Practical Overview of ^{123}I-Ioflupane Imaging in Parkinsonian Syndromes

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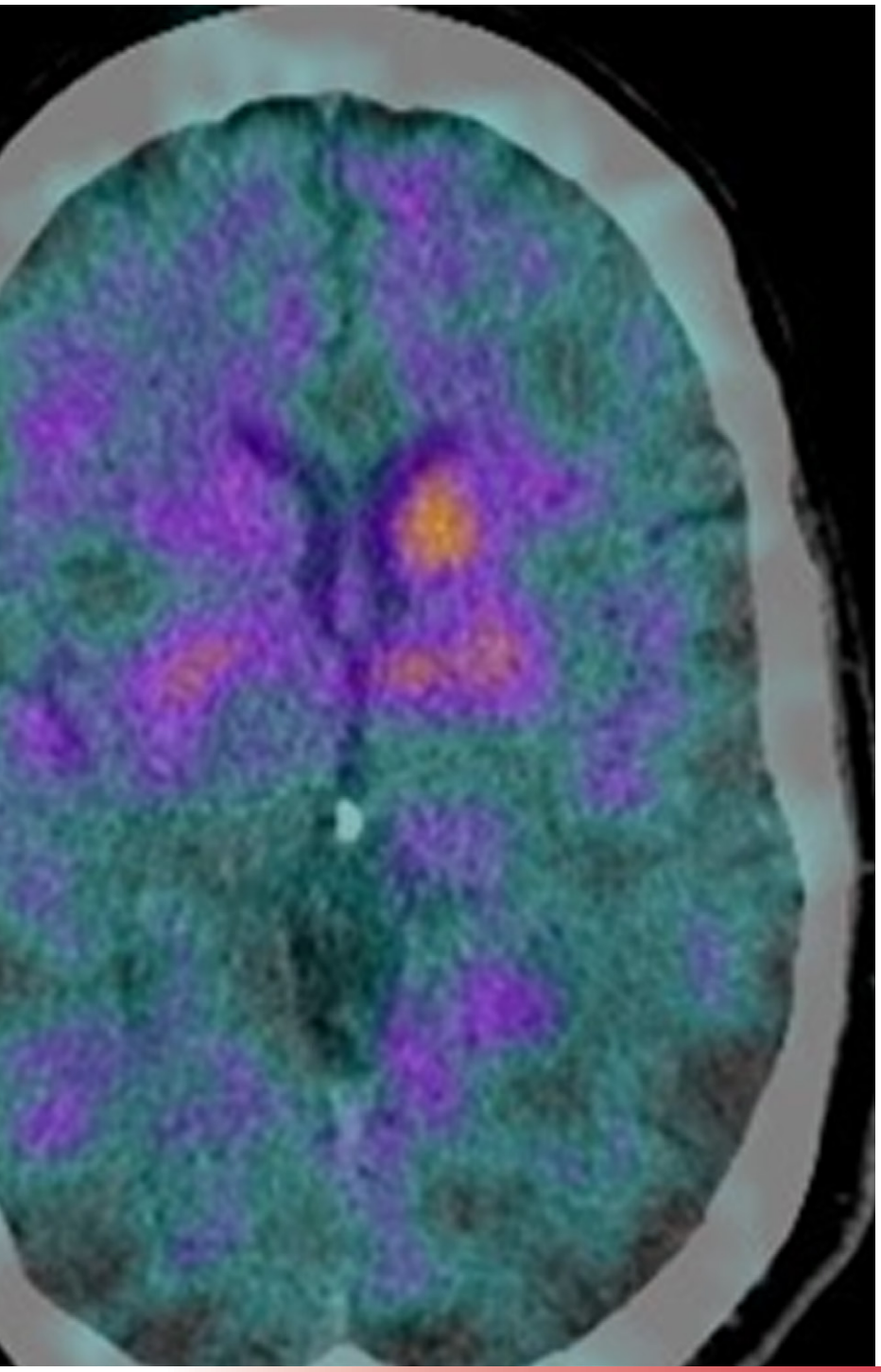
See the invited commentary by Intenzo and Colarossi in this issue.



Parkinsonian syndromes are a heterogeneous group of progressive neurodegenerative disorders involving the nigrostriatal dopaminergic pathway and are characterized by a wide spectrum of motor and nonmotor symptoms. These syndromes are quite common and can profoundly impact the lives of patients and their families. In addition to classic Parkinson disease, parkinsonian syndromes include multiple additional disorders known collectively as Parkinson-plus syndromes or atypical parkinsonism. These are characterized by the classic parkinsonian motor symptoms with additional distinguishing clinical features. Dopamine transporter SPECT has been developed as a diagnostic tool to assess the levels of dopamine transporters in the striatum. This imaging assessment, which uses iodine 123 (^{123}I) ioflupane, can be useful to differentiate parkinsonian syndromes caused by nigrostriatal degeneration from other clinical mimics such as essential tremor or psychogenic tremor. Dopamine transporter imaging plays a crucial role in diagnosing parkinsonian syndromes, particularly in patients who do not clearly fulfill the clinical criteria for diagnosis. Diagnostic clarification can allow early treatment in appropriate patients and avoid misdiagnosis. At present, only the qualitative interpretation of dopamine transporter SPECT is approved by the U.S. Food and Drug Administration, but quantitative interpretation is often used to supplement qualitative interpretation. The authors provide an overview of patient preparation, common imaging findings, and potential pitfalls that radiologists and nuclear medicine physicians should know when performing and interpreting dopamine transporter examinations. Alternatives to ^{123}I-ioflupane imaging for the evaluation of nigrostriatal degeneration are also briefly discussed.

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Abbreviations: CBD = corticobasal degeneration, DLB = dementia with Lewy bodies, FDA = U.S. Food and Drug Administration, FDG = fluorodeoxyglucose, MSA-P = multiple system atrophy–parkinsonian type, PD = Parkinson disease, PSP = progressive supranuclear palsy

TEACHING POINTS

- Dopamine transporter SPECT can cost-effectively improve diagnostic accuracy, change patient management, and improve patient and physician confidence.
- A normal examination shows two symmetric comma-shaped regions that are intense and distinct in comparison with the background brain tissue. The comma should overlie the striata and appear on both sides of the brain.
- About 50%–60% of the dopaminergic neurons are lost in symptomatic patients. Thus, imaging findings are generally not subtle in positive cases.
- An abnormal examination shows decreased ioflupane uptake, which may be symmetric or asymmetric. In the earliest stage of PD, this finding typically affects the putamen posteriorly (resulting in an oval or period shape). As the disease progresses, the anterior putamen and caudate, respectively, start losing their activity.
- Various pitfalls may confound dopamine transporter imaging interpretation, including motion artifact, poor patient positioning, scaling, off-peak acquisition, and prior cerebral infarction.

Introduction

Parkinsonian syndromes are a heterogeneous group of neurodegenerative disorders characterized by degeneration of the dopaminergic pathways and a deficiency of striatal dopamine. These syndromes include idiopathic Parkinson disease (PD) and Parkinson-plus syndromes. Parkinson-plus syndromes, also known as atypical parkinsonism, include clinical entities such as dementia with Lewy bodies (DLB), multiple system atrophy–parkinsonian type (MSA-P), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). These syndromes are characterized by parkinsonian motor symptoms (rigidity, tremor, and bradykinesia) and additional distinguishing clinical features (1).

In the brain, the nigrostriatal pathway is the largest of the four primary dopamine pathways (2). The dopaminergic neurons of the nigrostriatal pathway start in the substantia nigra and extend into the striatum (Fig 1A) (2,3). Degeneration of these neurons results in a reduction of dopamine levels in the basal ganglia and associated motor symptoms, including tremor at rest, balance problems, rigidity, and bradykinesia (2).

Parkinsonian syndromes have historically been diagnosed clinically. Even today, when the patient's symptoms at presentation are clear, a clinical diagnosis is often possible. In other cases, the clinical symptoms may not be clear, especially in the early phases of disease. For example, there may be an overlap of parkinsonism and nonparkinsonian signs and symptoms, making the clinical diagnosis challenging. In addition, many patients present with additional confounding factors, including use of certain medications, toxin exposure, or comorbidities (4,5). Multiple studies evaluating the accuracy of clinical diagnosis for the identification of parkinsonism have demonstrated that PD may be misdiagnosed in the early stages of the disease, with errors of diagnosis approaching 25%, even by movement disorder specialists. Thus, there is a need for more reliable diagnostic testing (6–9).

When the clinical diagnosis is difficult, diagnostic imaging may be helpful. Iodine 123 (^{123}I) ioflupane, a brain SPECT agent, is now widely used as a tool to differentiate parkinsonian syndromes from nonparkinsonian causes (4,5,10). It has been used in Europe since the early 2000s (2,4) and was approved by the U.S. Food and Drug Administration (FDA) in 2011 for the differentiation of essential tremor and parkinsonian tremor. In 2022, the FDA expanded its clinical approval to include adults with suspected DLB. Originally, interpretation of the imaging examinations was primarily visual, but semiquantitative interpretations have also been introduced (2,5). Dopamine transporter imaging can be used to support a parkinsonian diagnosis particularly in cases with a challenging clinical presentation (6).

This article provides an overview of patient preparation for imaging, common imaging findings, and pitfalls that interpreting radiologists and nuclear medicine physicians should know. Semiquantitative assessments are also discussed.

Epidemiology

Estimates of the incidence and prevalence of PD vary, but a recent meta-analysis of worldwide data supported an increasing prevalence with age, as well as some variability with sex and geographic location in certain age groups (11). In this meta-analysis, prevalence ranged from 41 per 100 000 (in those 40–49 years of age) to 1903 per 100 000 (in those over 80 years of age) (11). In North America, estimated prevalence in those over 45 years of age is 572 per 100 000 (12), with an incidence of 47–77 per 100 000 in those aged 45 years and older and 108–212 per 100 000 in those aged 65 years and older (13). In addition to other difficulties faced by patients, family members, and caregivers, the economic effects of this disease are significant. In the United States, the total estimated costs are nearly $52 billion for the estimated 1.04 million people in the United States with diagnosed PD (14).

Pathophysiology

In PD, the progressive degeneration of dopaminergic neurons in the substantia nigra results in a range of excitatory and inhibitory symptoms (15–17). The origin of neurodegeneration with PD remains uncertain, thought to be a result of both genetic and environmental factors (16,17). Multiple factors are thought to contribute, including mitochondrial malfunction, inflammation, and Lewy body deposition (3,16,18,19). Lewy bodies are eosinophilic inclusions composed of α-synuclein, a neural protein. Ultimately, these proteins become insoluble and accumulate as intracellular inclusions (19).

The Braak hypothesis for PD suggests that the disease progresses in the brain from a caudal to rostral direction, starting in the medulla and olfactory bulb (linked to rapid eye movement sleep behavior disorders and hyposmia), progressing to the substantia nigra (resulting in motor symptoms), and, finally, to the cerebral cortices (leading to cognitive symptoms)

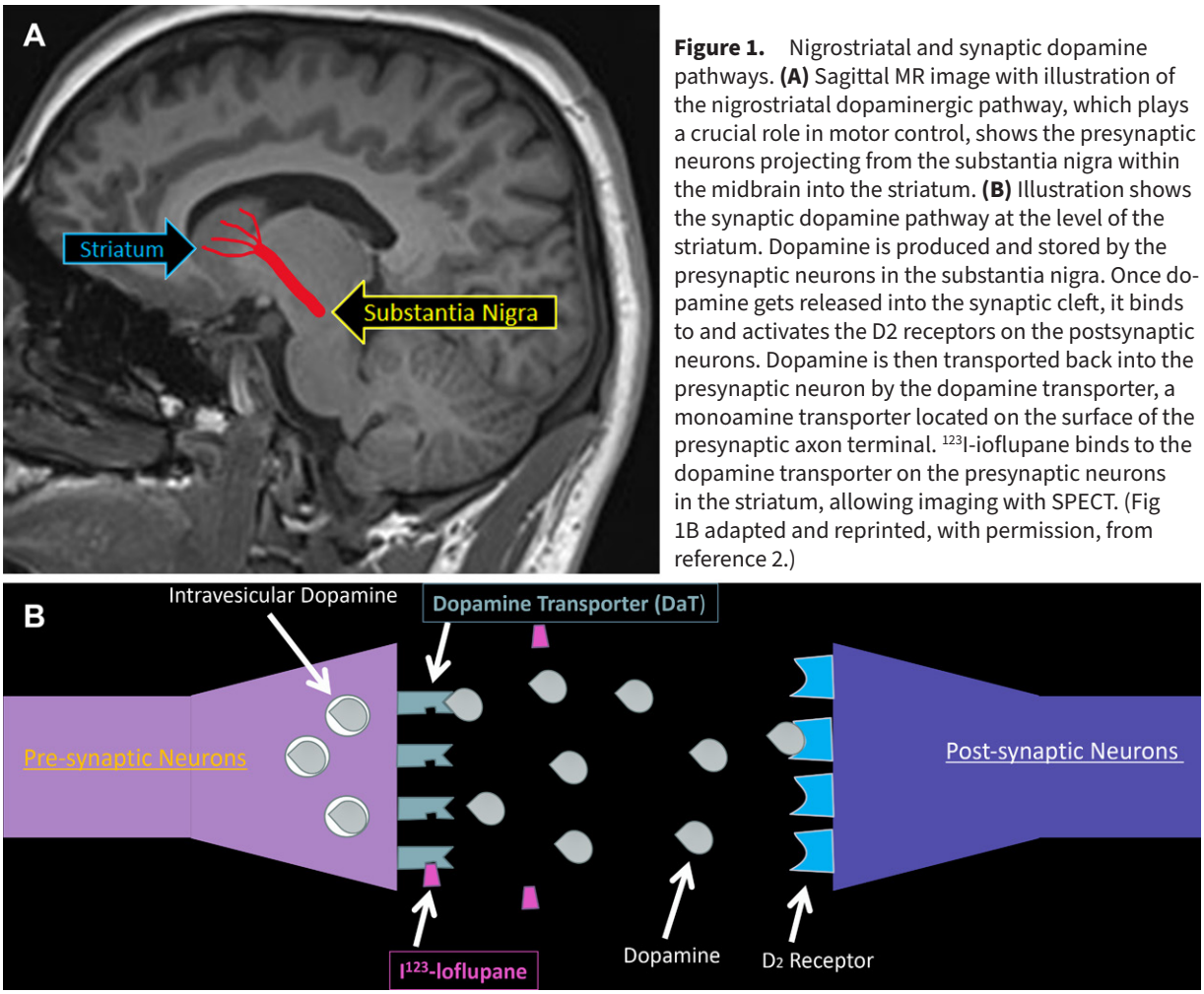


Figure 1. Nigrostriatal and synaptic dopamine pathways. **(A)** Sagittal MR image with illustration of the nigrostriatal dopaminergic pathway, which plays a crucial role in motor control, shows the presynaptic neurons projecting from the substantia nigra within the midbrain into the striatum. **(B)** Illustration shows the synaptic dopamine pathway at the level of the striatum. Dopamine is produced and stored by the presynaptic neurons in the substantia nigra. Once dopamine gets released into the synaptic cleft, it binds to and activates the D2 receptors on the postsynaptic neurons. Dopamine is then transported back into the presynaptic neuron by the dopamine transporter, a monoamine transporter located on the surface of the presynaptic axon terminal. ^{123}I-ioflupane binds to the dopamine transporter on the presynaptic neurons in the striatum, allowing imaging with SPECT. (Fig 1B adapted and reprinted, with permission, from reference 2.)

(18,20). Another theory is that it originates in gut microbiota and travels via the vagus nerve to the brain. This theory suggests that α-synuclein is not only present within the brain but also in the mucosal and submucosal gut nerve fibers. Alternatively, it has been proposed that gut microbiota produces amyloid-like proteins that promote α-synuclein–related diseases (21,22).

Both genetic and environmental factors may contribute (23,24). A meta-analysis of 30 potential risk factors identified 11 environmental factors associated with an increased likelihood of developing PD, with pesticide exposure being the strongest environmental risk factor. Smoking and caffeine consumption were among the factors associated with a decreased risk (19,23,24).

Clinical Presentation, Diagnosis, and Management

Although PD has been known primarily for its motor symptoms, it is important to note that PD has a wide spectrum of both motor and nonmotor symptoms (15). The median age of onset of motor symptoms in PD is around 73 years (25). Motor symptoms may include not only tremors, rigidity, and bradykinesia but also gait abnormalities, postural disturbances, and limited facial expression, also known as hypomimia (19). PD motor symptoms may be tremor dominant or non-tremor dominant, each with distinct features and progression rates (24). Nonmotor symptoms may be nonspecific, including constipation, fatigue, olfactory impairment, sleep disturbances, mood changes, and genitourinary symptoms (19,24,26). These nonmotor features can be a source of disease morbidity, may be debilitating, and may appear years before characteristic motor symptoms such as tremor (17,26). Since nonmotor symptoms may precede the motor symptoms by years, this may provide a window of opportunity for future disease-modifying therapy. At present, however, no such therapy exists.

Parkinson-plus syndromes are differentiated from PD by their characteristic symptoms beyond the classic tremor, bradykinesia, and rigidity. The most common forms are progressive supranuclear palsy (with gaze palsy, psychiatric disturbance, and gait abnormalities), MSA-P (with balance and autonomic symptoms), CBD (with apraxia, dystonia, and myoclonus), and DLB (with dementia and hallucinations) (27,28).

Since there is such variability in patient presentation, it may be difficult to determine the exact causes of a patient's symptoms in the early stage of the disease, as many patients may not fit a standard clinical mold. Although the diagnosis is frequently made clinically, a definitive diagnosis is made at autopsy by demonstrating substantia nigra degeneration and Lewy body pathologic features (8,17,24).

Table 1: Diseases and Conditions That Can Appear Abnormal or Normal at Dopamine Transporter Imaging

Abnormal appearance at dopamine transporter imaging
Parkinson disease (PD)
Corticobasal degeneration (CBD)
Primary supranuclear palsy
Multiple system atrophy
Dementia with Lewy bodies (DLB)
Normal appearance at dopamine transporter imaging
Essential tremor
Psychogenic tremor
Drug-induced tremor
Vascular parkinsonism
Alzheimer disease

Management of PD is primarily symptomatic, as none of the current therapies are known to affect disease progression (17,18). Current interventions include dopamine-replacement therapy (such as levodopa), physical therapy, and deep-brain stimulation (18). Although current pharmacologic therapy primarily involves dopamine replacement, nondopaminergic systems may also be affected, potentially explaining refractory symptoms (18).

Indications for Dopamine Transporter Imaging

Common indications for dopamine transporter imaging include differentiation of PD and Parkinson-plus syndromes, which are caused by nigrostriatal degeneration (and abnormal dopamine transporter imaging findings), from essential, psychogenic, and drug-induced tremors that are not associated with nigrostriatal degeneration (with expected normal imaging results) (29). Dopamine transporter imaging may also help differentiate Alzheimer disease (with expected normal imaging results) from DLB (with expected abnormal dopamine transporter imaging results), as their fluorine 18 (^{18}F)–fluorodeoxyglucose (FDG) PET patterns can appear quite similar (Table 1) (30,31).

Clinical Impact on Diagnosis and Management of Parkinsonism

Several studies have evaluated the cost-effectiveness of dopamine transporter SPECT for diagnosis and management of parkinsonian syndromes. In clinical cases with an ambiguous PD manifestation, it is reported that dopamine transporter SPECT results can modify the diagnosis and management in approximately 40%–50% of patients, resulting in a significant impact on the patient's quality of life, health resource use, and safety (32–36). By accurately diagnosing PD by using dopamine transporter SPECT, physicians can avoid unnecessary medication or surgery, thereby reducing the risk of side effects and complications. Another benefit of using dopamine transporter SPECT is the improvement in physician and patient confidence in the diagnosis and associated prognostic implications for the patient (37). Antonini et al (38) conducted a cost-effectiveness analysis of dopamine transporter SPECT for differentiation between PD and essential tremor. They found that using dopamine transporter SPECT was associated with lower costs and higher effectiveness than clinical evaluation alone, indicating that it was a cost-effective strategy for distinguishing essential tremor from PD (38). In summary, these studies suggest that dopamine transporter SPECT can cost-effectively improve diagnostic accuracy, change patient management, and improve patient and physician confidence.

Radiopharmaceutical Properties and Adverse Reactions

Dopamine transporter SPECT is performed with *N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)nortropane, commonly referred to as ^{123}I-ioflupane. Ioflupane is a cocaine analog that binds with high affinity to the presynaptic dopamine transporters in the striatum (Fig 1B) (30). Although initially classified as a Schedule II controlled substance, the small amount used for imaging does not produce any pharmacologic effect. ^{123}I, the radionuclide portion, is produced in a cyclotron and has a half-life of 13.2 hours and photon energy of 159 keV (2,29).

Following intravenous injection, ^{123}I-ioflupane is rapidly cleared from the blood, reaching the brain within 10 minutes following injection. It is predominantly renally excreted, with a lesser degree of fecal excretion. Patients with severe renal impairment may experience altered imaging quality and increased radiation dose. ^{123}I-ioflupane increases a patient's total lifetime cumulative radiation exposure, and thyroid accumulation of free ^{123}I is possible. Hypersensitivity reactions have been reported (including dyspnea, edema, erythema, rash, and pruritus); other adverse reactions, including nausea, headache, vertigo, dizziness, and dry mouth, were reported in 1% or less of patients (29).

According to the package insert, ^{123}I-ioflupane may cause fetal harm, and pregnant women should be advised about this (29). Lactating women are advised to interrupt breastfeeding for at least 6 days and to pump and discard breast milk during that period (29,30). According to the American College of Radiology (ACR)–American College of Nuclear Medicine (ACNM) practice parameter, pregnancy is considered a contraindication, and breastfeeding is a relative contraindication (30). The European Association of Nuclear Medicine (EANM)–Society of Nuclear Medicine and Molecular Imaging (SNMMI) procedure standard states that neither pregnancy nor breastfeeding are absolute contraindications. However, performing the examination in these scenarios should be justified (31). There is limited safety data about the use of ^{123}I-ioflupane in the pediatric population (29).

Patient Preparation and Imaging Protocol

Patient preparation is important (Fig 2). Before presenting for the imaging examination, patients should be screened for numerous drugs that can interact with the radiopharmaceutical. Medications that interfere with ioflupane binding, such as methylphenidate, ephedrine, fentanyl, and ketamine, should be held for at least five half-lives before the study (Table 2) (29,31,39,40; GE HealthCare Medical Communication, written communication, November 2023). Notably, anti-parkinson medications such as L-DOPA (l-3,4-dihydroxyphenylalanine), amantadine, monoamine oxidase

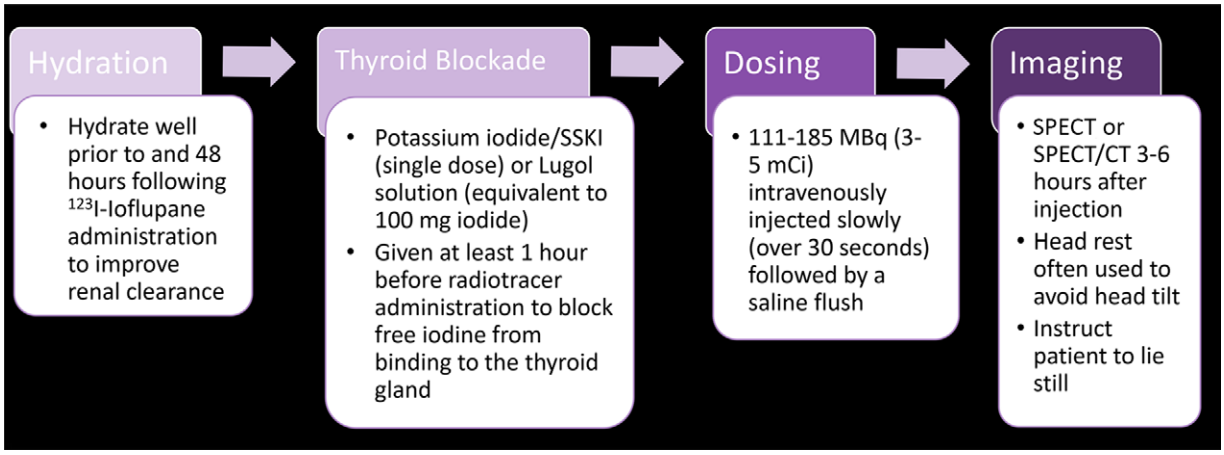


Figure 2. Diagram shows the patient preparation and imaging protocol for dopamine transporter imaging.

Table 2: Medications That Can Interfere with ^{123}I-Ioflupane, with Recommended Holding Period by Manufacturer

Medication	Recommended Holding Period (Approximately Five Half-lives)
Amphetamine, dexamphetamine, methamphetamine, methylphenidate, dexmethylphenidate	1–7 d
Armodafinil	3 d
Bupropion	5–8 d
Cocaine	1–2 d
Codeine	1 d
Ephedrine	1 d
Fentanyl	2–5 d
Haloperidol	5 d
Isoflurane	1 d
Ketamine	1 d
Mazindol	3 d
Modafinil	3 d
Phencyclidine	1 d
Phentermine	1–5 d

Source.—Adapted and reprinted, with permission, from GE HealthCare Medical Communication, written communication, November 2023.

B inhibitors, and *N*-methyl-D-aspartate receptor blockers are considered safe to continue because they do not affect ioflupane binding substantially. Selective serotonin reuptake inhibitors (SSRIs) and cholinesterase inhibitors are thought to have only minimal impact on ioflupane binding (31).

Premedication is administered to prevent thyroid uptake of ^{123}I. Premedication options include the equivalent of 100 mg iodide containing Lugol solution or a single dose of oral potassium iodide (SSKI) solution administered 1 hour before injection (29,31). Oral hydration before and after imaging is recommended to facilitate renal clearance.

The suggested dosage of ^{123}I-ioflupane, according to the prescribing information, is 111–185 MBq (3–5 mCi), given as a slow intravenous injection (lasting at least 20 seconds) followed by a saline flush (29,30). SPECT should be performed 3–6 hours after injection, at a photopeak of 159 keV (±10% energy window), with a minimum angular sampling of 120 views over 360 degrees and a low-energy high-resolution collimator. It is recommended that the patient's head be placed on a headrest, with the circular orbit set as small as possible (typically with 11–15-cm radius). If needed, soft or flexible restraint may be helpful to limit head motion (29). Optimally, a minimum of 1.5 million counts should be collected (29). American College of Radiology–American College of Nuclear Medicine (ACR-ACNM) guidelines recommend 4.5 million counts (30). However, unfortunately, high counts may not be possible in patients with minimal striatal activity (2,29).

Interpretation of Dopamine Transporter SPECT

The interpretation of dopamine transporter SPECT images is mainly done qualitatively by visually assessing the radiotracer uptake pattern in the striatum. The sensitivity and specificity of dopamine transporter SPECT for diagnosing PD were shown in multiple studies to exceed 90% (8). Dopamine transporter SPECT/CT has the advantage of providing anatomic information and attenuation-correction images. However, image quality and reader confidence agreement was shown to be similar between SPECT and SPECT/CT, suggesting that both modalities are acceptable for interpretation (41).

A normal examination shows two symmetric comma-shaped regions that are intense and distinct in comparison with the background brain tissue (Figs 3, 4). The comma should overlie the striata and appear on both sides of the brain. Mild asymmetry in striatal uptake may occur in healthy individuals and can be due to senescent changes (Fig 5) (42). It is also important to remember that about 50%–60% of the dopaminergic neurons are lost in symptomatic patients. Thus, imaging findings are generally not subtle in positive cases (19). When a patient with tremor and suspected PD demonstrates normal uptake at dopamine transporter SPECT, the term *scans without evidence for*

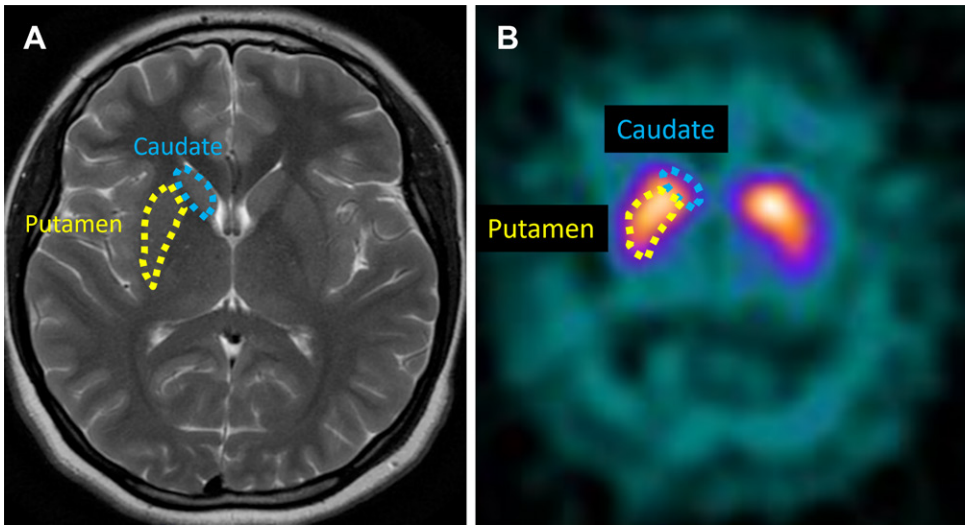


Figure 3. Anatomy of the striata. Axial T2-weighted MR **(A)** and ^{123}I-ioflupane SPECT **(B)** images show the caudate (blue dashed outline) and putamen (yellow dashed outline). The striatum appears as a continuous structure on ^{123}I-ioflupane SPECT images. Because of limited SPECT resolution, it is challenging to delineate the caudate and putamen.

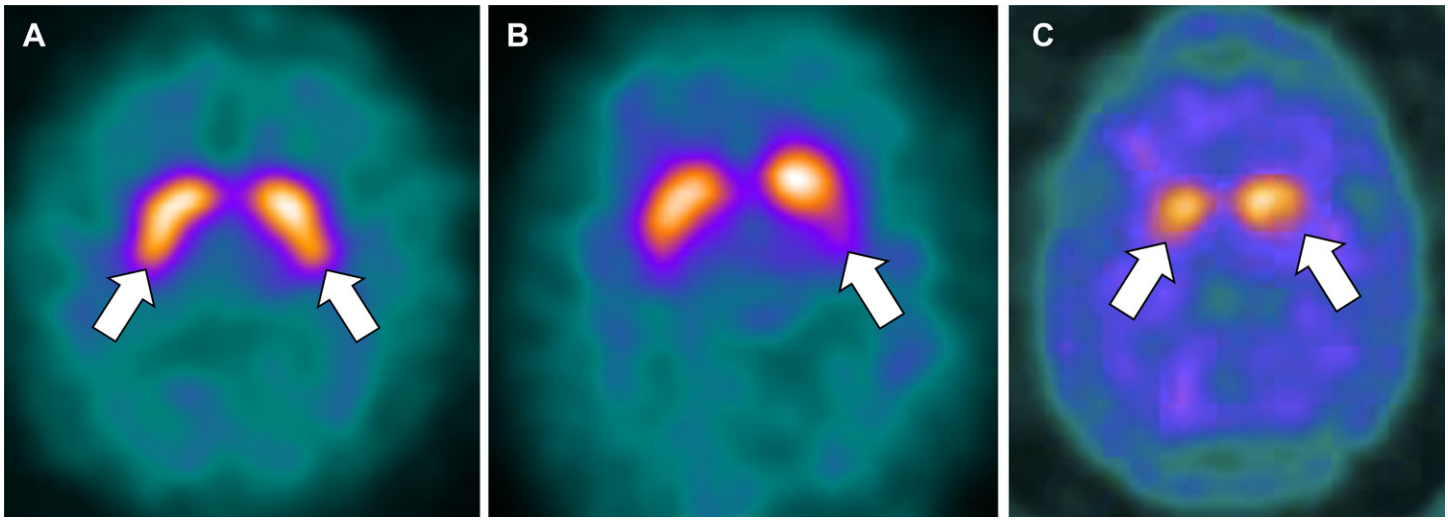


Figure 4. Classic normal and abnormal dopamine transporter imaging features on axial ^{123}I-ioflupane SPECT images. **(A)** Image shows symmetric comma-shaped activity in the bilateral caudate nuclei and putamina (arrows) with low background brain activity in a healthy patient. **(B)** Image in a different patient shows normal comma-shaped activity on the right with asymmetric shortening of the left putamen (arrow) with a period- or oval-shaped appearance, compatible with an abnormal examination. **(C)** Image in a patient with nigrostriatal degeneration shows symmetric decreased activity within the bilateral putamen, with a period-shaped appearance of the preserved caudate activity (arrows) and an increase in background brain activity. Activity in PD is typically first reduced posteriorly and then anteriorly (the putamen is typically affected before the caudate). In cases with unilaterally decreased activity, clinical symptoms (such as tremors) are typically contralateral to the more affected side.

dopaminergic defect (SWEDD) has been traditionally used. It is now thought that many of these patients have a variety of conditions unlikely related to PD (31,43).

An abnormal examination shows decreased ioflupane uptake, which may be symmetric or asymmetric. In the earliest stage of PD, this finding typically affects the putamen posteriorly (resulting in an oval or period shape) (Fig 4). As the disease progresses, the anterior putamen and caudate, respectively, start losing their activity. In the advanced stages of disease, the striatal-to-background contrast decreases (Fig 6).

Semiquantitative interpretation can be used to supplement visual interpretation, and it entails using a region of interest analysis to calculate striatal activity normalized by occipital background activity and comparing it to a normal database (Fig S1A) (29). A reduced striatal binding ratio (SBR) indicates dopamine transporter loss and nigrostriatal degeneration. A study by Neill et al (44) showed that the most reliable method for identifying nigrostriatal degeneration using the DaTQUANT (GE Healthcare) semiquantitative FDA-approved software was SBR of the posterior putamen, with recommended threshold values of SBR 1.0 or less, percent deviation (from the age-matched mean of the normal database) -0.34 or less, and Z-score of -1.8 or less (Fig S1B, S1C) (44). Note that these threshold values have only been validated for DaTQUANT and are not applicable to other quantitative software. For example, MIMneuro (MIM Software), another commonly used semiquantitative software, uses a Z-score threshold of less than -1.65 to identify abnormal striatal activity (Fig S1D, S1E) (45,46).

Semiquantitative interpretation provides a more objective assessment of dopamine transporter SPECT images, increases

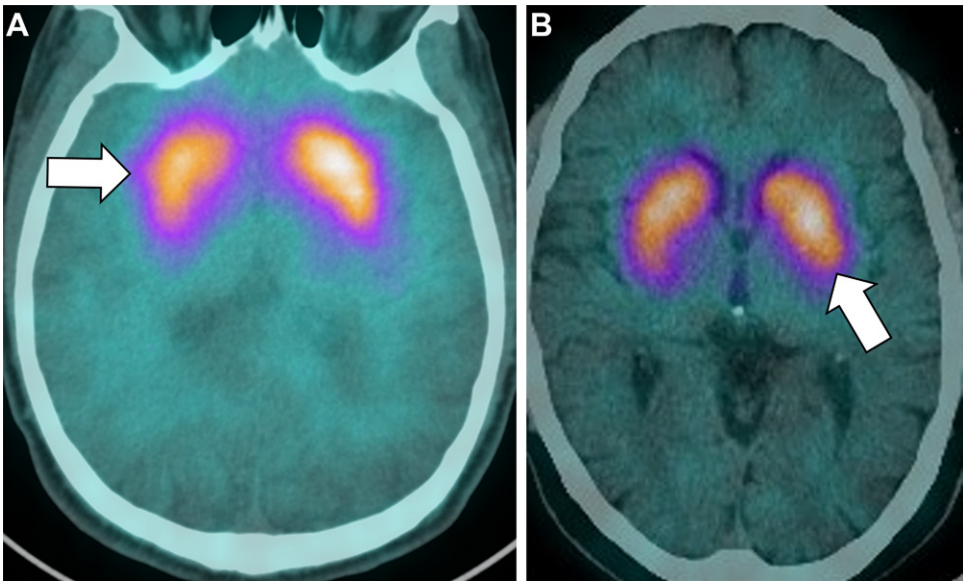


Figure 5. Normal findings that should not be confused with pathologic findings. Axial ^{123}I-ioflupane fused SPECT/CT images show subtle asymmetric diffuse decreased activity within the right putamen (arrow in **A**) and minimally asymmetric shortening of the left posterior putamen (arrow in **B**), which represent normal variations of radiotracer uptake and may be often related to aging. These normal variations should not be interpreted as abnormal. Note the low background activity and preservation of the comma-shape activity of the bilateral striata. In challenging cases, quantification software, which compares striatal activity to that in a normal database, may be helpful for confirmation.

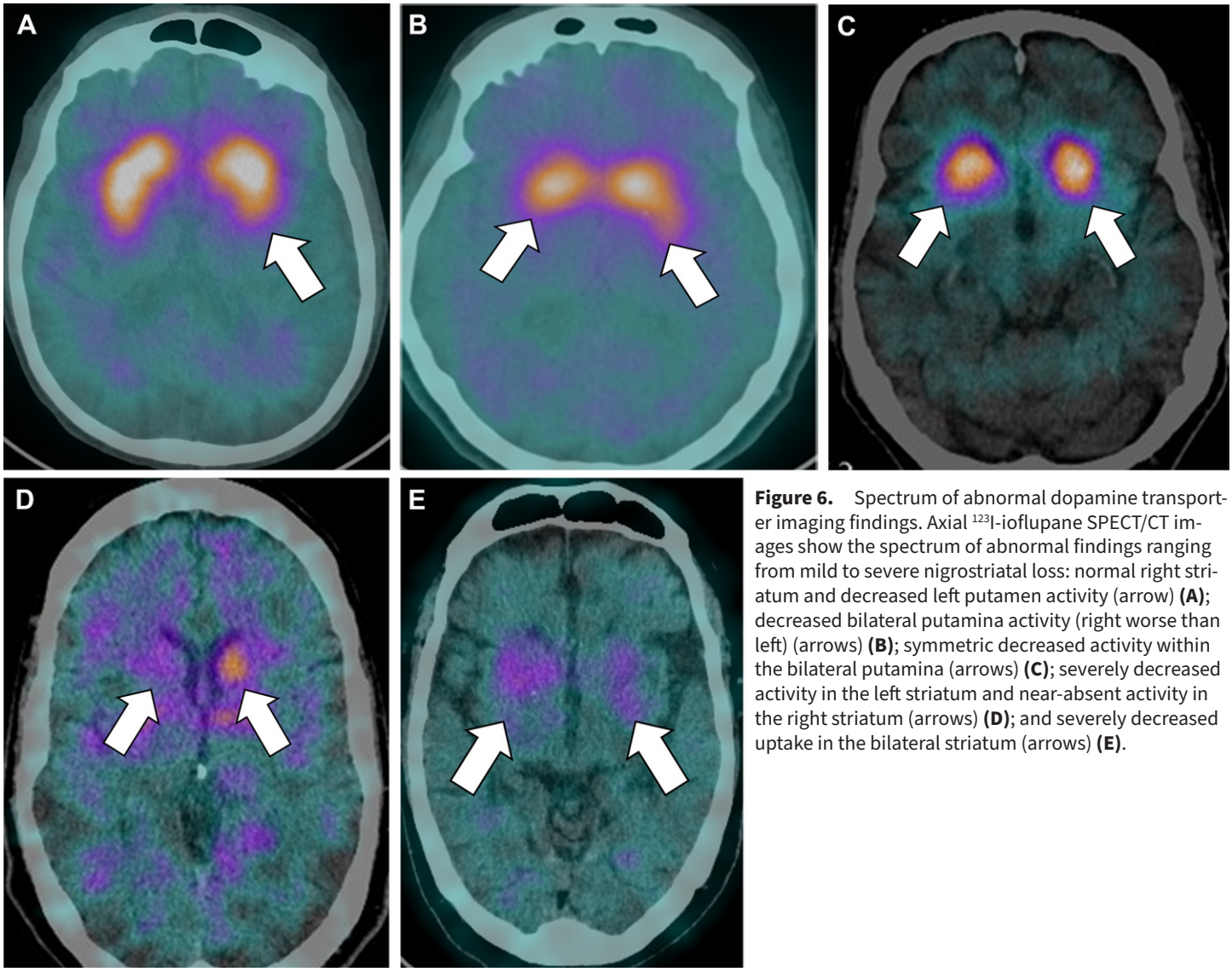


Figure 6. Spectrum of abnormal dopamine transporter imaging findings. Axial ^{123}I-ioflupane SPECT/CT images show the spectrum of abnormal findings ranging from mild to severe nigrostriatal loss: normal right striatum and decreased left putamen activity (arrow) **(A)**; decreased bilateral putamina activity (right worse than left) (arrows) **(B)**; symmetric decreased activity within the bilateral putamina (arrows) **(C)**; severely decreased activity in the left striatum and near-absent activity in the right striatum (arrows) **(D)**; and severely decreased uptake in the bilateral striatum (arrows) **(E)**.

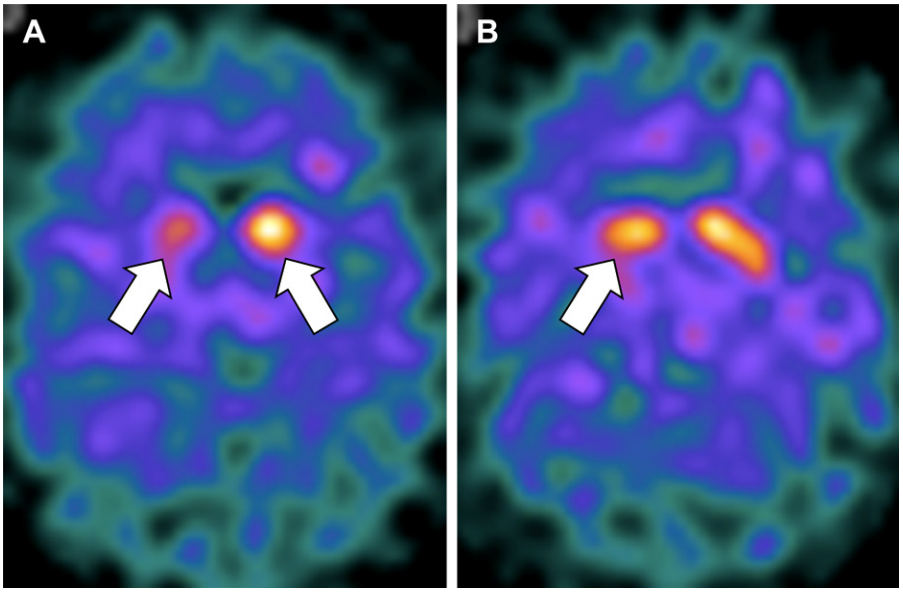


Figure 7. Motion artifact pitfall. **(A)** Axial ^{123}I-ioflupane SPECT image in a patient who was noted to have moved his head during the examination shows bilateral period-shaped configuration of the striata (arrows), resulting in an abnormal examination. **(B)** Axial ^{123}I-ioflupane SPECT image from a repeated examination without motion in the same patient shows improved striatal activity, particularly on the left. The right striatum remains abnormal (arrow). Motion is often best detected by watching for head and patient motion during the examination and reviewing the rotating whole brain raw cine projection. In patients who cannot lie still, diazepam may help decrease motion.

reader confidence, and may in the future be used to track disease progression, although this area is still under investigation (30,47,48). It is important to acknowledge that while some of the semiquantification software used for ioflupane presynaptic SPECT has received FDA approval, the current FDA-approved method for interpretation, as stated in the ioflupane package insert, remains solely visual and qualitative (29).

Pitfalls

Various pitfalls may confound dopamine transporter imaging interpretation, including motion artifact, poor patient positioning, scaling, off-peak acquisition, and prior cerebral infarction.

Motion Artifact

One of the most common pitfalls is motion artifact (Fig 7). Motion can cause blurred images, making it difficult to assess radiotracer uptake in the striatum visually, and potentially resulting in interpretation errors when using the quantification software. This is especially common in patients who have difficulties staying still. In patients with anxiety or discomfort, anxiolytic medication may help decrease motion. Interpreting physicians can assess for motion artifacts by reviewing cine images, which allow them to see the movement of the patient's head during the examination. It is important for technologists to be aware of this pitfall, as repeat imaging may be helpful in some cases.

Poor Patient Positioning

Another pitfall is asymmetric positioning or lateral head tilt, which may cause an asymmetric appearance of the basal ganglia on some of the sections, mimicking a positive examination (Fig 8). This pitfall can be avoided by scrolling through all the axial sections and reviewing the normal appearance of each basal ganglia and not making interpretations solely based on the asymmetric appearance of the striatal activity on a single image. Correction of the lateral tilt through manual or software-assisted manipulation may also help improve image quality. Similarly, forward head tilt, due to inappropriate positioning of the patient's head in the head holder, can also falsely suggest a loss of activity in the putamen on some of the images due to the caudate and putamen activity projecting on different axial sections, an artifact referred to as the semicolon sign (49). If the entire examination is not reviewed, the images can be incorrectly labeled as abnormal. Technologists should ensure the appropriate positioning of the patient's head in the head holder to avoid this artifact (49,50).

Scaling Artifact

Scaling artifact is another potential pitfall in dopamine transporter imaging. This artifact can occur when the salivary glands are included in the field during postprocessing. The intense uptake of the salivary gland can cause relative striatal uptake to appear minimal, resulting in a false-positive result (2). To avoid this pitfall, interpreting physicians should know the potential for scaling artifacts and review the entire examination to ensure that any observed uptake is not due to the salivary glands.

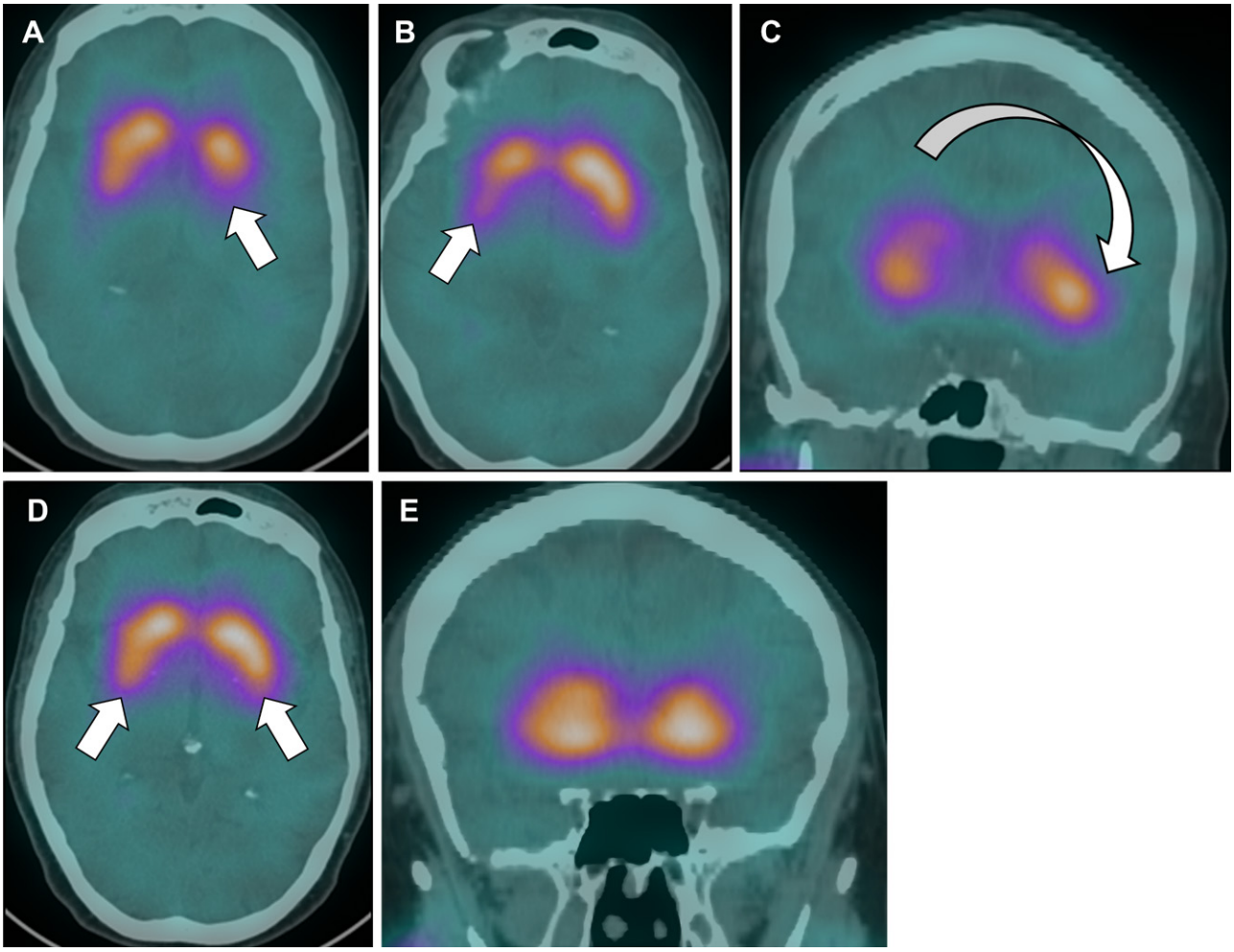
Off-peak Acquisition

Off-peak acquisition can also occur if the wrong brain imaging protocol is selected (Fig 9). For example, incorrectly selecting a brain perfusion acquisition protocol for a technetium 99m (^{99m}Tc)–labeled brain perfusion agent rather than the ^{123}I-labeled ioflupane SPECT protocol can result in an off-peak acquisition. To avoid this pitfall, it is important that nuclear medicine technologists ensure that the correct protocol is selected before the examination is performed.

Prior Cerebral Infarction

A prior infarct in the striatum or basal ganglia can also cause a false-positive interpretation due to the loss of dopaminergic neurons; this is referred to as vascular pseudo-parkinsonism (Fig 10) (51). To avoid this pitfall, a careful review of the anatomic CT images in patients who undergo SPECT/CT and a review of prior anatomic brain imaging can be helpful. This is

Figure 8. Lateral head tilt pitfall. **(A)** Axial ^{123}I-ioflupane–fused SPECT/CT image shows decreased activity in the left posterior putamen (arrow), with a normal right striatal appearance. **(B)** Axial ^{123}I-ioflupane–fused SPECT/CT subjacent image shows shortening of the right putamen (arrow), with a normal left striatal appearance. **(C)** Coronal ^{123}I-ioflupane–fused SPECT/CT image shows evidence of lateral head tilting (curved arrow). **(D, E)** Reformatted axial **(D)** and coronal **(E)** fused SPECT/CT images show a normal comma-shaped appearance of the bilateral striata (arrows in **D**), compatible with a normal examination. When reviewing dopamine-transporter images, it is important to scroll through the entire examination to confirm findings. If there is an apparent shortening of the striatum on some axial images but not on others, this may be due to lateral head tilt. This can be confirmed with coronal views.



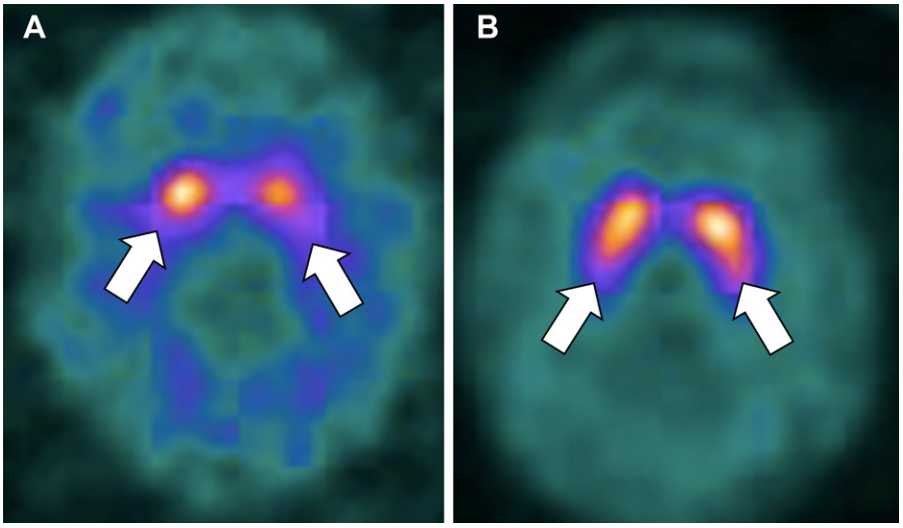


Figure 9. Off-peak acquisition pitfall. **(A)** Axial ^{123}I-ioflupane SPECT image obtained at the incorrect technetium 99m (^{99m}Tc) peak acquisition shows a bilateral period-shaped configuration of the striata (arrows), compatible with an abnormal examination. **(B)** Axial ^{123}I-ioflupane SPECT image from immediate repeat imaging in the same patient at the correct ^{123}I peak acquisition shows a comma-shaped appearance of the bilateral striata (arrows), compatible with a normal examination.

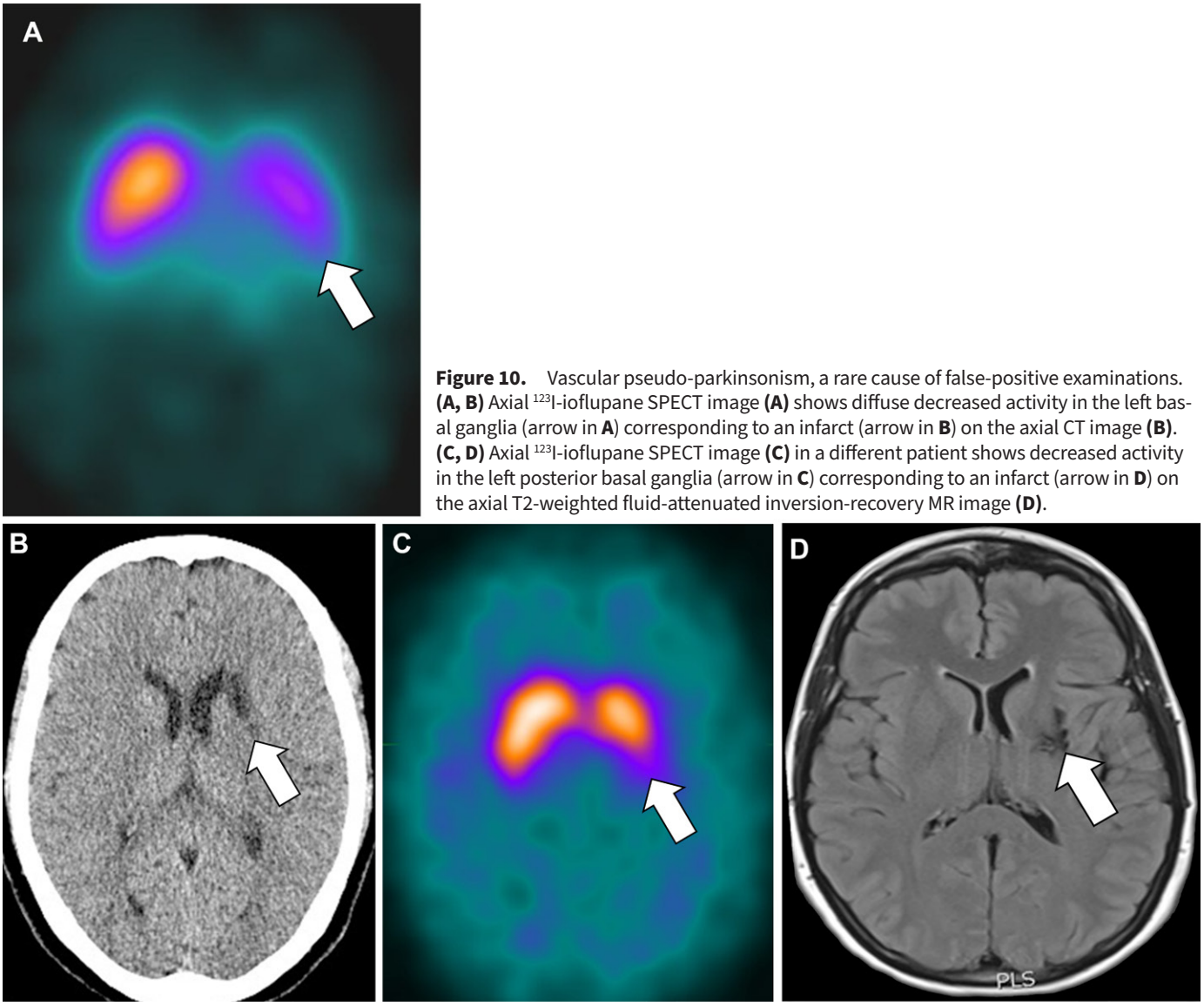


Figure 10. Vascular pseudo-parkinsonism, a rare cause of false-positive examinations. **(A, B)** Axial ^{123}I-ioflupane SPECT image **(A)** shows diffuse decreased activity in the left basal ganglia (arrow in **A**) corresponding to an infarct (arrow in **B**) on the axial CT image **(B)**. **(C, D)** Axial ^{123}I-ioflupane SPECT image **(C)** in a different patient shows decreased activity in the left posterior basal ganglia (arrow in **C**) corresponding to an infarct (arrow in **D**) on the axial T2-weighted fluid-attenuated inversion-recovery MR image **(D)**.

especially useful in patients with abnormal striatal activity that does not follow the typical posterior-worse-than-anterior gradient (for example, in a patient with absent caudate but preserved putamen activity). Correlation with MRI findings can also be helpful (52).

Reporting

Reports should include the technical aspects of the examination, including the radiopharmaceutical dose and route of administration, the time of acquisition (following injection), and any known technical limitations (30). The language should be easy to interpret to facilitate clinical interpretation (2). Reported findings should include whether there is a normal, unilateral, or bilateral loss of striatal activity and indicate which side is worse, if applicable. It is also recommended to indicate whether the striatal loss is diffuse or worse in the posterior aspect of the striatum. The report's conclusion should explicitly state whether there is evidence of dopaminergic loss in the striatum and whether the findings support the diagnosis of parkinsonian syndromes (2).

Alternatives to ^{123}I-Ioflupane Imaging

At this point, anatomic imaging modalities have not been as successful as molecular imaging in diagnosing PD because structural abnormalities at CT and MRI are typically evident only in later stages (2). It should be noted, however, that anatomic imaging may be helpful to assess for vascular disease and other potential confounding diagnoses.

^{18}F-fluorodopa, a PET imaging agent, is another FDA-approved radiopharmaceutical for evaluating nigrostriatal degeneration, although it is not yet widely commercially available (8). ^{18}F-fluorodopa uptake in neurons is dependent on the activity of the aromatic amino acid decarboxylase (AADC) enzyme, which converts dopa to dopamine, as well as the density of the presynaptic dopaminergic neurons (53). ^{18}F-fluorodopa has good sensitivity and specificity (in the range of 90%) for detecting nigrostriatal degeneration, similar to that of ^{123}I-ioflupane (53,54). Several other functional PET and SPECT agents that assess the pre- and postsynaptic dopaminergic nigrostriatal pathways are currently under development and hold promise for future clinical applications (53).

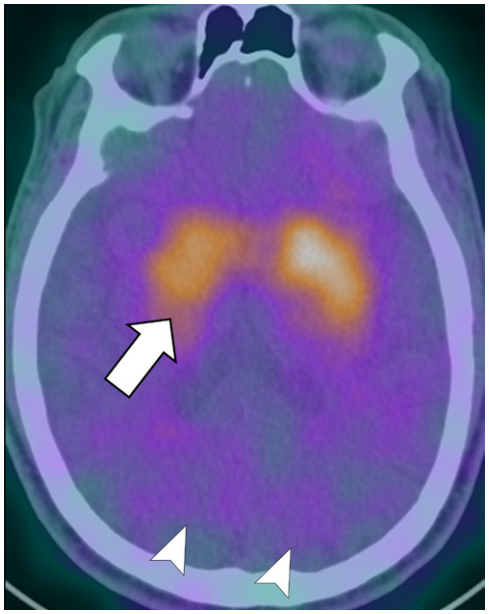


Figure 11. Complementary role of dopamine transporter imaging in the evaluation of dementia syndromes. Axial ^{123}I-ioflupane SPECT/CT image in a patient with DLB shows decreased right striatal activity and increased background brain parenchymal activity (arrowheads). In patients with atypical dementia symptoms and equivocal ^{18}F-FDG PET/CT brain findings, dopamine transport imaging may help differentiate Alzheimer disease (with normal dopamine transport imaging findings) from DLB (with abnormal dopamine transporter imaging findings).

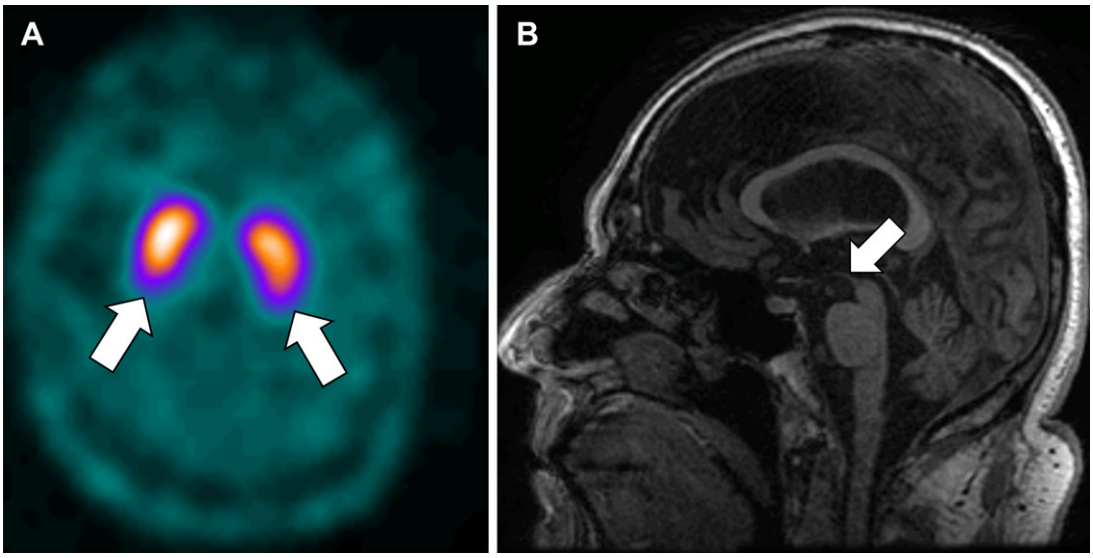


Figure 12. False-negative examination: complementary role of anatomic imaging. **(A)** Axial ^{123}I-ioflupane SPECT image shows a preserved comma-shaped appearance of the striata, compatible with a normal examination. **(B)** Concurrent sagittal T1-weighted MR image of the brain in the same patient shows atrophic "hummingbird morphology" in the midbrain, suggesting a diagnosis of PSP as the cause of tremors and instability. Dopamine transporter imaging sensitivity and specificity are reportedly high around 90%, but there are reported cases of false-negative imaging examinations.

Parkinsonian Syndromes: Additional Imaging Assessment

Dopamine transporter imaging is also a useful tool for diagnosing Parkinson-plus syndromes when clinical and ^{18}F-FDG PET/CT findings are inconclusive, particularly to differentiate Alzheimer disease from DLB (Fig 11). It is important to highlight that the sensitivity of dopamine transporter imaging for identifying nigrostriatal degeneration in Parkinson-plus syndromes is lower than that in PD, as findings may be more subtle in the former, and up to 10% of patients with DLB may have a negative imaging examination in the early stage of the disease (Fig 12) (55). The diagnostic features of Parkinson-plus syndromes at SPECT are often less distinct than those of PD. Parkinson-plus syndromes may manifest with mild diffuse decreased activity in the basal ganglia and early involvement of the anterior striatum rather than the classic posterior-to-anterior loss often seen with PD (56).

The findings on dopamine transporter images cannot be used to differentiate between PD and Parkinson-plus syndromes. To distinguish between the different entities, ^{18}F-FDG PET/CT may be used to identify patterns of regional hypometabolism in the cerebral cortex that are distinct for each entity (for example, regional hypometabolism within the sensorimotor cortex, which is characteristic of CBD, or decreased activity in the parietotemporal and occipital cortex, as seen with DLB) (57,58). MRI and CT can help evaluate for patterns of parenchymal loss specific for various entities (for example, the hummingbird sign characteristic of PSP), but anatomic imaging tends to lag behind the ^{18}F-FDG findings.

^{123}I-metaiodobenzylguanidine (MIBG) cardiac imaging has recently been suggested as a potential tool to differentiate PD and DLB from other Parkinson-plus syndromes. Sympathetic innervation to the heart is often lost in idiopathic PD and DLB, resulting in decreased myocardial activity at MIBG, while it is often maintained in other Parkinson-plus syndromes (Fig 13) (59,60).

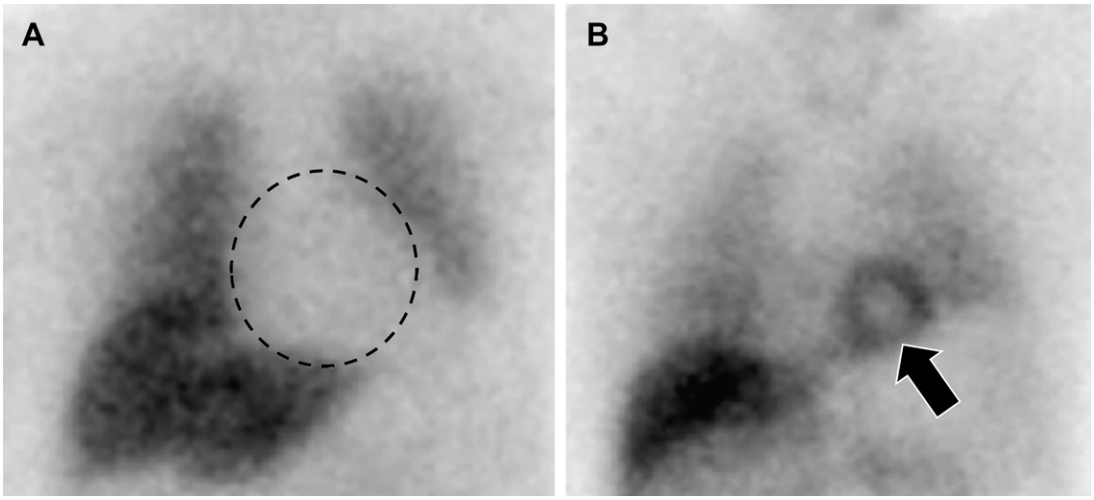


Figure 13. Cardiac adrenergic function assessment to help differentiate PD and DLB from the other atypical parkinsonian syndromes. Dopamine transporter imaging cannot differentiate the different forms of PD and Parkinson-plus syndromes. In patients with abnormal dopamine transporter imaging findings, myocardial ^{123}I-metaiodobenzylguanidine (MIBG) imaging has been proposed to help distinguish these clinical entities by showing abnormally decreased or absent MIBG activity within the expected location of the heart (circle in **A**) in patients with idiopathic PD and DLB and normal preserved myocardial MIBG activity (arrow in **B**) in the remaining Parkinson-plus syndromes (including MSA-P, PSP, and CBD), as depicted on the MIBG images.

Conclusion

Parkinsonian syndromes, a cluster of neurodegenerative disorders, are characterized by degeneration of dopaminergic pathways and deficiency of striatal dopamine. These syndromes may be challenging to diagnose clinically, as there can be an overlap of symptoms between parkinsonism and non-parkinsonian diseases, especially in the early stages of the disease. Dopamine transporter imaging can help differentiate parkinsonian syndromes from nonparkinsonian causes. In most cases, visual assessment is adequate, but quantification can be useful as an adjunct for interpretation. Several pitfalls exist, but most can be addressed by optimizing patient preparation and image acquisition and correlating findings with the patient's history. It is essential for the radiologist or nuclear medicine physician to carefully review the entire imaging examination and be aware of potential pitfalls to avoid misinterpretation of dopamine transporter imaging examinations.

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