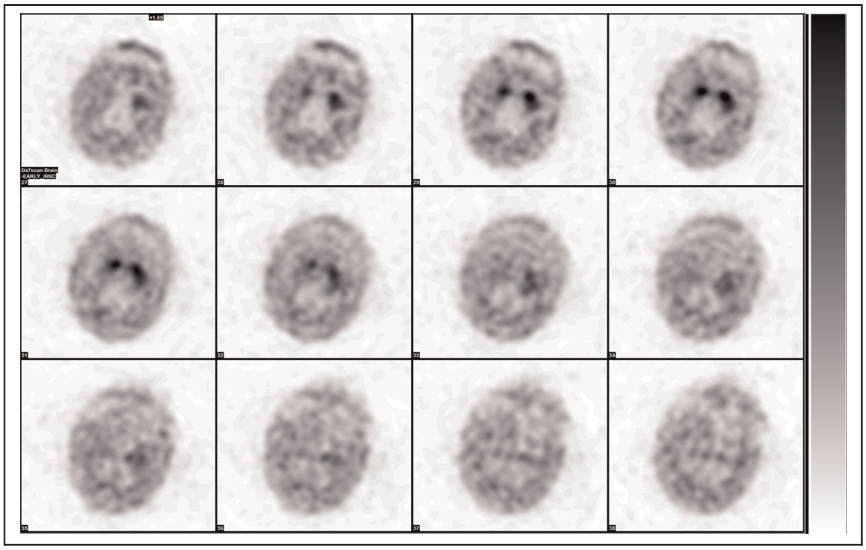

FIGURE 2. Axial brain SPECT images of 87-y-old woman with parkinsonian features, left-sided weakness, dysarthria, and generalized weakness. Images show head tilt, normal comma shape on left, decreased uptake in right putamen, and dilated ventricles.

Lateral rotation of the head during a SPECT acquisition can cause blurring, which gives a false impression of additional activity in the ipsilateral striatum. This artifact is known as the pinwheel artifact, in analogy with the rotatory motion and subsequent blurring of a pinwheel (*5*).

Another motion artifact that can occur during image acquisition is the kissing-caudates sign, caused by patient motion. This artifact is demonstrated when the left and right caudate nuclei appear to be fused anteriorly, without the normal gap between them (*1*).

Motion artifacts may also lead to quantification and interpretation errors. A motion assessment and a quality check should always be done before the images are submitted for interpretation. Movement artifacts are easier to spot in raw projection images in cine mode than in reconstructed SPECT slices. When detected before interpretation, motion artifacts will prompt the use of motion-correction algorithms or even rescanning if necessary (*3*).

MEDICATION INTERFERENCE

Artifacts may result from interactions of various medications with the striatal binding of ^{123}I-ioflupane. If the medication increases the uptake, the result will be a false-negative mimicking a degenerative disorder. On the other hand, if the medication competing with ^{123}I-ioflupane decreases the radiotracer's uptake in the synaptic cleft, a false-positive result will entail. It is therefore important to screen every patient for medication use before image acquisition so that drug interactions can be accounted for and the results will not be incorrectly interpreted (*1*). Table 2 lists the effect—or lack of effect—of some drugs on ^{123}I-ioflupane SPECT results, and Table 3 shows drugs that alter dopamine transporter uptake in more than 20% of cases and need to be discontinued before imaging if clinically safe to do so (*6*). For example, some antidepressants that increase dopamine transporter uptake of ^{123}I-ioflupane can significantly increase background uptake and render the exam nondiagnostic (Fig. 3).

TABLE 2
Effect of Drugs on Striatal ^{123}I-Ioflupane Binding

Effect type	Drug
Possible increase in binding	Opioid: fentanyl
	Eugeroic: modafinil
	Antidepressants: bupropion, mazindol, radafaxine
	Anticholinergic: benztropine
	Anesthetics: isoflurane, ketamine, phencyclidine
	Central nervous system stimulant: cocaine
Possible increase or decrease in binding	Adrenergic agonists: norepinephrine, phenylephrine
	Amphetamines: D-amphetamine, methamphetamine, methylphenidate
	Central nervous system stimulants: ephedrine, phentermine
No effect	Dopamine agonists
	N-methyl-D-aspartate receptor blockers
	Monoamine oxidase B inhibitors
	Catechol-*O*-methyltransferase inhibitors

Adapted from Djang et al. (3).

TABLE 3
Prescan Withdrawal Time for Drugs That Significantly Affect ^{123}I-Ioflupane SPECT

Drug	Withdrawal time (d)
Amphetamine	7
Benztropine	5
Bupropion	8
Cocaine	2
Dexamphetamine	7
Mazindol	3
Methylamphetamine	3
Methylphenidate	1–2
Modafinil	3
Phentermine	14

Adapted from Kägi et al. (6).

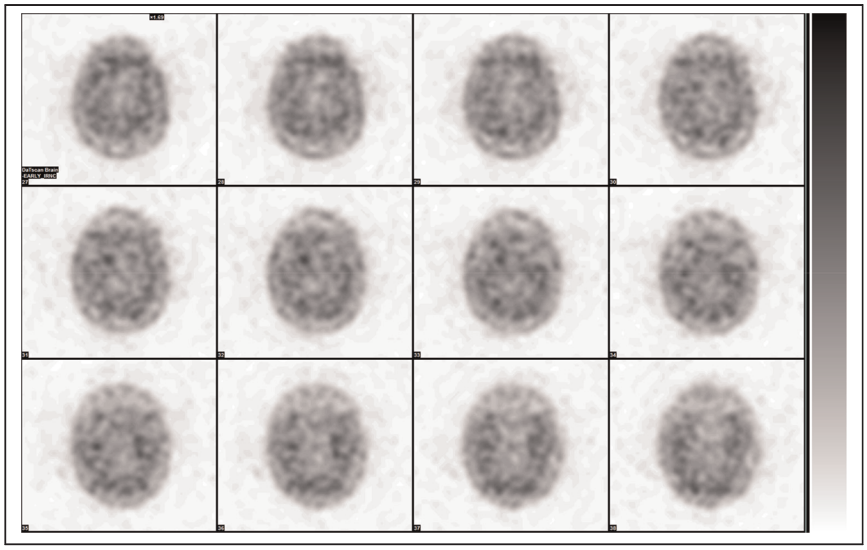

FIGURE 3. Axial brain SPECT images of 67-y-old woman who presented for evaluation of progressive gait instability with falls, micrographia, depth-perception problems, and vertical gaze palsy. Study was nondiagnostic because of increased background uptake from patient's medications, citalopram and bupropion.

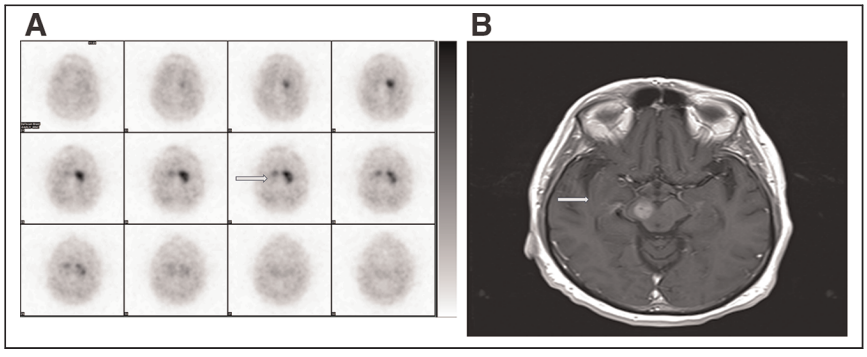

FIGURE 4. Images of 65-y-old man who had history of low-grade glioma in right midbrain and was being evaluated for right-arm rigidity and tremor. (Left) Axial brain SPECT image showing decreased uptake in right caudate nucleus and no uptake (arrow) in right putamen because of right midbrain glioma. Normal comma-shaped activity is seen in left caudate nucleus and putamen. (Right) Contrast-enhanced T1-weighted brain MR image showing enhancing lesion (arrow) in right midbrain consistent with history of low-grade glioma.

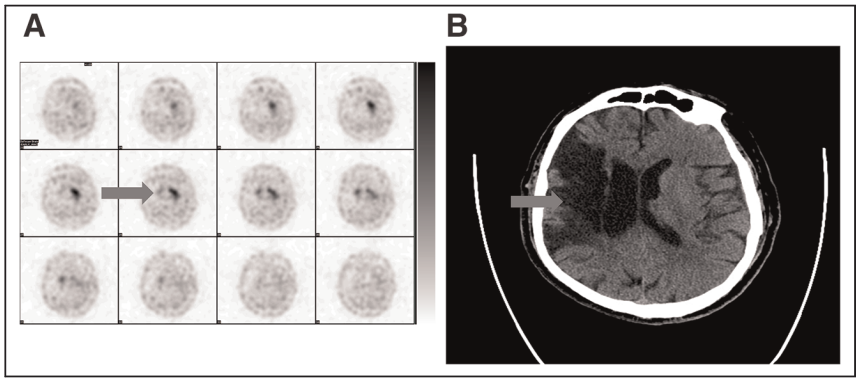

FIGURE 5. Images of 61-y-old man who had history of infarct in territory of right middle cerebral artery and was being evaluated for right-upper-extremity tremors of 2- to 4-mo duration. (Left) Axial brain SPECT image showing decreased to absent uptake (arrow) in right caudate nucleus and putamen because of prior infarct. (Right) Unenhanced axial CT scan of head showing infarct (arrow).

If possible, any medications or drugs that might interfere with the radiopharmaceutical's binding mechanism must be stopped for at least 5 half-lives (*3*). Interestingly, dopamine products used for the treatment of parkinsonian syndromes do not compete with ^{123}I-ioflupane. Thus, medications such as levodopa, dopamine agonists, and monoamine oxidase B inhibitors do not need to be discontinued before a patient undergoes ^{123}I-ioflupane SPECT (*1*).

Tumors, infarcts, and trauma affecting the putamen can obscure the striatum and mislead the reader into making an inaccurate diagnosis of parkinsonian syndromes. Decreased, or absence of, uptake in the caudate nucleus and putamen because of a prior infarct involving the middle cerebral artery territory or a tumor involving the midbrain can cause parkinsonian symptoms mimicking Parkinson disease (Figs. 4 and 5). A careful review of a patient's history and available prior imaging, including CT and MRI of the head, is paramount.

PATIENT BIOLOGIC FACTORS

Clinical factors such as sex, age, body habitus, ethnicity, and smoking are important in ^{123}I-ioflupane SPECT because they can potentially influence dopamine transporter density (*7*,*8*).

Although the sensitivity and specificity of ^{123}I-ioflupane are high among all patient groups with suspected PD, potential factors influencing dopamine transporter density, such as age and sex, must be considered because they may impact the performance of ^{123}I-ioflupane in detecting movement disorders. According to some, the sensitivity of ^{123}I-ioflupane SPECT is higher in men (*8*). Women were reported as having a 16% higher ^{123}I-ioflupane binding than men and a lower sensitivity of the test at earlier stages of the disease, defined as the time from disease onset through the first 10 y of follow-up. The clinical symptoms also differ between the sexes, with women having a milder course, which could explain differences in uptake patterns. Later in the disease, however, the sensitivity in women approximated that in men, prompting the conclusion that age also plays a significant role in ^{123}I-ioflupane binding.

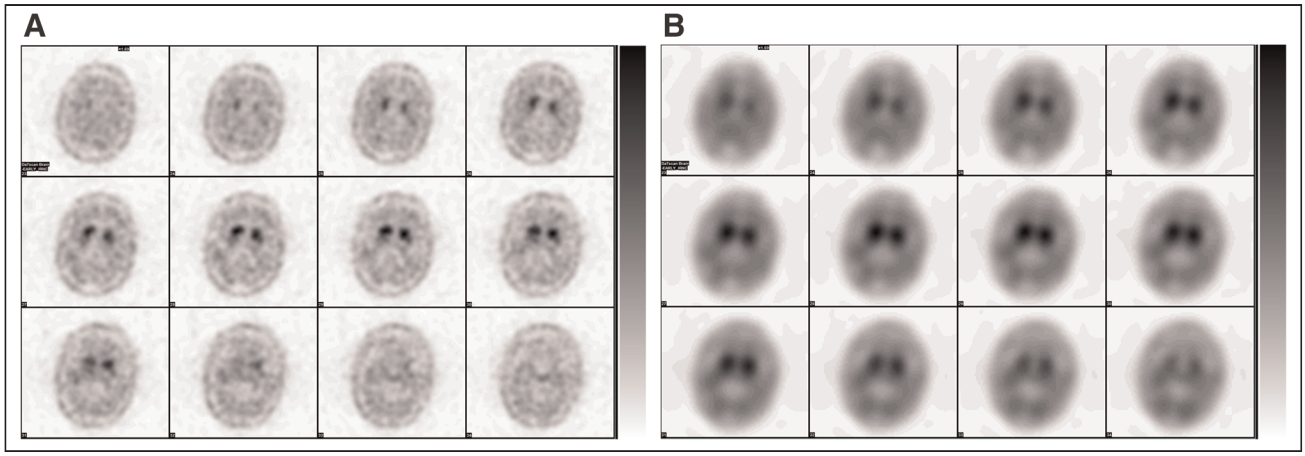

FIGURE 6. Axial brain SPECT images of 80-y-old man on carbidopa–levodopa without improvement of tremors, shuffling gait, and bradykinesia for 2–3 mo. (Left) Images showing decreased uptake bilaterally in putamen and loss of normal comma shape. These findings are scintigraphic evidence of presynaptic-deficit parkinsonian syndrome with probable age-associated changes due to no improvement with medication. (Right) Images showing oversmoothing artifact.

Another important factor is that dopamine transporter concentration in the striatum decreases with age by up to 65%–75%, and this decrease is linear and symmetric in both the caudate nucleus and the putamen. Besides, advanced age may cause a decrease in striatal size secondary to age-related brain atrophy (Fig. 6). Thus, it is crucial to evaluate CT or MR images concurrently with ^{123}I-ioflupane SPECT images (*7*). In older subjects (>75 y), the sensitivity of ^{123}I-ioflupane SPECT was found to be lower for Parkinson disease and higher for Lewy body dementia. It is not clear how relevant these differences are in clinical practice, yet they can potentially affect the diagnostic performance of ^{123}I-ioflupane SPECT (*8*). Finally, head circumference for SPECT must be within 11–15 cm (SPECT rotational radius as small and close to head as possible) as increased circumference can cause blurring of the images in patients with increased body habitus (Fig. 7).

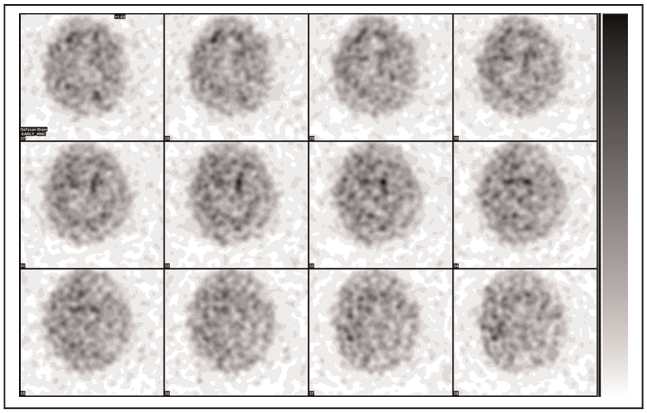

FIGURE 7. Axial brain SPECT images of 76-y-old man on primidone with history of resting and action tremors and cogwheel rigidity for 5 y. Images show decreased uptake bilaterally in putamen and right caudate nucleus, with loss of normal comma shape on right and scintigraphic evidence of probable presynaptic-deficit parkinsonian syndrome. Study was limited because of patient's body habitus and inability to perform SPECT rotation closer to patient's head with required diameter of 11–15 cm.

Racial disparities in the prevalence of neurodegenerative diseases are well documented. For instance, Parkinson disease and essential tremors are more common among Caucasian patients. However, studies comparing the accuracy of ^{123}I-ioflupane SPECT both between Caucasian and non-Caucasian patients and between Hispanic and non-Hispanic patients failed to demonstrate a statistically significant difference in ^{123}I-ioflupane SPECT accuracy among these racial groups (*9*,*10*).

There is evidence for lower dopamine transporter availability in smokers, with a moderate to large effect size but normal D_2 dopamine receptor availability (*11*). This finding suggests that dopamine transporter abnormalities either are involved in the pathophysiology of tobacco dependence or are a biologic response to long-term exposure to tobacco. Further studies are needed to determine the nature of alterations in other aspects of the dopamine system and whether there are longitudinal changes in dopamine transporter levels during the acquisition of a smoking habit (*11*).

The interpretation of ^{123}I-ioflupane SPECT images is based mainly on visual reads. SBRquant (GE Healthcare) is a software program that automatically measures the striatal binding ratio in ^{123}I-ioflupane SPECT images but has yet to be optimized (*12*). Many factors influence quantification, such as the type of camera, calibration, collimator, acquisition procedure, and correction (attenuation, scatter, and partial-volume effect) (*3*). By following the recently updated European Association of Nuclear Medicine/Society of Nuclear Medicine and Molecular Imaging guidelines and thoroughly understanding the various artifacts of striatal binding ratio, one can improve the quality of ^{123}I-ioflupane SPECT and ^{18}F-fluorodopa PET imaging (*13*). However, biological, technical factors, interobserver variation, and errors during the placement of the regions of interest can affect SBR (*13*).

CONCLUSION

In comparison with other articles on ^{123}I-ioflupane SPECT artifacts (*4*–*6*), our article has a primary focus of improving the quality of imaging, providing continuing education, and promoting the professional development of technologists and interpreting physicians.

Early and accurate diagnosis of neurodegenerative parkinsonian syndromes is vital to improving the patient's quality of life and overall outcome. Clinical diagnosis can be difficult, because several neurodegenerative conditions have similar presentations and show similar anatomic changes on conventional radiologic examinations (*6*). ^{123}I-ioflupane SPECT has proved to be useful in diagnosing parkinsonian syndromes when the clinical features are not sufficiently clear. Referring physicians need an accurate diagnosis, particularly in clinically difficult cases. However, image interpretation is riddled with many pitfalls and can be challenging. Interpreting physicians should be aware of these pitfalls to avoid misinterpretations, render an accurate diagnosis, prevent unnecessary treatment, reduce healthcare costs, and decrease the burden on the patient and family members. Interpreting physicians must also be aware of age-related changes in striatal uptake and anatomic variations and compare the ^{123}I-ioflupane SPECT images with available anatomic images. Semiquantitative analysis may help in difficult-to-interpret cases but has yet to be optimized with the current software programs.

It is crucial that technologists understand how medications affect image quality, as the imaging study may need to be rescheduled if the patient was not adequately screened and medications were not discontinued a sufficient interval beforehand. We hope this review article is useful to the technologists who must identify the most common of these pitfalls during imaging and processing to avoid unreliable or undiagnostic results and the need to repeat the study, with the associated waste of time and resources and additional radiation exposure.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENT

We thank Maribeth E. Borrello, CNMT, for posing for Figure 1.

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