EFECTIVIDAD DIAGNÓSTICA DEL SPECT CEREBRAL CON [^{123}I]IOFLUPANO EN LA ATROFIA MULTISISTÉMICA

DIAGNOSTIC EFFECTIVENESS OF [^{123}I]IOFLUPANE BRAIN SPECT IN MULTIPLE SYSTEM ATROPHY

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TÍTULO DE LA TESIS: Efectividad diagnóstica del SPECT cerebral con [^{123}I]Ioflupano en la atrofia multisistémica

DOCTORANDO: Javier Villena Salinas

INFORME RAZONADO DEL/DE LOS DIRECTOR/ES DE LA TESIS

Durante el desarrollo de la presente Tesis Doctoral, en el periodo comprendido entre noviembre de 2020 y enero de 2024, el doctorando Javier Villena Salinas además de superar con creces los objetivos inicialmente trazados, ha ido más allá habiendo propuesto y desarrollado estrategias en la interpretación de estudios mediante técnicas de imagen implementados en servicios hospitalarios de Medicina Nuclear, a fin de aplicarlas en el diagnóstico precoz y en el seguimiento de una entidad neurodegenerativa como es la atrofia multisistémica (AMS). La aludidas técnicas han sido el SPECT con [^{123}I]Ioflupano y la gammagrafía con [^{123}I]-MIBG.

Habida cuenta de la amplia casuística de enfermos estudiada (inicialmente 139 pacientes, en una patología de escasa incidencia como es la AMS), ha podido obtener inferencias novedosas. Entre ellas cabría reseñar: 1) la asimetría inter-hemisférica cerebral al iniciarse la enfermedad y su mantenimiento durante el avance del proceso neurodegenerativo; 2) la mayor sensibilidad y especificidad diagnósticas del SPECT con [^{123}I]Ioflupano frente a otras técnicas de neuroimagen y su pertinencia para el seguimiento evolutivo de los enfermos de AMS; y 3) la evolución independiente en el deterioro neuro-encefálico y miocárdico en la AMS. Esto ha dado lugar a tres artículos en revistas indexadas, dos de ellos en primer cuartil y otro el segundo cuartil según el 'Journal Citation Reports' (JCR). De esto partió el planteamiento de presentar el trabajo de Tesis Doctoral como compendio de artículos.

Cabe reseñar que la idea, temática y metodología del presente trabajo de Tesis Doctoral fueron iniciativa del doctorando. Tal hecho, unido al tiempo de ejecución inicialmente reseñado, hacen patente la iniciativa y gran capacidad de trabajo del aludido doctorando.

Por todo ello, se autoriza la presentación de la tesis doctoral.

Córdoba, 4 de abril de 2024

Firma del director

A MI ABUELO ADOLFO

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Gracias.

ÍNDICE DE ABREVIATURAS

- **2-[^{18}F]FDG:** Fluordesoxiglucosa marcada con Flúor-18
- **AMS:** Atrofia Multisistémica
- **DAT:** transportador de dopamina
- **DCL:** Demencia con Cuerpos de Lewy
- **DCBG:** Degeneración Corticobasal Ganglionic
- **DJ-1**: Desglicasa 1
- **DSM:** Manual Diagnóstico y Estadístico de los Trastornos Mentales (*Diagnostic and Statistical Manual of Mental Disorders*)
- **ELISA:** Ensayo por inmunoadsorción ligado a enzimas
- **EMSA-SG:** Grupo Europeo de Estudio de la AMS *(European MSA Study Group)*
- **EP:** Enfermedad de Parkinson
- **E/0:** Índice Estriado/Occipital
- **FP-CIT:** N-ω-fluoropropil-2β-carbometoxi-3β-(4-iodofenil) nortropano
- **IBZM:**^{123}I-(S)-2-hidroxi-3-yodo-6-metoxi-N-[etil-2-pirrodinilo)-etil]benzamida
- **ISRS:** Inhibidores Selectivos de la Recaptación de Serotonina
- **L-AAAD:** L-aminoácido aromático descarboxilasa
- **LCR:** Líquido Cefalorraquídeo
- **MIBG:** Metayodobencilguanidina

- **NfL:** Cadena ligera del neurofilamento
- **PET:** Tomografía por Emisión de Positrones (*Positron Emission Tomography*)
- **PMCA:** Ca2+-ATPasa de la membrana plasmática
- **PSP:** Parálisis Supranuclear Progresiva
- **ROI:** Región de Interés (*Region of Interest*)
- **RT-QUIC:** Conversión de proteína priónica inducida por agitación en tiempo real
- **RVP:** Residuo Vesical Postmiccional
- **SBR:** Serotonin Binding Ratio
- **SCA:** Ataxia Espinocerebelosa
- **SNC:** Sistema Nervioso Central
- **SNA:** Sistema Nervioso Autónomo
- **SPECT:** Tomografía por Emisión de Fotón Único (*Single Photon Emission Computed Tomography*)
- **SWI:** Imagen potenciada en susceptibilidad magnética
- **T2W:** Secuencia ponderada en T2
- **TCSR:** Trastorno de Conducta del Sueño REM
- **TC:** Tomografía Computarizada
- **TE:** Temblor Esencial

- **UMSARS:** escala unificada de clasificación de AMS *(Unified Multiple System Atrophy Rating Scale)*
- **UPDRS:** Escala Unificada de la Enfermedad de Parkinson (*Unified Parkinson's Disease Rating Scale*)
- **VMAT2:** Transportador vesicular de monoaminas tipo 2
- **VPP:** Valor Predictivo Positivo

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RESUMEN

La atrofia multisistémica (AMS) es una patología degenerativa del sistema nervioso central y autónomo, de curso rápidamente progresivo. Se caracteriza por una amplia variedad de manifestaciones clínicas graves y limitantes que pueden parecerse en sus etapas iniciales a otras enfermedades neurodegenerativas. No tiene tratamiento curativo ni modificadores de la enfermedad, por lo que su pronóstico es desolador, pues conduce al fallecimiento en menos de 10 años desde el inicio de los síntomas. Por todo lo expuesto, un diagnóstico precoz y preciso es esencial.

Nuestra investigación ha demostrado que la técnica de imagen SPECT cerebral con [^{123}I]-Ioflupano posee un buen rendimiento diagnóstico en la AMS y sus subtipos, especialmente en etapas iniciales y sobre todo en comparación con otras pruebas convencionales como la resonancia magnética nuclear. En la interpretación del SPECT, la valoración cualitativa del médico nuclear es fundamental, mientras que los programas de cuantificación constituyen herramientas complementarias de apoyo.

Como primicias, los primeros resultados mostraron una posible lateralización de la afectación inicial de la enfermedad, lo que podría ser interesante por su posible utilidad en el diagnóstico de la AMS, especialmente para identificar casos incipientes de esta enfermedad. Además, el estudio longitudinal permitió conocer que la progresión de la AMS en ambos núcleos estriados es similar, con una disfunción de un tercio de la función de la vía nigroestriada a los 12 meses. En este sentido, el papel del SPECT evolutivo ante casos no concluyentes es

crucial, mejorando los parámetros diagnósticos respecto al SPECT basal y permitiendo confirmar o descartar esta patología en la totalidad de ese grupo pacientes.

En última instancia, nuestra investigación se centró en la comparación directa entre dos pruebas de neuroimagen funcional, SPECT cerebral con [^{123}I]-Ioflupano y gammagrafía de inervación cardíaca con [^{123}I]-MIBG. Ambas técnicas han demostrado ser efectivas en el diagnóstico de la AMS sin clara superioridad de una sobre la otra, por lo que ambas deben considerarse para un diagnóstico correcto. También como primicia hemos propuesto puntos de corte óptimos en el análisis cuantitativo de ambas exploraciones, destacando el hecho de que el índice corazón-mediastino tardío en la gammagrafía con [^{123}I]-MIBG muestra una relación directa con el riesgo de padecer AMS.

ABSTRACT

Multiple system atrophy (MSA) is a rapidly progressive degenerative pathology of the central and autonomic nervous systems. It is characterised by a wide variety of severe and limiting clinical manifestations that may resemble other neurodegenerative diseases in their initial stages. There is no curative treatment or disease modifiers, resulting in a poor prognosis, leading to death within less than 10 years from the onset of symptoms. Therefore, an early and accurate diagnosis is essential.

Our research has demonstrated that the brain imaging technique SPECT with [^{123}I]-Ioflupane has good diagnostic performance in MSA and its subtypes, especially in the early stages and particularly when compared to other conventional tests such as nuclear magnetic resonance imaging. In the interpretation of SPECT, the qualitative assessment by the nuclear physician is crucial, while quantification programs provide complementary support tools.

As a novelty, initial results showed a possible lateralization of the initial disease involvement, which could be of interest due to its potential usefulness in diagnosing MSA, particularly in identifying early-stage cases. Furthermore, the longitudinal study revealed that the progression of MSA in both striatal nuclei is similar, with one-third dysfunction of the function of the nigrostriatal pathway at 12 months. In this regard, the role of evolutionary SPECT in inconclusive cases is critical, improving diagnostic parameters compared to baseline SPECT and allowing confirmation or exclusion of this pathology in the entirety of that patient group.

Finally, our research focused on the direct comparison between two functional neuroimaging tests, brain [^{123}I]-Ioflupane SPECT and cardiac innervation scintigraphy with [^{123}I]-MIBG. Both techniques have proven effective in the diagnosis of MSA without a clear superiority of one over the other, so both should be considered for an accurate diagnosis. Additionally, as a novelty, we have proposed optimal cut-offs in the quantitative analysis of both explorations, highlighting the fact that the late heart-mediastinum index in [^{123}I]-MIBG scintigraphy shows a direct relationship with the risk of developing MSA.

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I. INTRODUCCIÓN

ANTECEDENTES HISTÓRICOS

Al inicio del siglo XX, en el año 1900, dos autores, Dejerine y Thomas, introdujeron el término de atrofia olivopontocerebelosa para describir una forma de síndrome cerebeloso que ocurría de forma esporádica y con inicio tardío, además de estar acompañada de parkinsonismo y disautonomía (1).

En 1925, Bradbury y Eggleston reportaron una casuística de tres pacientes afectos por esta entidad, describiendo por primera vez la hipotensión ortostática como manifestación de insuficiencia autonómica. Con ello, este cuadro pasó a conocerse como síndrome Bradbury-Eggleston, actualmente denominado fallo autonómico puro (2).

En 1960, Shy y Drager describieron pacientes con clínica autonómica consistente en hipotensión ortostática, impotencia y alteración urinaria, que posteriormente desarrollaban trastorno de la marcha, temblores y fasciculaciones (3). También se notificaron los primeros casos de un síndrome parkinsoniano rígido-acinético predominantemente asimétrico (4,5).

En 1969, Graham y Oppenheimer introdujeron el término atrofia multisistémica (AMS) para combinar la degeneración estriato-nígrica, la ataxia olivo-pontocerebelosa esporádica y el síndrome de Shy-Drager. Afirmaban que, en realidad, eran diferentes manifestaciones de una misma enfermedad (6).

Pero fue 20 años después, en 1989, cuando se describieron por primera vez las inclusiones citoplasmáticas en las células gliales cerebrales de pacientes afectos de AMS, independientemente de la forma clínica de presentación (7). La comprobación de la presencia abundante de estas inclusiones en todos los subtipos clínicos de AMS contribuyó al reconocimiento del término propuesto por Graham y Oppenheimer, ya que debía tratarse, en efecto, de una entidad única caracterizada por degeneración neuronal multisistémica e inclusiones oligodendrogliales (6).

Este descubrimiento llevó, a finales de la década de los 90, al reconocimiento de la AMS como una α-sinucleinopatía. Paralelamente, se fueron introduciendo los criterios diagnósticos que permiten la identificación de esta entidad (8–10), lo que, en ocasiones, resulta ciertamente difícil, como se comentará posteriormente.

DEFINICIÓN

La AMS es un proceso degenerativo y rápidamente progresivo del sistema nervioso central (SNC) y autónomo (SNA). Debuta en la edad adulta, con una incidencia esporádica, provocando limitaciones generales crecientes, que implican una discapacidad severa a medio plazo y aboca al fallecimiento en un periodo temporal inferior a 10 años (11,12).

EPIDEMIOLOGÍA

Se estima una incidencia mundial de 0,6-0,7 casos por cada 100.000 personas al año, con rangos que pueden oscilar entre un mínimo y un máximo, respectivamente, de 0,1-3 casos por 100.000 personas y año (13,14). Los datos recogidos hasta la fecha indican que la incidencia aumenta conforme la edad de los pacientes, encontrándose situaciones de 3 casos/100.000 habitantes año en mayores de 50 años y de 12 casos/100.000 habitantes año en mayores de 70 años (14).

La prevalencia se sitúa en un rango de 2-5 casos por 100.000 habitantes, pudiendo alcanzar en personas mayores de 40 años, 7,8 casos cada 100.000 habitantes (14,15). No obstante, se estima que hasta un 10% de los pacientes con clínica de parkinsonismo podrían tener una AMS subyacente, lo que elevaría estos datos hasta los 16,4 casos por 100.000 habitantes (16).

En la actualidad, no se conocen factores de riesgo ni factores protectores para la AMS. Encontramos resultados dispares en la literatura sin una clara relación con los agentes ambientales reportados (17). Se trata de una enfermedad esporádica, aunque existen casos descritos con una probable asociación familiar de herencia autosómica recesiva (14,18–20). La edad media de inicio oscila entre los 54 y los 60 años (21–25).

Esta entidad afecta de forma similar a varones y mujeres, sin predilección racial. Sin embargo, se diagnostican de 2 a 9 veces más hombres que mujeres, y se

cree que esto se debe a la mayor demanda de consulta de éstos refiriendo disfunción eréctil, que es un síntoma precoz propio de esta enfermedad (26,27).

La AMS se puede subdividir, según los síntomas predominantes en el momento de la evaluación diagnóstica inicial en AMS-P si predominan los síntomas parkinsonianos o AMS-C cuando lo hace la afectación cerebelosa. Actualmente, se entiende esta entidad de forma dinámica, de modo que dicha subdivisión puede variar según la evolución clínica del paciente (9). Existe un predominio de AMS-P en Europa y Estados Unidos y de AMS-C en Asia. En España, al contrario que en el resto de los países europeos estudiados, parece existir una mayoría de AMS-C (14,24,28,29).

Actualmente, no se dispone de tratamiento curativo para la AMS, y se estima una supervivencia media de 6 a 9 años desde el diagnóstico (14,25,30).

ETIOPATOGENIA

Se encuentra dentro del grupo de las α-sinucleinopatías, debido a la acumulación de esta proteína, mal plegada, en las inclusiones citoplasmáticas oligodendrogliales y neuronales del SNC y SNA.

A nivel del SNC, estas inclusiones ocurren en la sustancia negra, ganglios basales, núcleo olivar inferior, puente troncoencefálico y células de Purkinje

cerebelosas, correspondientes a los sistemas estriatonígrico y olivopontocerebeloso, respectivamente (16,31).

El SNA también se ve comprometido tanto a nivel supraespinal, incluyendo el núcleo motor dorsal del nervio vago, locus coeruleus y neuronas catecolaminérgicas ventrolaterales del bulbo, como a nivel medular, afectando las columnas intermediolaterales y núcleo de Onuf (16,31).

Se ha considerado que en la AMS coexisten dos procesos degenerativos que ocurren de forma paralalela: 1) el acúmulo de proteínas α-sinucleínas en el núcleo y en el citosol neuronal, el cual origina una neurodegeneración primaria; 2) al mismo tiempo, en las inclusiones citoplasmáticas de las células gliales se produce una degeneración neuronal secundaria (11).

La proteína α-sinucleína está codificada por el gen *SNCA* localizado en el brazo largo de cromosoma 4 (Cr4q22.1). Su acumulación excesiva en forma de oligómeros o conglomerados fibrilares en las distintas organelas neuronales induce citotoxicidad. Se ha comprobado que estos oligómeros tienden a formas poros en las membranas celulares ricas en cardiolipinas, como ocurre a nivel mitocondrial. Además, la interacción con otras proteínas clave, como la proteína tau, provocan a su vez estructuras proteicas aberrantes relacionadas con procesos neurodegenerativos. Por esta razón, en la actualidad la AMS se incluye en las α-sinucleinopatías, junto con la enfermedad de Parkinson (EP), el Fallo Autonómico Puro y la demencia de cuerpos de Lewy (DCL) (32,33).

Existen evidencias de que la α-sinucleína puede comportarse de forma similar a una enfermedad priónica, ya que se ha comprobado que la inoculación en ratones transgénicos de muestras cerebrales procedentes de pacientes afectos de AMS provoca fenómenos de agregación y propagación de la α-sinucleína, además de una infección fenotípicamente similar a la AMS. En este sentido, existen indicios que apoyan que una respuesta temprana al estrés celular puede preceder al proceso neurodegenerativo. No obstante, el mecanismo molecular íntimo es aún desconocido (34).

Estos cambios a nivel celular y tisular ocurrirían con años de anterioridad al inicio de los síntomas. Los datos apuntan a la existencia de una correlación directa entre la densidad y extensión de estas modificaciones neuropatológicas, y la duración y severidad de la enfermedad. Todos estos hallazgos anatomopatológicos, en las localizaciones descritas, permiten proporcionar el diagnóstico definitivo (8).

CLÍNICA

El rasgo distintivo de esta enfermedad es la afectación, de forma variable y en cualquier combinación, de los sistemas estriato-nígrico, olivopontocerebeloso, autonómico y corticoespinal, junto con la ausencia de respuesta al tratamiento con levodopa (11).

La afectación de la vía neuronal estriato-nígrica se caracteriza por el desarrollo del síndrome parkinsoniano, el cual se manifiesta con temblor, bradicinesia/rigidez e inestabilidad postural. El temblor predominante en la AMS es de acción y postural, espasmódico e irregular y, en menor frecuencia, se presenta temblor en reposo (22).

La lentitud en los movimientos, en mayor o menor medida (acinesia o bradicinesia), junto con la rigidez, empeoran de forma rápidamente progresiva a medida que avanza la enfermedad. Son características las caídas debidas a la inestabilidad postural, las cuales suelen preceder a los síntomas motores. Todo ello provoca a medio plazo anomalías posturales como la flexión severa del tronco (camptocormia) y la anteriorización de la cabeza (antecollis) (35–37).

En menor frecuencia, se pueden presentar distonías orofaciales o discinesias, que en ocasiones recuerdan a la risa sardónica (expresión de sonrisa distorsionada por espasmos involuntarios de la musculatura facial, típica de pacientes con infección por *Clostridium tetani*) o al síndrome de Pisa, consistente en una distonía axial subaguda que provoca la flexión lateral severa de la cabeza y el cuello, así como la rotación axial del tronco. Además, la extensión de la degeneración a nivel putaminal está directamente implicada con la ausencia de respuesta adecuada al tratamiento con levodopa (38).

La afectación del sistema olivopontocerebeloso se caracteriza por desarrollar ataxia de la marcha y de las extremidades, disartria atáxica, disdiadococinesia y

habla escándida. Así mismo, se pueden desarrollar anomalías oculares como nistagmo con la evocación de la mirada y dismetría (35).

La neurodegeneración del sistema corticoespinal también es frecuente en esta enfermedad, aunque su afectación no se considera factor determinante en los criterios diagnósticos actuales (10). Dentro de los signos piramidales propios de los pacientes afectos de AMS, se encuentra la respuesta plantar extensora (8,9).

Los mecanismos más frecuentemente implicados en el desarrollo de los síntomas autonómicos (disautonomía) están relacionados directamente con el núcleo pontino de la micción y el núcleo de Onuf a nivel de la médula espinal sacra. Por un lado, se produce una pérdida en la entrada de señal inhibitoria en el centro pontino de la micción, provocando hiperreflexia del músculo detrusor; y, por otro lado, se produce pérdida de neuronas del factor liberador de corticotropina en el área pontina de la micción y en la vejiga. Por todo ello, es típico encontrar alteraciones urinarias como incontinencia, nicturia, urgencia miccional y polaquiuria. El daño severo del núcleo de Onuf en la médula espinal sacra provoca atonía vesical y disfunción eréctil en los hombres (39,40).

La pérdida de neuronas catecolaminérgicas del área C1 de la médula ventrolateral se manifiesta por una variabilidad severa en la presión arterial y en la frecuencia cardíaca, llegando incluso a hipotensión ortostática, síncope o hipotensión posprandial (39).

La pérdida de neuronas colinérgicas mesopontinas junto con la degeneración a nivel del locus ceruleus, preservándose las del rafe rostral, pueden contribuir al desarrollo del Trastorno de Conducta del Sueño REM (TCSR), típicamente asociado a fases prodrómicas de otras α-sinucleinopatías (41,42). Otras manifestaciones secundarias a la afectación troncoencefálica son las anomalías respiratorias como el estridor laríngeo y la disfunción en la regulación de la temperatura corporal (35,39,43).

DIAGNÓSTICO

Debido a las peculiaridades anteriormente descritas, en ocasiones resulta difícil establecer el diagnóstico de la entidad. Éste se realiza con relación a una serie de factores:

CRITERIOS DIAGNÓSTICOS.

La primera conferencia de consenso acerca del diagnóstico de la AMS tuvo lugar en 1998 y se resume en la tabla 1. En ella, se describió la AMS como una enfermedad donde se afectan cuatro dominios: 1) sistema autonómico-urinario; 2) parkinsonismo; 3) cerebelo; y 4) tracto corticoespinal. Además, para considerar que un dominio está afecto, deben cumplirse una serie de manifestaciones clínicas particulares. Ello permite clasificar la enfermedad según

el grado de certeza diagnóstica en tres categorías: **posible, probable** o **definitiva.**

- **Posible:** debe cumplir un criterio (dominio), más dos manifestaciones clínicas de dos dominios diferentes.

- **Probable:** afectación del sistema autonómico-urinario, más ausencia de respuesta a levodopa o clínica cerebelosa.

- **Definitiva:** confirmación anatomopatológica de inclusiones citoplasmáticas ricas en α-sinucleína, junto con neurodegeneración nigroestriatal u olivopontocerebelosa (8).

Finalmente, también se establecen criterios de exclusión en función de la historia clínica, la exploración física, y las pruebas de laboratorio, que se resume en la tabla 2 (8).

Tabla 1. Resumen de los criterios diagnósticos según consenso de 1998.

Dominios, características clínicas y criterios para el diagnóstico de AMS
Disfunción autonómica y urinaria
A) Manifestaciones clínicas 1. Hipotensión ortostática (20 mmHg TA sistólica o 10 mmHg TA diastólica). 2. Incontinencia urinaria o vaciado vesical incompleto. B) Criterio de fallo autonómico o disfunción urinaria en AMS: hipotensión ortostática (30 mmHg sistólica o 15 mmHg diastólica) o alteración urinaria (vaciado vesical involuntario, persistente, disfunción eréctil).
Parkinsonismo.
A) Manifestaciones clínicas: 1. Bradicinesia 2. Rigidez 3. Inestabilidad postural (no causada por alteración vestibular, propioceptiva, visual o cerebelosa). 4. Temblor. B) Criterio de parkinsonismo en AMS: Bradicinesia más al menos otra de las manifestaciones clínicas descritas.
Disfunción cerebelosa.
A) Manifestaciones clínicas: 1. Ataxia de la marcha. 2. Disartria atáxica 3. Ataxia de extremidades. 4. Nistagmo sostenido evocado por la mirada. B) Criterio para disfunción cerebelosa en AMS: ataxia de la marcha más al menos otra manifestación clínica.
Alteración del tracto corticoespinal (Su afectación no es criterio diagnóstico)**.**
A) Manifestaciones clínicas: • Respuesta plantar extensora con hiperreflexia.

Tabla 2. Criterios de exclusión para el diagnóstico de AMS.

Historia clínica
• Inicio de sintomatología antes de los 30 años. • Antecedentes familiares de un trastorno similar. • Enfermedad sistémica u otra causa que explique los síntomas. • Alucinaciones no relacionadas con la medicación.
Exploración física
• Criterios de demencia por DSM*. • Gran enlentecimiento de los movimientos sacádicos verticales o parálisis supranuclear de la mirada vertical (>50%). • Disfunción cortical (parietal o afasia) o síndrome de la mano ajena.
Pruebas complementarias
• Evidencias metabólicas, genéticas o de imagen compatibles con una causa alternativa de la clínica.

*DSM: 'Diagnostic and Statistical Manual of Mental Disorders'. Manual Diagnóstico y Estadístico de los Trastornos Mentales de la Asociación Americana de Psiquiatría.

El avance en el conocimiento de la enfermedad, así como de las distintas pruebas diagnósticas disponibles, llevó a la celebración de la segunda conferencia de consenso en 2007, donde se actualizaron los criterios diagnósticos, incluyendo por primera vez las pruebas de neuroimagen (9).

En esta conferencia se reafirman las tres categorías diagnósticas (probable, posible y definitiva) así como los subtipos clínicos de AMS según afectación

predominante (AMS-P y AMS-C, respectivamente, según dicho predominio sea parkinsoniano o cerebeloso) añadiendo la particularidad de que esta nomenclatura puede cambiar según la evolución de la propia enfermedad. Además, se actualizó la definición para AMS posible.

- **AMS posible:** debe tratarse de una enfermedad esporádica y progresiva, de inicio en adultos, donde además de la afectación parkinsoniana o cerebelosa, cumpla una manifestación clínica de disautonomía y otra característica adicional (clínica o de imagen).

Estas nuevas características adicionales para el diagnóstico de AMS posible se exponen en la tabla 3 (9).

Tabla 3. Características adicionales para diagnóstico de AMS posible.

Posible AMS-P o AMS-C
• Signo de Babinski positivo con hiperreflexia. • Estridor laríngeo.
Posible AMS-P
• Parkinsonismo rápidamente progresivo. • Pobre respuesta a tratamiento con levodopa. • Inestabilidad postural a los tres años del inicio de la clínica motora. • Ataxia de la marcha o de las extremidades, disartria cerebelosa o alteración oculomotora de origen cerebeloso. • Disfagia a los cinco años del inicio de la clínica motora. • Atrofia en la resonancia magnética (RMN) del núcleo putamen, pedúnculo cerebeloso medio, protuberancia o cerebelo. • Hipometabolismo putaminal, troncoencefálico, o cerebeloso en PET con 2-[^{18}F]FDG.
Posible AMS-C
• Parkinsomismo (rigidez y bradicinesia). • Atrofia en la resonancia magnética del putamen, pedúnculo cerebeloso medio o protuberancia. • Hipometabolismo putaminal en PET con 2-[^{18}F]FDG. • Denervación dopaminérgica nigroestriatal presináptica en técnicas SPECT o PET

PET: tomografía de emisión de positrones. 2-[^{18}F]FDG: fluordesoxiglucosa. SPECT: tomografía computarizada por emisión de fotón único.

La presencia de estridor laríngeo posee un alto valor predictivo positivo (VPP) para el diagnóstico de AMS y representa un síntoma de mal pronóstico (29,44).

Finalmente, también se vieron modificadas las características que pueden apoyar o excluir el diagnóstico de AMS, conociéndose como banderas rojas (‘red flags’ en inglés), las cuales se muestran en tabla 4 (9).

Tabla 4. Banderas rojas (‘red flags’) en el diagnóstico de AMS.

Características compatibles
• Distonía orofacial. • Antecollis desproporcionada. • Camptocormia y/o síndrome de Pisa. • Contracturas en manos o pies. • Signos inspiratorios. • Disfonía severa. • Disartria severa. • Aparición o aumento de ronquidos durante el sueño. • Manos y pies fríos. • Risa o llanto patológicos. • Temblor de acción o postural mioclónico espasmódico.
Características que no apoyan el diagnóstico
• Temblor de reposo clásico de “pill-rolling”. • Neuropatía clínicamente significativa. • Alucinaciones no provocadas por fármacos. • Comienzo a partir de los 75 años. • Historia familiar de ataxia o parkinsonismo. • Demencia diagnosticada según clasificación DSM-IV. • Lesiones en la sustancia blanca que sugieran esclerosis múltiple.

En ese mismo año, el Grupo Europeo de Estudio de la AMS (EMSA-SG, por sus siglas 'European MSA Study Group') publicó un análisis de las "red flags" más frecuentes en una cohorte formada por 57 pacientes con AMS-P probable y 116 pacientes con EP, tras un período de seguimiento de dos años. Aquellas banderas rojas que mostraron una especificidad superior al 95% y una mayor frecuencia en pacientes afectos de AMS-P respecto EP se exponen en la tabla 5 (45).

Tabla 5. Banderas rojas para AMS-P según la EMSA-SG.

Inestabilidad precoz.
Progresión rápida
Posturas anormales Incluye: Síndrome Pisa, antecollis severa y/o contracturas de manos y pies.
Disfunción bulbar Incluye: disfonía severa, disartria y/o disfagia.
Alteración respiratoria. Incluye: estridor y/o suspiros inspiratorios.
Incontinencia emocional. Incluye: llanto y/o risa inapropiados.

La combinación de al menos dos categorías apoya el diagnóstico (con sensibilidad y especificidad altas) de AMS-P probable, en comparación con pacientes con EP.

Posteriormente, en una cohorte de 59 pacientes, se analizaron estos nuevos criterios de consenso con respecto a los antiguos y se obtuvo una mejora en la precisión del diagnóstico clínico para la categoría de AMS posible, en comparación con los antiguos criterios de consenso (46).

Se han propuesto características clínicas que permitan identificar una posible AMS prodrómica, entre las que destacarían el TCSR y la disfunción autonómica, aunque actualmente no existen unos criterios de consenso en ese sentido (47).

Es interesante conocer aquellas pruebas diagnósticas que permitirían identificar y diagnosticar pacientes con AMS en ausencia de estudio histopatológico. En este contexto, destacan las pruebas de imagen actualmente disponibles, como herramienta diagnóstica no invasiva.

Recientemente, se han revisado los criterios diagnósticos de la AMS por parte de la Sociedad de Trastornos del Movimiento (10). En este trabajo, plantean establecer tres categorías diagnósticas que sustituyen a las clásicas AMS posible y AMS probable. Las nuevas categorías son: AMS clínicamente establecida, AMS clínicamente probable y AMS posible prodrómica, cuyas características principales se resumen en las tablas 6, 7, 8 y 11, respectivamente. La categoría AMS definitiva pasa a conocerse como AMS neuropatológicamente establecida, pero tanto su definición como sus criterios permanecen sin variación (10).

En estos criterios, las pruebas de neuroimagen, gammagrafía con [^{123}I]-MIBG y PET con 2-[^{18}F]FDG constituyen biomarcadores de apoyo que sugieren AMS, pero no son necesarios para el diagnóstico. Se omite la SPECT con [^{123}I]-Ioflupano.

Tabla 6. Criterios diagnósticos para AMS clínicamente establecida.

Características esenciales
• Enfermedad esporádica, progresiva y de inicio en la edad adulta (>30 años).
Características clínicas básicas
1. Disfunción autonómica. Para ello se requiere al menos una de las siguientes características: ⇒ Dificultad miccional inexplicable, con un volumen de residuo vesical postmiccional (RVP) ≥100 ml. ⇒ Incontinencia urinaria de urgencia no explicada por otras causas. ⇒ Hipotensión ortostática neurogénica: reducción de la presión arterial en los tres minutos siguientes a la bipedestación de ≥20 mmHg sistólica o ≥10 mmHg diastólica. 2. Junto con al menos una de las siguientes: ⇒ Síndrome parkinsoniano con escasa respuesta a la levodopa. ⇒ Síndrome cerebeloso. Al menos dos: ataxia de la marcha, ataxia de las extremidades, disartria cerebelosa, disfunción oculomotora.
Características clínicas de apoyo (motoras o no motoras).
Al menos dos. Recogidos en tabla 9
RMN cerebral
Al menos una de las resumidas en la tabla 10.
Ausencia de alguno de los criterios de exclusión (tabla 10).

Tabla 7. Criterios diagnósticos para AMS clínicamente probable.

Características esenciales
• Enfermedad esporádica, progresiva y de inicio en la edad adulta (>30 años).
Características clínicas básicas (Se requieren al menos dos)
• Disfunción autonómica. Para ello se requiere al menos una de las siguientes características: ⇒ Dificultades miccionales inexplicables con RVP de cualquier volumen. ⇒ Incontinencia urinaria de urgencia no explicada por otras causas. ⇒ Hipotensión ortostática neurogénica definida como una reducción de la presión arterial en los 10 minutos siguientes a la bipedestación de ≥20 mmHg sistólica o ≥10 mmHg diastólica. • Síndrome parkinsoniano. • Síndrome cerebeloso. Al menos uno: ataxia de la marcha, ataxia de las extremidades, disartria cerebelosa, disfunción oculomotora.
Características clínicas de apoyo (motoras y no motoras).
Al menos una de las resumidas en la tabla 9
RMN cerebral
No requiere.
Ausencia de alguno de los criterios de exclusión presentes en la tabla 10.

Tabla 8. Características clínicas de apoyo para el diagnóstico de AMS clínicamente establecida y AMS clínicamente probable.

Clínica motora	Clínica no motora
• Progresión rápida de la enfermedad en los tres años siguientes a la aparición de clínica motora. • Inestabilidad postural (moderada a grave) en los tres años siguientes a la aparición del trastorno motor. • Distonía craneocervical inducida o exacerbada por levodopa en ausencia de discinesia de las extremidades. • Deterioro grave del habla en los tres años siguientes a la aparición del trastorno motor. • Disfagia grave en los tres años siguientes a la aparición del trastorno motor. • Signo de Babinski no explicado por otras causas. • Temblor mioclónico postural o cinético (minipolimioclonía). • Deformidades posturales	• Estridor • Suspiros inspiratorios • Manos y pies descoloridos por el frío • Disfunción eréctil (por debajo de los 60 años para clínicamente probable) • Risa o llanto patológicos.

Tabla 9. Características de imagen por RMN para el diagnóstico de AMS clínicamente establecida.

Para AMS-P	Para AMS-C
• Atrofia del putamen (y disminución de la señal en secuencias sensibles al hierro), pedúnculo cerebeloso medio, puente de Varolio y/o cerebelo; • Signo “Hot cross bun”. • Aumento de la difusión en putamen y/o pedúnculo cerebeloso medio.	• Atrofia del putamen (y disminución de la señal en secuencias sensibles al hierro), estructuras infratentoriales (puente de Varolio y pedúnculo cerebeloso medio). • Signo “Hot cross bun”. • Aumento de la difusión en putamen.

Tabla 10. Criterios de exclusión para el diagnóstico de AMS clínicamente establecida y AMS clínicamente probable.

• Respuesta beneficiosa sustancial y persistente a los medicamentos dopaminérgicos • Anosmia inexplicable en pruebas olfativas. • Cognición fluctuante con variación pronunciada de la atención y el estado de alerta y deterioro precoz de las capacidades visuoperceptivas. • Alucinaciones visuales recurrentes no inducidas por fármacos en los 3 años siguientes al inicio de la enfermedad. • Demencia según el DSM-V en los 3 años siguientes al inicio de la enfermedad. • Parálisis supranuclear de la mirada descendente o enlentecimiento de las sacadas verticales. • Hallazgos en la resonancia magnética cerebral que sugieran un diagnóstico alternativo (p. ej., PSP, esclerosis múltiple, parkinsonismo vascular, enfermedad cerebelosa sintomática, etc.). • Documentación de una enfermedad alternativa (similar a la AMS, incluida la ataxia y el parkinsonismo genéticos o sintomáticos) que se sepa que produce insuficiencia autonómica, ataxia o parkinsonismo y que pueda estar relacionada con los síntomas del paciente.

Tabla 11. Criterios diagnósticos para AMS clínicamente prodrómica.

Características esenciales
• Enfermedad esporádica, progresiva y de inicio en la edad adulta (>30 años).
Características clínicas básicas (Se requieren al menos dos)
• Disfunción autonómica. Para ello se tiene que dar al menos una de las siguientes características: ⇒ Dificultades miccionales inexplicables con RVP de cualquier volumen. ⇒ Incontinencia urinaria de urgencia no explicada por otras causas. ⇒ Hipotensión ortostática neurogénica definida como una reducción de la presión arterial en los 10 minutos siguientes a la bipedestación de ≥20 mmHg sistólica o ≥10 mmHg diastólica. • Síndrome parkinsoniano. • Síndrome cerebeloso. Al menos uno: ataxia de la marcha, ataxia de las extremidades, disartria cerebelosa, disfunción oculomotora.
Características clínicas de apoyo (motoras o no motoras).
Al menos una de las resumidas en la tabla 9
RMN cerebral
No requiere.
Ausencia de alguno de los criterios de exclusión presentes en la tabla 10. También es criterio de exclusión la inervación miocárdica anormal en la gammagrafía con [^{123}I]-MIBG

Estudio SPECT (tomografía de emisión de fotón único o 'Single Photon Emission Computed Tomography') **de transportadores presinápticos de dopamina.**

Se trata de una prueba de imagen que permite, de una forma "in vivo" y no invasiva, detectar cambios a nivel molecular que conllevan o conllevarán una afectación en la función dopaminérgica cerebral, concretamente de la vía nigroestriada, a nivel del terminal presináptico.

En pacientes con EP o parkinsonismos atípicos (como la AMS), a nivel presináptico se han descrito notables reducciones en el número de transportadores vesiculares de monoaminas tipo 2 (VMAT2), transportadores de dopamina (DAT) y aminoácido L-aromático descarboxilasa (L-AAAD) (48).

Dicho SPECT cerebral permite visualizar la densidad de los transportadores presinápticos de dopamina a nivel de ambos núcleos estriados, permitiendo diferenciar una enfermedad degenerativa de una no degenerativa (como parkinsonismos secundarios a fármacos, o temblores esenciales). Para ello, se utilizan radiotrazadores derivados del tropano (análogos de la cocaína), como el [^{123}I]-Ioflupano, [^{123}I]N-ω-fluoropropil-2β-carbometoxi-3β-(4-iodofenil) nortropano (FP-CIT), que se une de manera selectiva a los transportadores de dopamina del terminal presináptico. Este radiofármaco también posee afinidad a los transportadores de serotonina, aunque en menor medida, con una ratio de 2,8:1

(49). Por ello, en pacientes con enfermedad avanzada donde existe menor expresión de transportadores de dopamina y en pacientes con tratamiento con inhibidores selectivos de la recaptación de serotonina (ISRS), se puede observar una presencia más relevante de actividad inespecífica cortical (actividad de fondo).

Hasta la actualidad, se ha demostrado ampliamente el valor y la utilidad del SPECT de transportadores presinápticos de dopamina en el diagnóstico de la EP, así como en los síndromes parkinsonianos clínicamente inciertos, incluso en estadios iniciales. Detecta cambios en la captación estriatal en sujetos con síntomas premotores de EP, así como en pacientes asintomáticos portadores de mutaciones genéticas de EP familiar (49). En consecuencia, ante un resultado patológico, el médico confía en una alta probabilidad diagnóstica de parkinsonismo (50).

Las indicaciones actuales (51) son:

- Diagnóstico diferencial entre síndrome parkinsoniano neurodegenerativo y temblor esencial (TE).
- Distinguir entre DCL y otras demencias como la enfermedad de Alzheimer.
- Diagnóstico diferencial entre parkinsonismo con déficit de dopamina presináptica (como la EP) y parkinsonismos secundarios (psicógeno, inducido por fármacos, o vascular).
- Detección precoz de síndromes parkinsonianos con afectación presináptica.

Los falsos positivos en este SPECT, normalmente por interferencia farmacológica (sustancias antidopaminérgicas) o artefactos en la realización del

estudio, son poco frecuentes. Por otro lado, los falsos negativos son aún más raros, mostrándose en la literatura un valor VPP superior al 90% (49). Se ha descrito que el tratamiento con metilfenidato puede bloquear completamente la captación fisiológica de este radiofármaco, por lo que es importante su retirada antes del estudio (52).

La interpretación de este estudio de imagen consta de una valoración visual, tras el procesado de la imagen y correcta reorientación, donde se visualizan la captación y distribución del radiofármaco en los dos núcleos estriados. Así mismo, la alta expresión de transportadores presinápticos de dopamina, unido a la alta sensibilidad (y, por el contrario, menor resolución) de la imagen adquirida, ofrece una imagen donde se observan, aparentemente fusionados, los núcleos caudado y putamen.

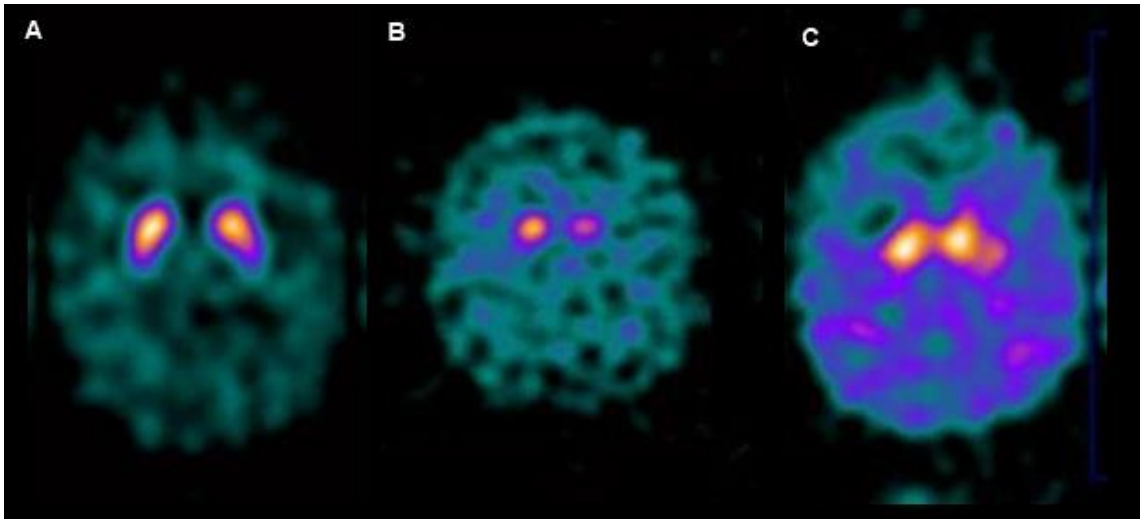

Figura 1. Estudios SPECT [^{123}I]-Ioflupano.

A) Paciente sano. Visualización de captación bilateral, homogénea y simétrica a nivel de ambos núcleos estriados (caudados y putámenes). **B)** Paciente con EP.

Se observa hipocaptación del radiotrazador en ambos núcleos estriados, con una distribución asimétrica de predominio izquierdo y con anulación de núcleos putámenes. **C)** Paciente con parkinsonismo atípico. Se aprecia hipocaptación estriatal bilateral, relativamente simétrica, con anulación de núcleos putámenes y significativa presencia de actividad inespecífica cortical (fondo).

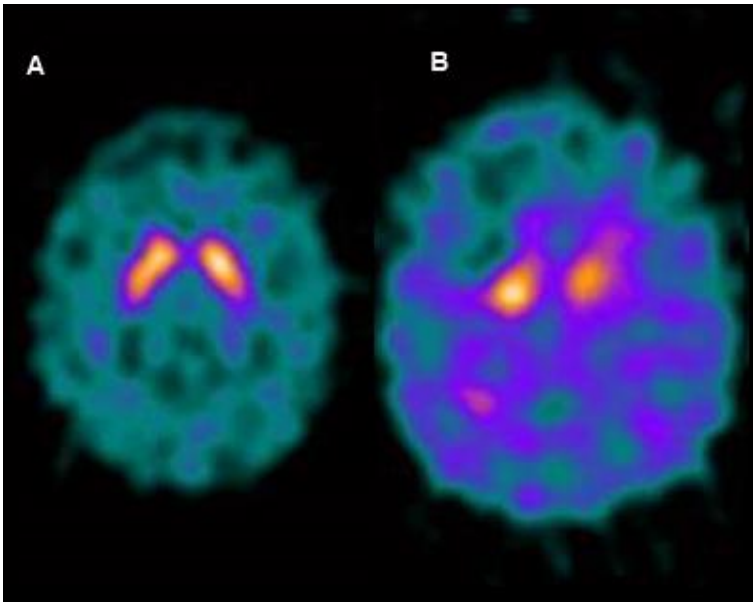

Figura 2. SPECT [^{123}I]-Ioflupano en paciente con AMS-C.

A) Estudio basal ante la sospecha clínica inicial. **B)** Estudio evolutivo a los 12 meses que muestra una marcada pérdida neuronal dopaminérgica de la vía nigroestriada.

Hasta el momento presente, no se ha demostrado que sea posible discriminar de forma fiable entre la EP y la AMS mediante la obtención de imágenes con su patrón característico de pérdida de la función dopaminérgica presináptica. Los casos de AMS muestran una pérdida asimétrica de la función del núcleo putamen

similar a la EP idiopática, pero la cabeza del núcleo caudado tiende a estar más afectada (53). Otros estudios han obtenido una disminución más severa de la función dopaminérgica presináptica en ambos núcleos estriados, de forma rápida y simétrica en sujetos con AMS respecto a EP (54).

Como herramienta de apoyo al análisis visual y para ayudar al especialista en medicina nuclear en la interpretación del estudio, surgieron distintas opciones de software que permiten establecer índices de captación. Dichos índices sirven para evaluar la densidad de transportadores de dopamina en cada uno de los núcleos caudado y putamen, o en ambos, al compararlos con el área de una región similar en la que no exista una alta expresión de los transportadores de dopamina (región de actividad inespecífica), empleándose habitualmente la región occipital (55).

En este sentido, el análisis consiste en realizar, bien de forma automática, semiautomática o manual, “Regiones de Interés” (ROIs) en las áreas de actividad específica y en el área de actividad inespecífica (lóbulo occipital) para obtener así el índice estriado/occipital (E/0), que resulta de la división entre las cuentas medias (radiactividad media mensurada) de ambas regiones (56).

$$\text{Índice } E/O = \frac{cuentas\ medias\ ROI\ de\ la\ región\ de\ actividad\ específica}{cuentas\ medias\ ROI\ de\ la\ región\ de\ actividad\ inepecífica}$$

Para obtener un resultado global, se realiza la media aritmética entre ambos índices E/O (57).

Se han llevado a cabo diversos estudios comparando los índices obtenidos según la utilización de distintas regiones de actividad inespecífica: mesencéfalo, cerebelo y lóbulo occipital, obteniéndose índices más específicos en ésta última, al ser de las tres regiones la que tiene menor expresión fisiológica de receptores de serotonina (56).

Los softwares disponibles para el análisis semicuantitativo varían entre sí, por lo que en la práctica clínica puede resultar difícil su interpretación si, además, disponemos de más de un estudio de un mismo paciente, sobre todo si está realizado en gammacámaras distintas. A fin de estudiar esta variabilidad, se realizó un estudio que consistió en realizar el análisis semicuantitativo dibujando ROIs predefinidas en morfología y número de píxeles, obtenidos de distintas gammacámaras, obteniendo finalmente resultados transferibles o bioequivalentes entre los diferentes dispositivos. Sobre la imagen resultante de la suma de los 6 cortes axiales más representativos (con mayor captación estriatal en el análisis visual), se trazaron ROIs rectangulares de 250 píxeles para cada núcleo estriado y una ROI rectangular de 350 píxeles para la región occipital (56), como ilustra la siguiente figura (figura 3).

Ejemplos de análisis semicuantitativo, siguiendo el caso anterior de AMS-C (Figuras 3 a 6).

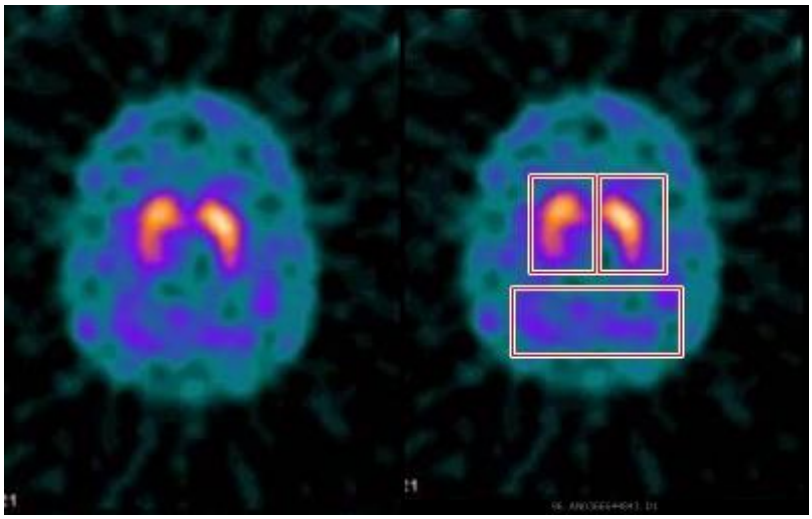

Figura 3. Cuantificación SPECT [^{123}I]-Ioflupano mediante ROIs.

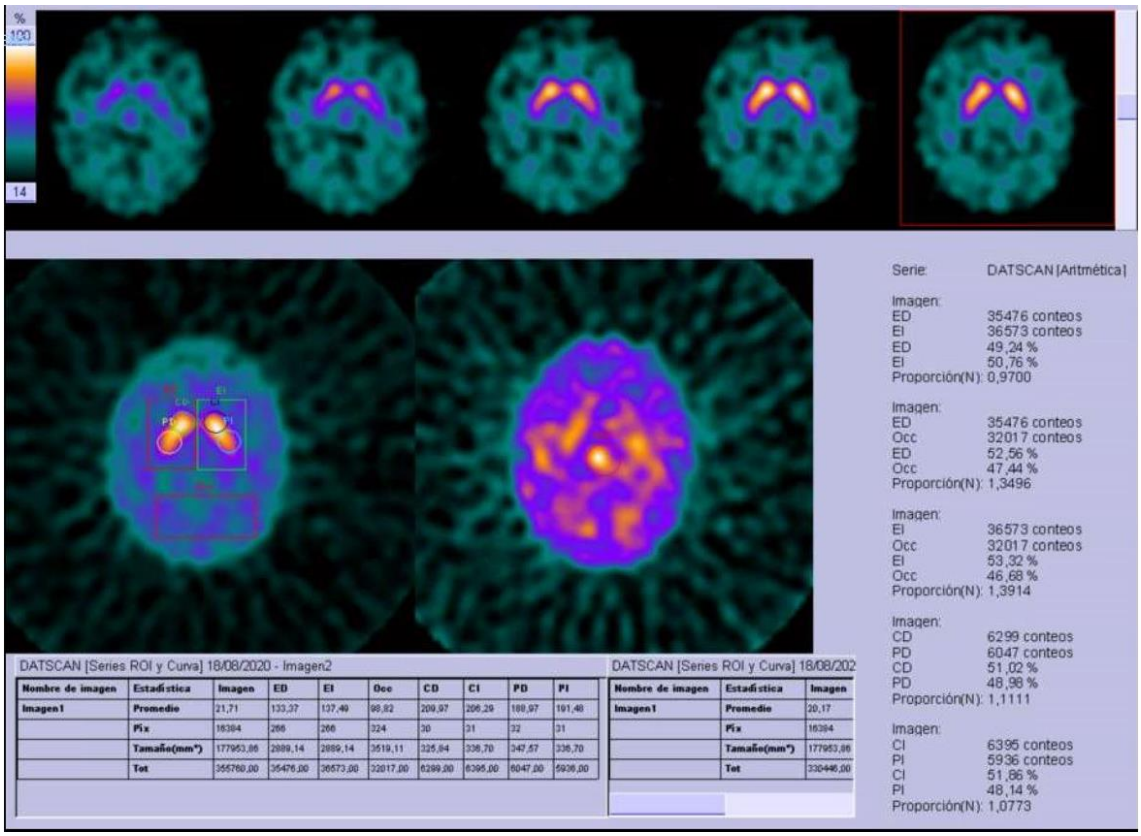

Figura 4. Cuantificación SPECT [^{123}I]-Ioflupano en sujeto sano.

Software de Siemens Healthineers® para la gammacámara modelo Symbia™ (Erlangen, Alemania). Permite realizar de forma semiautomática ROIs tanto de cada núcleo estriado de manera global como individualizada en los núcleos caudado y putamen. Se obtienen los conteos de cada ROI, así como el porcentaje de captación. Para ello, se toman como referencia áreas de actividad inespecífica el lóbulo occipital y el mesencéfalo.

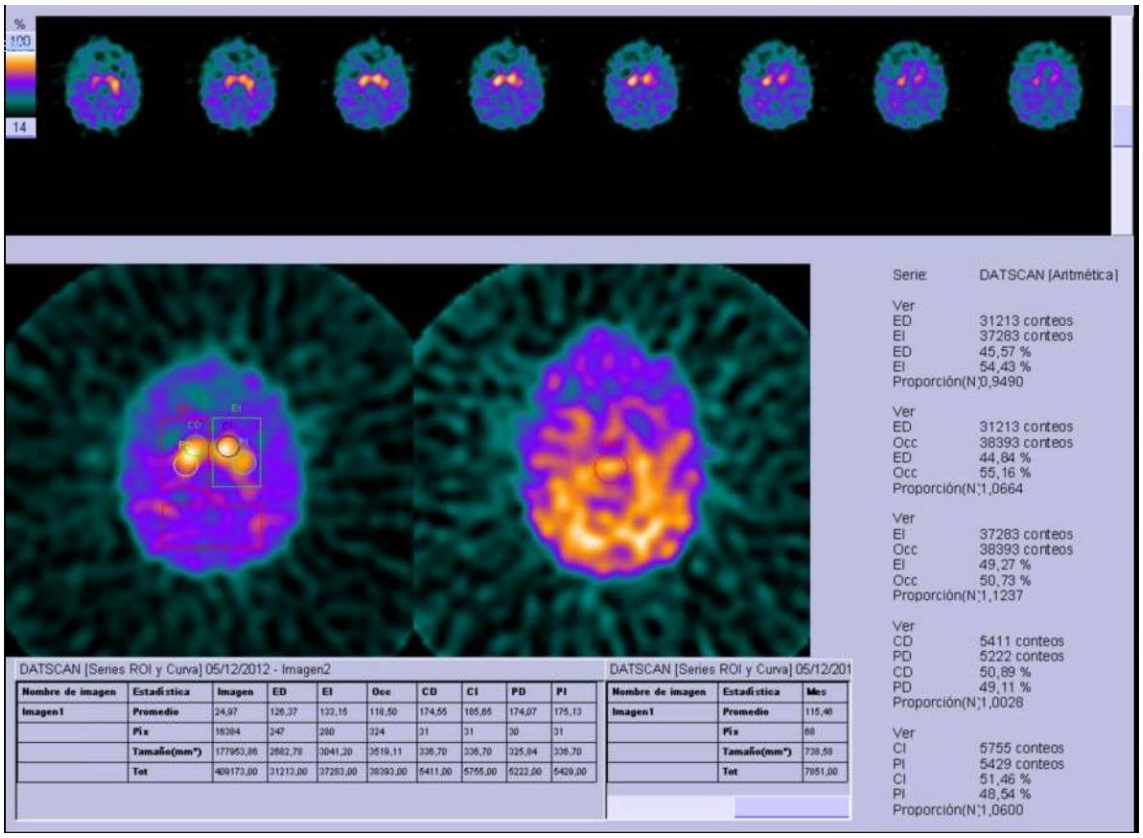

Figura 5. Cuantificación SPECT [^{123}I]-Ioflupano en paciente con AMS-P.

Software de Siemens Healthineers® para la gammacámara mencionada anteriormente. El resultado concuerda con el análisis visual de hipocaptación estriatal bilateral, con predominio derecho. También se observa un aumento de la actividad cortical inespecífica (fondo).

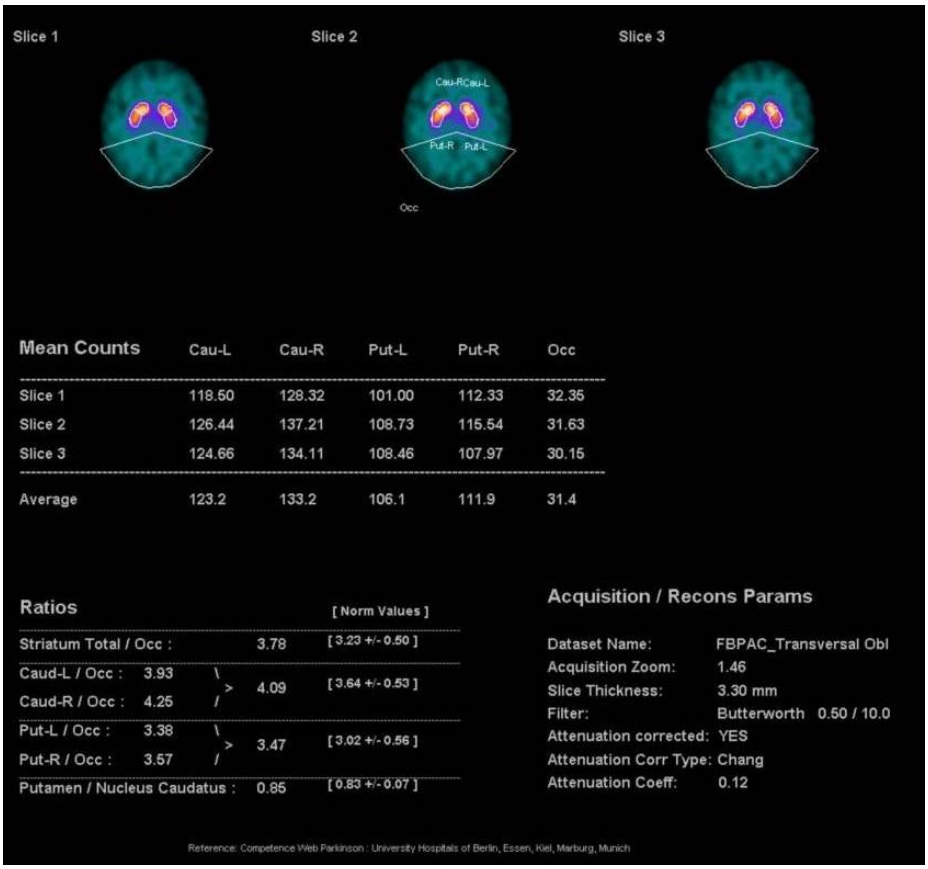

Figura 6. Cuantificación SPECT [^{123}I]-Ioflupano en paciente con TE. Software de GE Healthcare® para la gammacámara modelo Infinia^{TM} Hawkeye (General Electric, EEUU). El estudio es normal, con datos que superan el punto de corte considerado patológico según la base de datos, teniendo en cuenta la edad y el sexo del paciente.

Existen evidencias de que un resultado patológico en el análisis semicuantitativo se relaciona en la EP con una mayor gravedad (medida según la escala unificada de la EP -UPDRS-) y duración de esta enfermedad, además de correlacionarse

positivamente con la presencia de bradicinesia, pero no con rigidez ni temblor (58).

En cuanto a los Parkinson plus, como la parálisis supranuclear progresiva (PSP), degeneración corticobasal (DGCB) y la AMS, los resultados son menos precisos a la hora de diferenciarlos de la EP.

Además, existe disparidad de resultados sobre la utilidad del análisis semicuantitativo en el diagnóstico de los síndromes parkinsonianos, obteniendo algunos estudios un alto rendimiento diagnóstico para diferenciar EP, PSP y DCL, pero no en el caso de AMS (59).

Se han obtenido valores de otro índice de cuantificación diferente al estriado-occipital, el SBR o 'Serotonin Binding Ratio', más bajos en pacientes con EP y AMS con respecto a sujetos control (60). De forma similar, los pacientes con AMS-P y PSP muestran valores inferiores con respecto a EP y AMS-C, lo que podría contribuir al diagnóstico diferencial (61). También se han obtenido resultados que sugieren una disminución más rápida de transportadores presinápticos de dopamina en AMS-P en comparación con EP (62).

La mayor dificultad se encuentra al analizar los subtipos de AMS (AMS-P y AMS-C). En estudios realizados en PET con otro radiotrazador derivado del propano, se encontró que, de forma más específica, los pacientes afectos de AMS-P mostraron una mayor afectación de la vía nigroestriada con respecto a los

pacientes con AMS-C, en los que se observaba un patrón más uniforme. Además, en algunos casos de AMS-C, el estudio resultó normal (63).

Estos datos son congruentes con los primeros estudios de supervivencia, que postulaban un deterioro funcional más rápido en pacientes afectos de AMS-P con respecto a AMS-C (28).

Más recientemente, se ha realizado un metaanálisis en el que se revisaron 35 estudios, incluyendo un total de 356 pacientes con AMS-P, 62 con AMS-C, 204 con PSP y 79 con DCBG. Se obtuvieron valores de densidad de transportadores presinápticos de dopamina a nivel estriatal menores en sujetos con PSP que en los pacientes con EP y AMS-P, así como en pacientes con AMS-P al compararlos con AMS-C (64).

De forma similar, otro trabajo centrado en el análisis semicuantitativo mostró en los pacientes con AMS-P y AMS-C diferentes patrones: marcada hipocaptación y asimetría en AMS-P y valores límite para AMS-C (65).

Otro estudio se elaboró con la finalidad de establecer un patrón específico de afectación en los casos de AMS-C, utilizando el radiotrazador [^{123}I]β-CIT. Se observó una severa pérdida neuronal dopaminérgica en el mesencéfalo y puente, aunque relativamente menor con respecto a AMS-P. Además, la afectación en el núcleo estriado y mesencéfalo en la AMS-C, permitirían el diagnóstico diferencial con otra entidad como la ataxia esporádica de inicio en el adulto (66).

Tras la revisión de los criterios diagnósticos para la AMS en 2008, se incluyó como criterio diagnóstico de AMS-C posible, un resultado positivo de transportadores presinápticos de dopamina en el SPECT. En este sentido, se realizó un estudio para evaluar la contribución de esta técnica cuando no se alcanzan los criterios de consenso. Se obtuvo que el 43% de los pacientes no reunían los requisitos hasta la realización del SPECT. Además, se mostró muy útil en pacientes con enfermedad de menor duración, mientras que un estudio negativo no excluye el diagnóstico de AMS (67).

En la evaluación de 30 pacientes con AMS-C (posible o probable) sin parkinsonismo asociado, se encontraron signos de déficit dopaminérgico nigroestriatal subclínico en el SPECT con [^{123}I]-Ioflupano. No se estableció relación entre dicha afectación y la duración de la enfermedad, ni tampoco correlación con la disfunción cerebelosa ni con la atrofia pontina en la RMN (68).

Dado que un estudio normal no permite excluir el diagnóstico de AMS y que, además, la AMS-C puede mostrar aparente normalidad en la densidad de transportadores presinápticos de dopamina en el análisis visual y/o valores límite en el análisis semicuantitativo, cobra especial relevancia realizar estudios de seguimiento en ambos casos. Todo ello, sumado a la rápida progresión de la AMS, permite controlar su evolución con la realización de SPECT con [^{123}I]-Ioflupano (62).

En este sentido, mientras que la realización de estudios seriados en pacientes con EP no parece estar justificada, sí lo estaría en pacientes con sospecha de

AMS y, especialmente en AMS-C en estadios iniciales (69), aunque estas propuestas no han sido suficientemente contrastadas. De hecho, un artículo más reciente estudió a 7 pacientes con AMS-C, 5 con AMS-P y 18 con EP, concluyendo que el estudio mediante SPECT con trasportadores presinápticos de dopamina y el análisis semicuantitativo mediante SBR, constituyen un marcador fisiopatológico importante que refleja la progresión específica de la enfermedad, así como el subtipo de degeneración dopaminérgica en AMS y EP (70).

Gammagrafía de inervación cardíaca con [^{123}I]-MIBG (metayodobencilguanidina).

Se trata de una prueba de imagen utilizada inicialmente en el campo de la cardiología nuclear, que también tiene como una de sus indicaciones el diagnóstico precoz de las α-sinucleinopatías (EP, DCL).

El fármaco utilizado es un análogo de la guanetidina y de la noradrenalina que se deposita inicialmente en las vesículas presinápticas de las terminaciones nerviosas simpáticas para liberarse posteriormente en respuesta a estímulos específicos. Por tanto, refleja la actividad nerviosa en el miocardio (71). Juega un papel importante en la diferenciación entre EP o DCL y otros parkinsonismos atípicos (AMS, PSP, DCBG), encontrando un resultado patológico en los primeros y normal en los segundos.

En la AMS, además, se ha descrito en algunos estudios una disminución de la actividad adrenérgica cardíaca, que podría solaparse con la EP, aunque normalmente suele ser de menor cuantía, ya que el desarrollo de disautonomía se debe principalmente a una alteración presináptica, estando las fibras adrenérgicas postsinápticas respetadas (16,53,65,72). Además, esta reducción es más simétrica en la AMS con respecto a pacientes con EP (51).

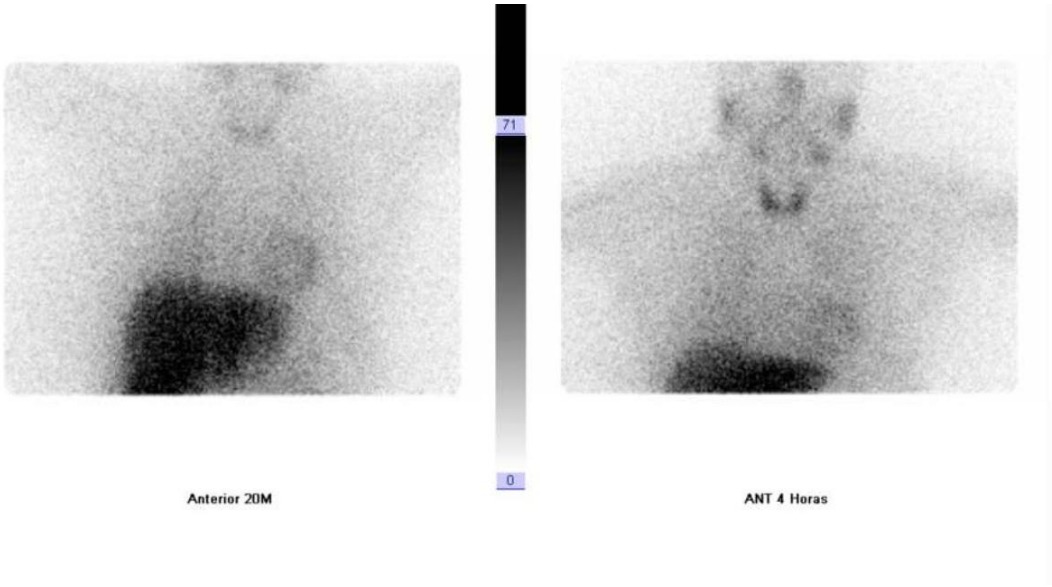

Figura 7. Gammagrafía de inervación cardíaca con [^{123}I]-MIBG en AMS. Imágenes estáticas en proyección anterior de tórax: precoz (izquierda), a los 20 minutos tras administración del radiofármaco, y tardía (derecha) a las 4 horas postinyección. El estudio muestra una disminución significativa en la inervación adrenérgica cardíaca, que permanece estable al final del estudio.

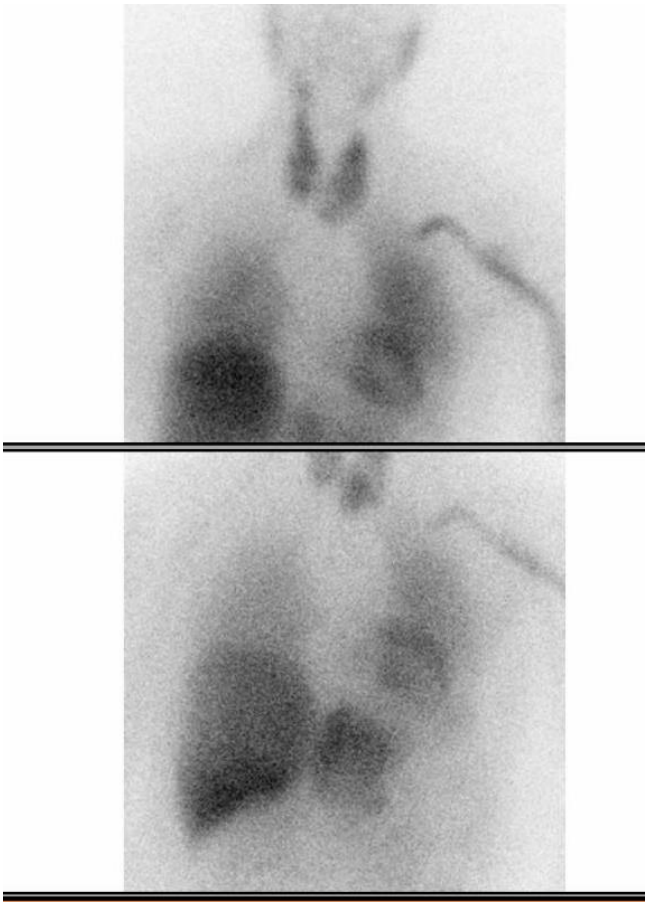

Figura 8. Gammagrafía de inervación cardíaca con [^{123}I]-MIBG en paciente con parkinsonismo plus.

Imagen precoz (superior) e imagen tardía (inferior). Se observa una captación conservada en el miocardio que permanece de forma significativa al final del estudio, lo que descarta EP y DCL.

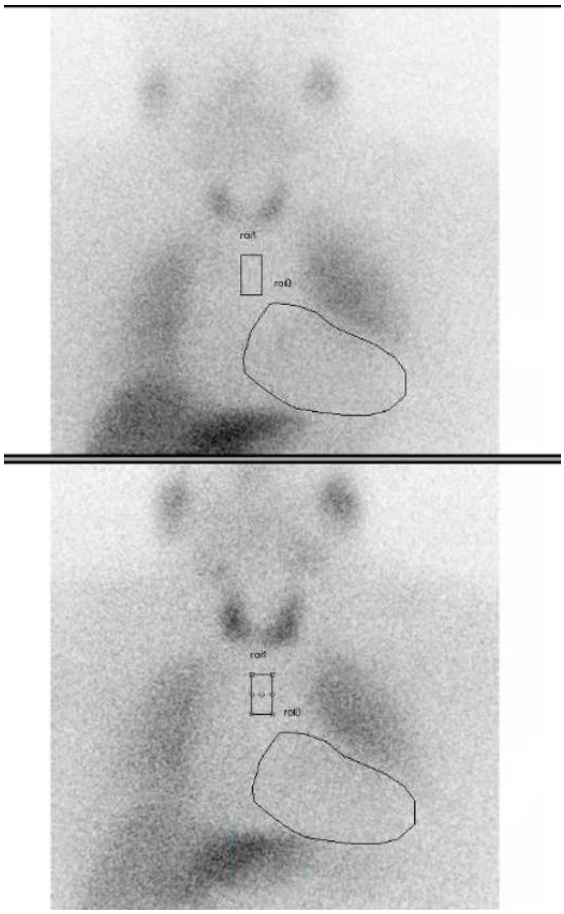

Figura 9. Gammagrafía de inervación cardíaca con [^{123}I]-MIBG en paciente con EP o DCL.

Se muestra un ejemplo de análisis semicuantitativo donde se han dibujado regiones de interés (ROIs) en el área miocárdica y mediastínica. Se comparan las cuentas medias obtenidas en cada una para calcular el índice corazón-mediastino. En este caso, el análisis visual revela la ausencia de captación a nivel cardíaco, indicando denervación adrenérgica.

En este estudio también cobra vital importancia el análisis semicuantitativo. Para ello, se compara la actividad cardíaca con la actividad en mediastino para obtener los índices corazón-mediastino precoz y tardío, respectivamente, así

como el porcentaje de lavado (“washout") (71). En la literatura, no existe un consenso claro sobre el punto de corte óptimo para considerar un estudio como normal (73).

Un estudio reciente analizó los índices corazón-mediastino obtenidos al realizar la gammagrafía con [^{123}I]-MIBG en pacientes japoneses afectos de AMS-P con demencia comparándolos con aquellos sin demencia. Se encontraron valores significativamente reducidos en el primer grupo, concluyendo que la gammagrafía con índices reducidos podría ser un buen indicador de la existencia de pacientes con AMS-P (74).

Tras la revisión de los criterios diagnósticos de la AMS, la gammagrafía con [^{123}I]-MIBG se considera un marcador diagnóstico de apoyo para las categorías de AMS: clínicamente establecida, clínicamente probable y posible prodrómica. En esta última, los hallazgos anormales en esta técnica son un criterio de exclusión (10).

PET (tomografía de emisión de positrones, por sus siglas en inglés) **y PET/CT** (cuando integra además una TC).

Esta técnica de imagen requiere, para su uso en estudios de neurología, el empleo de fármacos marcados con los radionúclidos ^{11}C o ^{18}F. Estos radiofármacos resultantes, se caracterizan por tener una vida media corta (20-110 minutos) en comparación con los utilizados en la modalidad SPECT. De forma análoga, la actividad radiactiva emisora, en este caso de positrones, puede ser detectada por un tomógrafo dedicado después de la inyección intravenosa al paciente.

El radioligando más utilizado en la actualidad por su disponibilidad y vida media (110 minutos), es la 2-[^{18} F]-fluoro-2-Deoxi-D-glucosa (2-[^{18}F]FDG) que permite medir el metabolismo glicídico del organismo, reflejando en este caso la actividad del SNC (72).

Los síndromes parkinsonianos atípicos suelen mostrar una marcada reducción del metabolismo de la glucosa. Así, en la AMS-P se puede objetivar un importante hipometabolismo en el núcleo estriado, sobre todo a nivel del núcleo putamen posterior; mientras que en la AMS-C suele ocurrir en el puente de Varolio y en el cerebelo. Además, estos hallazgos son detectados en estadios iniciales de la enfermedad (16,72).

Cuando comparamos la AMS con la EP en PET con 2-[^{18}F]FDG, generalmente el metabolismo está más respetado en la segunda. Ello se puede evidenciar

topográficamente en el cerebelo (tanto en el vermis como en los hemisferios cerebelosos), en el tálamo medial, en el núcleo putamen posterior, en los núcleos caudados, en el hipotálamo, en las áreas límbicas (regiones cinguladas medias y cortezas de la ínsula), y en las regiones laterales de los lóbulos frontales; localizaciones donde sí existe reducción del metabolismo en la AMS. Por otro lado, es característico que las áreas talámicas laterales y las cortezas asociativas (córtex asociativo y lóbulos frontales inferiores) se encuentren más comprometidas en la EP que en la AMS (75).

Actualmente, la PET con 2-[^{18}F]FDG es un marcador de apoyo para el diagnóstico de AMS en los nuevos criterios. El diagnóstico debe basarse en el análisis visual de un médico especialista en medicina nuclear. El hipometabolismo en el putamen, el troncoencéfalo y el cerebelo apoya una AMS-P, mientras que el hipometabolismo exclusivamente en el putamen sugiere una AMS-C (10).

La técnica PET con 2-[^{18}F]FDG ha demostrado ser un biomarcador fiable de la evolución y progresión en las enfermedades neurodegenerativas, reflejando con precisión su distribución topográfica, estadio e impacto funcional (76). Estudios recientes indican que esta técnica puede proporcionar una mayor precisión diagnóstica que la gammagrafía con [^{123}I]-MIBG para la diferenciación entre DCL y no DCL, así como entre EP y MSA, utilizando el diagnóstico de seguimiento como estándar de referencia (77).

Otro radiofármaco para técnica PET, la L-6-[^{18}F]fluorodopa, actúa como análogo de la levodopa. Permite estimar la actividad enzimática de la L-aminoácido aromático descarboxilasa, la cual se encarga de convertir la levodopa en dopamina en las neuronas presinápticas de la sustancia negra. Sin embargo, debido a la regulación al alza de esta enzima, como mecanismo compensatorio en las enfermedades degenerativas, es probable que se subestime el grado de lesión nigroestriatal, por lo que no resulta útil en la diferenciación de los distintos parkinsonismos (72).

La búsqueda de un ligando PET para la α-sinucleína que permita diferenciar la AMS de otros parkinsonismos atípicos es un reto. En este sentido, recientemente ha surgido el ligando [^{18}F]ACI-12589, que parece mostrar buena afinidad y especificidad in vitro para la α-sinucleína aberrante en tejidos de pacientes con EP y AMS (78).

Receptores dopaminérgicos postsinápticos

Es posible evaluar la densidad de los receptores dopaminérgicos a nivel postsináptico (receptores D2) mediante ligandos SPECT y PET.

En el primer caso, se puede utilizar, de forma similar al FP-CIT, un radioligando marcado con ^{123}I, el ^{123}I-(S)-2-hidroxi-3-yodo-6-metoxi-N-[etil-2-pirrodinilo)-etil]benzamida (IBZM) para técnica SPECT. Los sujetos con EP y DCBG muestran, estén o no con tratamiento dopaminérgico, una densidad de receptores D2 normal, mientras que sujetos afectos de AMS y PSP presentan una reducción severa de los mismos (54,72). Se ha propuesto monitorizar la progresión de la AMS mediante la utilización de este estudio, describiéndose una pérdida anual de receptores D2 a nivel putaminal del 10% en una serie de AMS (53).

El radiotrazador PET más utilizado para evaluar los receptores D2 postsinápticos es el raclopride, marcado con ^{11}C. Suele mostrar valores normales o aumentados en sujetos con EP sin tratamiento, en contraste con la severa reducción observada en sujetos con AMS, PSP y EP con mediación dopaminérgica (53).

NEUROIMAGEN MORFOLÓGICA

Resonancia Magnética Nuclear (RMN)

Esta técnica de imagen suele mostrar signos inespecíficos en los parkinsonismos atípicos, y las alteraciones estructurales suelen aparecer cuando la enfermedad está avanzada (72).

En sujetos con AMS-P, la RMN convencional muestra atrofia putaminal, hipointensidad en secuencia ponderada en T2 (T2W) e hiperintensidades marginales "en forma de hendidura". Por otro lado, en AMS-C, destaca la atrofia del tronco cerebral inferior, protuberancia, pedúnculos cerebelosos medios y vermis, con hiperintensidad cruciforme pontina en T2W. Las alteraciones a nivel de puente y cerebelo permiten distinguir a la AMS de una EP, pero no así de una PSP (72).

La pérdida de señal del putamen dorsolateral en las secuencias T2* y de eco de gradiente tiene una especificidad superior al 91% para la AMS. La sensibilidad es menor, pudiendo alcanzar valores en torno al 97% si se combina con la presencia de un borde lateral hiperintenso en las secuencias de recuperación de inversión atenuada por fluidos (FLAIR). La imagen potenciada en susceptibilidad magnética (por sus siglas en inglés, SWI) mejora la sensibilidad para detectar la AMS temprana del 25% al 75%, al tiempo que conserva una alta especificidad, en torno al 91%, al detectar anomalías nigrales tempranas. Los valores de SWI

del putamen y el pulvinar, que muestran una menor deposición de hierro, también pueden ayudar a diferenciar la AMS-P de la EP. La hipointensidad del núcleo rojo discrimina la PSP de la AMS-P y la EP, mientras que la hipointensidad putaminal separa la PSP y la AMS de la EP (75).

Las imágenes ponderadas por difusión se han utilizado ampliamente para detectar y cuantificar cambios degenerativos tempranos en pacientes con AMS, lo que permite diferenciar esta patología de la EP (79). En este sentido, algunos autores proponen realizar estudios de seguimiento mediante esta técnica para monitorizar la neurodegeneración en las distintas regiones cerebrales (80). El aumento de la difusión en putamen constituye el marcador diagnóstico más claro, estando descrito, junto con otros hallazgos, en los actuales criterios diagnósticos de AMS (10).

Signos característicos de AMS en RMN.

- Signo de borde putaminal hiperintenso (o “hyperintense putaminal rim sign”). En las secuencias T2W, se visualiza a lo largo del margen exterior del putamen, que normalmente sería hipointenso debido al depósito de hierro, junto con leve atrofia putaminal. La especificidad y el VPP son del 100% en la AMS-P frente a la EP y los controles utilizando RMN de 1,5 Teslas. Los estudios de imágenes PET han correlacionado este hallazgo con la reducción del metabolismo de la glucosa en el putamen y la densidad de los receptores de dopamina postsinápticos en la AMS. Sin embargo, también se puede encontrar este signo en la EP (75).

- Signo del "bollo caliente" (o “hot cross bun” sign). Se caracteriza por la presencia de hiperintensidad de morfología cruciforme a nivel pontino en secuencias T2W debido a la pérdida selectiva de fibras pontocerebelosas transversas mielinizadas en el rafe pontino con preservación selectiva de los tractos corticoespinales. Es uno de los signos descritos como más específicos de la AMS (100%); sin embargo, puede observarse en otras degeneraciones cerebelosas (por ejemplo, ataxias espinocerebelosas), vasculitis y en la enfermedad de Creutzfeldt-Jacob, por lo que la sensibilidad para la AMS disminuye al 35,7% (75).

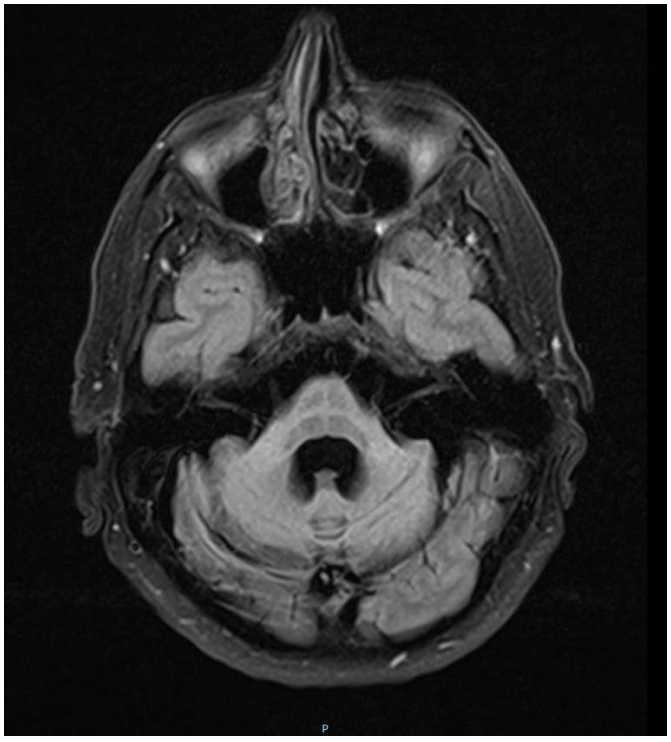

Figura 10. Signo “hot cross bun” en RMN de paciente con sospecha de AMS. Se puede visualizar la hiperintensidad en secuencia T2W a nivel del puente de Varolio, con la característica morfología en forma de cruz.

En cuanto al análisis volumétrico, se encontraron valores significativamente reducidos a nivel de cerebelo, tálamo, putamen y troncoencéfalo en pacientes con AMS en comparación con pacientes con EP y sujetos control (75).

OTRAS HERRAMIENTAS DIAGNÓSTICAS.

Biomarcadores en líquido cefalorraquídeo (LCR).

Actualmente no existe ningún biomarcador fiable para el diagnóstico y el pronóstico de la AMS. De acuerdo con los criterios diagnósticos actuales, son hallazgos de apoyo en el diagnóstico de AMS la detección de oligómeros de α-sinucleína detectados en LCR por PMCA (Ca^{2+}-ATPasa de la membrana plasmática) o RT-QUIC (conversión de proteína priónica inducida por agitación en tiempo real), y el aumento de la cadena ligera del neurofilamento (NfL) en LCR o plasma detectado por técnica ELISA (ensayo por inmunoadsorción ligado a enzimas) (10,81).

Entre los biomarcadores en LCR que se encuentran en investigación, y parecen establecerse como los más útiles clínicamente, se incluyen la combinación de NfL elevada en AMS con respecto a la EP y los sujetos controles, metabolitos de la vía de las catecolaminas y proteínas como la α-sinucleína, la desglicasa 1 (DJ-1) y la tau total (82,83). De hecho, se está explorando el papel de la proteína NfL como un biomarcador potencial, ya que parece correlacionarse con la gravedad clínica de la enfermedad, la progresión y el pronóstico (84).

DIAGNÓSTICO DIFERENCIAL

Dentro del diagnóstico diferencial, el error más frecuente ocurre al confundir la AMS-P con la EP. La preservación del olfato, la aparición de clínica urinaria (como retención urinaria) y respiratoria (como estridor e insuficiencia respiratoria), así como la ausencia de déficits cognitivos significativos, pueden ser características clínicas que permitan distinguir la AMS de la EP y la DCL (47).

De forma similar, la presentación autonómica de la AMS puede confundirse con el fallo autonómico puro, debiéndose descartar, además, otras entidades como la PSP y DCBG.

En cuanto a la variante cerebelosa, existen patologías como la ataxia de Friedrich de inicio tardío y, aunque mucho menos frecuente, la forma dominante de adrenoleucodistrofia ligada al cromosoma X, que pueden ser catalogadas erróneamente como AMS-C (83).

Otras entidades, como las ataxias espinocerebelosas 2, 3 y 8 (conocidas por sus siglas en inglés, SCA), y el síndrome del cromosoma X frágil asociado a temblor/ataxia, presentan una combinación de características cerebelosas y parkinsonianas que pueden imitar a la AMS (83).

También es muy importante descartar previamente todas aquellas patologías que puedan desarrollar una clínica similar a la AMS (conocidas como AMS-like) (85).

PRONÓSTICO

El pronóstico de la AMS es desalentador. Como se ha comentado anteriormente, se estima una supervivencia media de menos de 10 años desde el comienzo de los síntomas (21,25,26,28,30).

Estudios, en su mayoría retrospectivos, estiman la mediana del tiempo desde el inicio de la enfermedad hasta el desarrollo de disfunción autonómica en 2,5 años, la necesidad de ayuda para caminar a los 3 años, el confinamiento en silla de ruedas de 3,5 a 5 años y el estado de encamamiento entre los 5 y 8 años desde el inicio (28,86).

El intervalo de tiempo desde el síntoma inicial y el desarrollo combinado de clínica motora y autonómica, ya se había descrito como factores determinantes de progresión de la AMS en una cohorte japonesa, postulándose que estos podrían predecir el deterioro funcional y la supervivencia (28).

También se ha postulado la posible y relativa ralentización de la progresión de la enfermedad durante el segundo año de seguimiento (25).

Investigaciones más recientes sugieren que los pacientes con un inicio de la enfermedad antes de los 40 años (conocidos como AMS de inicio joven) pueden tener una supervivencia más larga que la que se registra habitualmente para la AMS en general (87).

El diagnóstico del subtipo AMS-P, la edad avanzada al inicio de la enfermedad , síntomas como el vaciado incompleto de la vejiga (vejiga neurógena), el inicio precoz del estridor (3 años desde el inicio de clínica motora o autonómica), la presencia de disautonomía o discapacidad precoz o grave y el sexo femenino, se han relacionado con una menor supervivencia (21,25,93,28,42,86,88–92). La afectación por sí sola del SNA también se ha considerado factor de mal pronóstico en algunos estudios (16).

De forma similar, se han descrito como factores predictores de progresión rápida de la enfermedad dentro de la escala de calificación de la atrofia multisistémica: la menor duración de los síntomas al inicio y la ausencia de respuesta al tratamiento con levodopa (25).

Una de las causas de muerte más frecuente es la bronconeumonía (30,94).

TRATAMIENTO

En la actualidad, no existe ningún tratamiento que permita modificar o detener satisfactoriamente la progresión de la enfermedad, lo que lleva el manejo de estos pacientes a tratamientos, medidas y terapias exclusivamente sintomáticos para mejora de la calidad de vida (11,95,96). Dado el amplio abanico de manifestaciones clínicas que puede desarrollar la AMS, el tratamiento ha de ser individualizado (16).

Se ha desarrollado un instrumento de calificación específico para la AMS, la Escala de Calificación Unificada de la AMS (UMSARS por sus siglas en inglés), para estandarizar las evaluaciones de gravedad en clínicas especializadas y programas de investigación en todo el mundo (16,25).

Las terapias farmacológicas disponibles se centran, principalmente, en el tratamiento de la clínica parkinsoniana y de la disautonomía (11,16).

En el **tratamiento de la sintomatología parkinsoniana,** el empleo de levodopa solo ha demostrado eficacia de forma transitoria en algunos estudios. No se ha encontrado claro beneficio en ensayos clínicos con los fármacos amantadina (antagonista del N-metil-D-aspartato) ni riluzol (benzotiazol). La rasagilina, un inhibidor selectivo e irreversible de la monoamina de la monoaminoxidasa B, se encuentra bajo estudio en un ensayo de fase III. También se están analizando agentes contra la agregación de α-sinucleína, como la rifampicina. Sí se observó cierta mejoría en la clínica motora con el uso de paroxetina (11,16,95,97).

Las posturas anormales que adoptan los pacientes afectos de AMS pueden tratarse con toxina botulínica, aunque se debe tener precaución en aquellos con antecollis debido al riesgo de provocar disfagia. La opción quirúrgica rara vez ha resultado útil, habiéndose dado casos donde se practicó una palidotomía medial sin mejoría motora posterior. Además, no existen estudios sobre eficacia y efectos adversos de la estimulación cerebral profunda. Como alternativa a las opciones farmacológicas, apoyo psicológico y las terapias físicas, ocupacionales y del habla son útiles para reducir la discapacidad del paciente y mantener su

independencia. Además, el entrenamiento de la marcha y el uso de dispositivos de ayuda son importantes para prevenir caídas, especialmente debido a la afectación cerebelosa característica de la AMS-C que puede confinar a los pacientes a una silla de ruedas (11,14,16).

Tratamiento de la disfunción autonómica. Ante síntomas incapacitantes de hipotensión ortostática, se recomiendan medidas conservadoras como evitar factores agravantes (comidas copiosas, alcohol, esfuerzos, ciertos medicamentos), el uso de medias elásticas, inclinación de la cama hacia arriba por la noche y el aumento de la ingesta de sal. Cuando las medidas anteriores fracasan, los fármacos de elección son la fludrocortisona o la midodrina, aunque solo esta última ha sido probada frente a placebo en ensayos clínicos aleatorizados. Otros agentes son el precursor de la norepinefrina, la L-treo-dihidroxi-fenilserina (cuya disponibilidad es limitada), la desmopresina, la eritropoyetina y la octreotida (16).

El tratamiento de la vejiga neurógena en la AMS suele consistir en sondaje intermitente y el uso de anticolinérgicos si existen hiperreflexia del músculo detrusor. Los antagonistas de los receptores adrenérgicos pueden mejorar el vaciado y reducir los volúmenes residuales. Para la disfunción eréctil en los hombres, se puede emplear el sildenafilo, probado frente a placebo en un estudio doble ciego, aunque puede exacerbar la hipotensión ortostática (16).

El estreñimiento puede aliviarse aumentando la ingesta de agua y con el uso de macrogol 3350 (laxante), mostrándose eficaz y seguro. La presión positiva

continua en las vías respiratorias puede ser útil en pacientes con estridor nocturno. Sin embargo, la quimiosensibilidad a la hipercapnia está intacta en pacientes con AMS. Por otro lado, la traqueotomía sigue siendo el tratamiento de elección para determinados pacientes con estridor diurno, cuerdas vocales inmóviles o estridor intratable a la presión positiva continua en las vías respiratorias, aunque puede exacerbar fatalmente la apnea del sueño (16).

Recientemente se ha probado la terapia con hormona del crecimiento en un intento de modificar la progresión de la enfermedad, sin obtener resultados clínicamente significativos (11,16).

Las estrategias terapéuticas que se están investigando actualmente no están resultando positivas y muchas de ellas fracasan en fase preclínica. Los esfuerzos más novedosos incluyen la reducción de la agregación y patología de la α-sinucleína, así como la modulación de la neuroinflamación. Otros estudios que proponen una posible vacunación se encuentran en las primeras fases de ensayo, al igual que el desarrollo de la inmunoterapia mediante anticuerpos contra un epítopo similar a la α-sinucleína (98,99).

II. HIPÓTESIS Y OBJETIVOS

HIPÓTESIS

¿Cuál es la validez del SPECT cerebral con [^{123}I]Ioflupano como herramienta diagnóstica para la AMS?

OBJETIVOS

1) Determinar la efectividad diagnóstica del SPECT cerebral con [^{123}I]Ioflupano en la AMS y sus subtipos, analizando las posibles diferencias entre los análisis cuantitativos y cualitativos de esta técnica.

Objetivo respondido en el artículo 1.

2) Comprender las variaciones que muestran estos estudios de neuroimagen en pacientes con AMS a medida que avanza el tiempo, para identificar posibles cambios típicos de la progresión de esta enfermedad.

Objetivo respondido en el artículo 2.

3) Comparar el rendimiento diagnóstico del SPECT cerebral con [^{123}I]Ioflupano y la gammagrafía [^{123}I]MIBG en la AMS.

Objetivo respondido en el artículo 3.

III. ARTÍCULOS CIENTÍFICOS PUBLICADOS

ARTÍCULO 1

TÍTULO:

Diagnostic Effectiveness of [^{123}I]Ioflupane Single Photon Emission Computed Tomography (SPECT) in Multiple System Atrophy

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Article

Diagnostic Effectiveness of [^{123}I]Ioflupane Single Photon Emission Computed Tomography (SPECT) in Multiple System Atrophy

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Abstract: Background: Multiple system atrophy (MSA) is a rapidly progressive neurodegenerative disorder that has no curative treatment. Diagnosis is based on a set of criteria established by Gilman (1998 and 2008) and recently updated by Wenning (2022). We aim to determine the effectiveness of [^{123}I]Ioflupane SPECT in MSA, especially at the initial clinical suspicion. Methods: A cross-sectional study of patients at the initial clinical suspicion of MSA, referred for [^{123}I]Ioflupane SPECT. Results: Overall, 139 patients (68 men, 71 women) were included, 104 being MSA-probable and 35 MSA-possible. MRI was normal in 89.2%, while SPECT was positive in 78.45%. SPECT showed high sensitivity (82.46%) and positive predictive value (86.24), reaching maximum sensitivity in MSA-P (97.26%). Significant differences were found when relating both SPECT assessments in the healthy–sick and inconclusive–sick groups. We also found an association when relating SPECT to the subtype (MSA-C or MSA-P), as well as to the presence of parkinsonian symptoms. Lateralization of striatal involvement was detected (left side). Conclusions: [^{123}I]Ioflupane SPECT is a useful and reliable tool for diagnosing MSA, with good effectiveness and accuracy. Qualitative assessment shows a clear superiority when distinguishing between the healthy–sick categories, as well as between the parkinsonian (MSA-P) and cerebellar (MSA-C) subtypes at initial clinical suspicion.

Keywords: multiple system atrophy; dysautonomia; functional neuroimaging testing; diagnostic accuracy; Ioflupane-123; cross-sectional study

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1. Introduction

Multiple system atrophy (MSA) is a progressive degenerative process of the central and autonomic nervous systems. It usually happens in adulthood, with sporadic incidence. It causes severe disability in the medium term and leads to death in less than 10 years [1,2]. The disease affects (variably and in any combination) the nigrostriatal, olivopontocerebellar, autonomic, and corticospinal systems, along with a lack of response to levodopa treatment [1]. The involvement of the nigrostriatal neuronal pathway develops the parkinsonian syndrome consisting of tremors, bradykinesia/rigidity and postural instability [3].

The diagnosis of MSA is based on widely accepted criteria that classify the disease as possible, probable or definite (depending on the patient's symptoms) [4]. These criteria were reviewed in 2008, including neuroimaging tests [5]. One of them was brain SPECT with presynaptic dopamine transporters, which was included for possible MSA type C until the latest revision of the diagnostic criteria [6].

This SPECT allows detecting "in vivo" changes at the molecular level that affect brain dopaminergic function, specifically the nigrostriatal pathway. One of the most widely used radiopharmaceuticals is [^{123}I]Ioflupane, which makes it possible to visualize the density of presynaptic dopamine transporters in both striatal nuclei. The interpretation of this study consists of a qualitative assessment, where the uptake and distribution of the radiopharmaceutical in the striated nuclei are visualized. This visual analysis is sufficient for diagnosis. On the other hand, numerous image analysis software tools have emerged, which could help nuclear medicine physicians. However, there is currently no clear standardization in this respect and each company has its own quantification software.

The validity and usefulness of SPECT in the diagnosis of Parkinson's disease (PD), as well as in clinically uncertain parkinsonian syndromes, even in early stages, has so far been demonstrated [7–9]. The main indications for SPECT are: (i) differential diagnosis between neurodegenerative parkinsonian syndrome and essential tremor; (ii) distinguishing between Lewy body dementia and other dementias such as Alzheimer's disease; (iii) differential diagnosis between parkinsonism with presynaptic dopamine deficit (such as PD) and secondary parkinsonism (psychogenic, drug-induced, or vascular); and (iv) early detection of parkinsonian syndromes with presynaptic involvement [10].

It has not been demonstrated that it is possible to reliably discriminate between PD and MSA by SPECT. There are a multitude of studies that address this question, seeking both qualitative and quantitative differences, with varying results [11–14]. The greatest diagnostic difficulty is found when analyzing the subtypes of MSA: parkinsonian (MSA-P) and cerebellar (MSA-C) and the usefulness of [^{123}I]Ioflupane SPECT. There is a certain consensus on its usefulness in MSA-P, being more questioned in the MSA-C subtype, given that, at the onset of the disease, SPECT can be completely normal [15–17]. For this reason, a negative result does not exclude the diagnosis of MSA [18]. In addition, it has been proposed to monitor the evolution of MSA by performing [^{123}I]Ioflupane SPECT. In fact, it is postulated that this test could be an important biomarker of disease progression, as well as the subtype of dopaminergic degeneration [16,19].

The aim of this work is to determine the diagnostic effectiveness of brain [^{123}I]Ioflupane SPECT in both subtypes of MSA, while addressing all the aforementioned controversies and lack of consensus. Possible differences between quantitative and qualitative analyses of this technique will also be analyzed.

2. Materials and Methods

2.1. Study Design and Subjects

A single-center observational cross-sectional study. Patients over 18 years of age, with clinical suspicion compatible with MSA according to Gilman's criteria (probable/possible/definite), who had undergone [^{123}I]Ioflupane SPECT during the period 2004–2020, were included. All DAT-SPECT scans were requested by the Movement Disorders Unit of the Neurology Department of our hospital, after the initial interview with the patient. All of them had to be able to understand the diagnostic procedure and give informed consent. All patients who did not meet these requirements were excluded, as well as those who showed signs of "red flags" [20] or were taking medication that could interfere with the SPECT result (qualitative and quantitative).

Demographic and clinical variables were obtained by means of a clinical interview conducted by the neurologist of the movement disorders unit, prior to SPECT. The mean time from clinical onset to neurologist visit was 5–9 days (mean 1 week). The mean time from onset from neurologist requesting SPECT to SPECT was 2 weeks (mean 1–3 weeks).

2.2. SPECT of Presynaptic Dopamine Transporters with [^{123}I]Ioflupane

The SPECT tomographic study was performed with a Siemens Healthineers® gamma camera, (Erlangen, Germany) model Symbia™, equipped with a double head and a low energy and high resolution collimator. The images were obtained after a period of 3 to 4 h

of intravenous administration of 185 MBq of the radiotracer [^{123}I]Ioflupane, after thyroid blockade with lugol solution.

A 360° circular orbit around the skull was performed, with 3° intervals, acquiring 60 images with a duration of 35 s per interval, and a 128 × 128 matrix. Images were reconstructed using filtered back projection algorithms without attenuation correction, with the application of a Hanning filter (frequency of 0.7), and images were obtained according to transaxial slices and orbito-meatal orientation.

This study was first evaluated by qualitative analysis by three nuclear medicine physicians, two of them with extensive experience in the field of movement disorders. The type of MSA and its diagnostic classification (possible/probable) were blinded. A kappa index of 100% was obtained. The studies were also evaluated by semi-quantitative analysis, establishing uptake indices (after the sum of the six most representative axial images) between regions of interest (ROI) of an area of specific activity (striatal nuclei) and an area of non-specific activity (occipital cortex), obtaining the striatal/occipital index (S/O) [21]. This analysis can be performed independently of the gamma camera used and is highly reproducible.

2.3. Convectional MRI

Conventional MRI was performed in all patients. The MRI protocol performed included the following sequences: sagittal T1, axial T2, FLAIR, diffusion and echogradient. Contrast was not used. In Parkinson's disease there are no findings, or they are non-specific, so MRI is performed to carry out the differential diagnosis with other parkinsonisms that can show neuroimaging findings.

2.4. Ethical Considerations

Authorization for this study was obtained from the Biomedical Research Ethics Committee of the province of Malaga. At all times, the harmonized tripartite standards of the Helsinki declaration, the Organic Law on Biomedical Research of 15/1999 of 3 July, the Organic Law on Personal Data Protection (LOPD) of 13 December 2018, the code of ethics of the Organización Médica Colegial (OMC), the basic regulatory law 41/2002 on patient autonomy and rights and obligations regarding clinical information and documentation, of 14 November, as well as the standards of good clinical practice, were respected.

2.5. Statistical Study

First, a descriptive study was performed, showing absolute and percentage frequencies for qualitative variables. Continuous quantitative variables were expressed as mean and standard deviation. The Shapiro–Wilk test was used to check whether the values of these variables followed a normal distribution.

To calculate the association between qualitative variables, the Chi-square test was applied with Fisher's correction if appropriate. To analyze the differences between continuous quantitative variables, the Student *t* test (parametric) or Mann–Whitney U test (nonparametric) was used for two independent groups, and the ANOVA test (parametric) or Kruskal–Wallis test (nonparametric) in three or more independent groups. ROC curves were performed for different cut-off points according to quantitative SPECT analysis. A significance level was considered for $p < 0.05$. Confidence intervals were established at 95%.

3. Results

A total of 139 patients were studied: 68 males (48.9%) and 71 females (51.1%). The mean age was 68 years, with minimum and maximum ages of 47 and 85 years, respectively, and a standard deviation of 9. 104 cases were classified according to clinical criteria as MSA-probable (74.8%), 35 as MSA-possible (25.2%), and no subject was found with MSA-definite. The predominant subtype was MSA-P (62.6%) versus MSA-C (37.4%). Of the patients, 84.2% had parkinsonian syndrome, 40.3% had cerebellar symptomatology, 62.6% had

dysautonomia and 20.1% had corticospinal symptoms. Some 94.2% showed no response to levodopa treatment, while the remaining 5.8% had a transient response.

Convectional MRI was anodyne in 89.2% of patients. The SPECT study with [^{123}I]Ioflupane was compatible with nigrostriatal pathway involvement in 78.45%, with a non-pathological study in 21.55% (16.6% being normal and 5% inconclusive). The mean scores of the uptake indices obtained by SPECT were 1.35 ± 1.74 (0.9–1.88) for the global S/O index, 1.36 ± 1.8 (0.9–1.86) for the right S/O index and 1.34 ± 1.7 (0.91–1.89) for the left S/O.

3.1. Diagnostic Validity Study

Accuracy values were calculated for the entire MSA caseload (139 patients) and for both types of the disease: MSA-P (87 patients) and MSA-C (52 patients), shown in Table 1.

Table 1. Diagnostic accuracy values.

	MSA	MSA-P	MSA-C
N	139	87	52
S	82.46% (75.04–89.88)	97.26% (92.83–100.00)	56.10% (39.69–72.51)
E	40% (18.80–61.20)	21.43% (0.00–46.49)	63.64% (30.66–96.61)
PPV	86.24% (79.31–93.16)	86.59% (78.60–94.57)	85.19% (69.93–100.00)
PNV	33.33% (14.80–51.87)	60.00% (7.06–100.00)	28% (8.40–47.60)
FP	60%	79%	36%
FN	18%	3%	44%
Accuracy	10%	85%	58%

MSA: Multiple System Atrophy; MSA-P: Multiple System Atrophy Parkinsonian Type; MSA-C: Multiple System Atrophy Cerebellar Type; N: Number of patients; S: Sensitivity; E: Specificity; PPV: Positive predictive value; PNV: Negative predictive value; FP: False positives; FN: False negatives. The 95% confidence interval is shown in parentheses.

3.2. Qualitative vs. Quantitative SPECT Categorization

It is observed that there are significant differences in the scores of the three S/O indexes analyzed (global, right and left), in two of the groups defined by the qualitative assessment made by the nuclear medicine physician: pathological vs. inconclusive group ($p < 0.05$) and pathological vs. normal group ($p < 0.001$), as shown in Table 2.

Table 2. Analysis of relations between qualitative and quantitative SPECT categorizations.

S/O Indices	Groups			*p*-Value
	Pathological	Normal	Inconclusive	
Global	1.279 (0.135) ϯ	1.522 (0.155)	1.467 (0.064)	<0.001 ***
Right	1.287 (0.142) ϯ	1.530 (0.161)	1.478 (0.077)	<0.001 ***
Left	1.271 (0.136) ϯ	1.515 (0.152)	1.455 (0.057)	<0.001 ***

S/O: Striatum/Occipital; ϯ $p < 0.05$ pathological vs. inconclusive; *** $p < 0.001$ pathological vs. normal.

3.3. Relationship between SPECT Categorizations (Qualitative and Quantitative) and Clinical Diagnosis (Gilman's Criteria, 2008)

We analyzed whether there are significant differences between the scores of the three quantitative indices, as well as between the three groups defined by visual assessment, according to the diagnostic classification (probable MSA, possible MSA), but no significant differences were obtained.

3.4. Cut-Off Proposition for the Overall S/O Index in Relation to the Qualitative Categorization Performed by the Nuclear Medicine Physician

The optimal cut-off for the global S/O index in relation to the qualitative categorization for the normal vs. pathological groups was established at 1.4. Based on this, a sensitivity of 80% and a specificity of 86.7% were obtained. The area under the curve (AUC) was 89.9%, and the range was 83.3–96.5% (Figure 1).

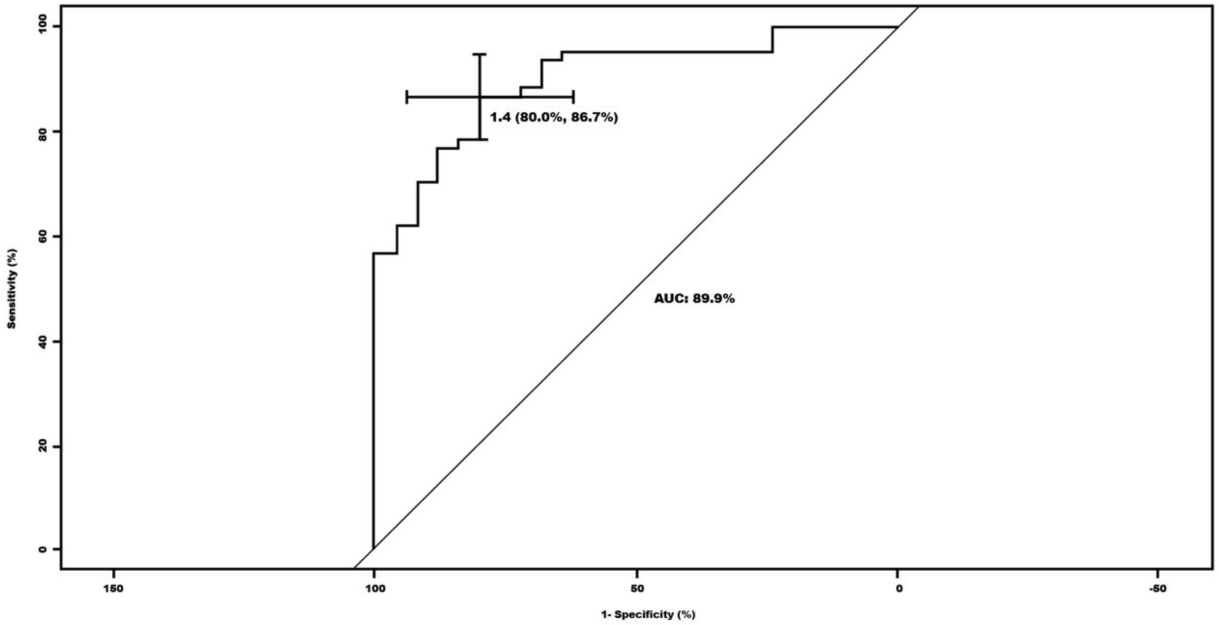

Figure 1. ROC curve for the global striatum/occipital (S/O) index in relation to the qualitative categorization of the nuclear medicine physicians for the normal versus pathological groups.

3.5. Cut-Off Proposition for the Global S/O Index in Relation to Clinical Diagnosis

When comparing this index with the diagnostic classification made by the neurologist (Gilman's criteria) in both groups mentioned (normal vs. pathological), an optimal cut-off of 1.5 was obtained, according to which we have a sensitivity of 28.6% and a specificity of 90.6%. The area under the ROC curve (AUC) was 54%, and the range was 38.6–69.4% (Figure 2).

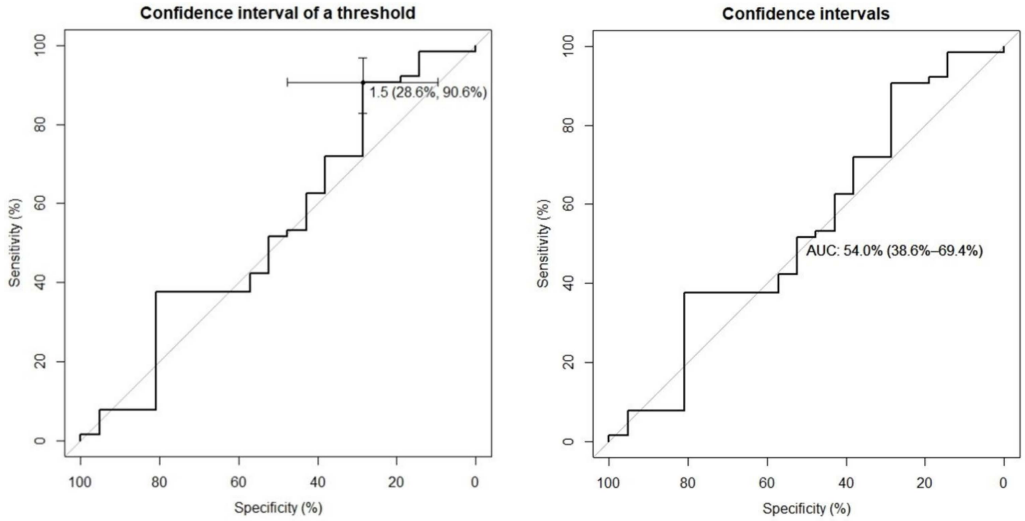

Figure 2. ROC curves for the global striatum/occipital (S/O) index in relation to the clinical diagnosis, for the normal versus pathological groups.

3.6. Relationship between MSA Subtypes, SPECT Categorization (Qualitative and Quantitative) and Clinical Diagnosis

Significant differences were found between MSA subtype (MSA-C or MSA-P) and both SPECT categorizations (both with $p < 0.01$), but not so with clinical diagnosis ($p = 0.11$) (Table 3).

Table 3. Relations between MSA subtypes, SPECT categorizations and diagnosis.

Variables		MSA Type		*p* Value
		AMS-C	AMS-P	
Diagnosis	Probable	43 (82.7%)	61 (70.1%)	$p > 0.05$
	Possible	9 (17.3%)	26 (29.9%)	
SPECT qualitative assessment	Pathological	27 (51.9%)	82 (94.2%)	***
	Normal	20 (38.5%)	3 (3.4%)	
	Inconclusive	5 (9.6%)	2 (2.3%)	
SPECT quantitative assessment	Global S/O	1.452 (0.177)	1.271 (0.128)	***
	Right S/O	1.459 (0.185)	1.280 (0.133)	***
	Left S/O	1.445 (0.172)	1.262 (0.130)	***

S/O: Striatum/Occipital; MSA: Multiple System Atrophy; MSA-P: Multiple System Atrophy Parkinsonian Type; MSA-C: Multiple System Atrophy Cerebellar Type; *** $p < 0.001$.

3.7. Lateralization in Striatal Involvement of MSA

We studied whether one cerebral hemisphere is more affected than the other at the onset or during the development of the disease and whether this preponderance has an impact on other variables. In this regard, according to the quantitative SPECT assessment, we observed that there are significant differences between the mean values of the striatal nuclei of both cerebral hemispheres, obtained from the right S/O index and left S/O index (mean 1.4 (SD 0.2) vs. mean 1.3 (SD 0.2), $p < 0.05$). Similarly, according to the visual assessment performed by the nuclear medicine physician, it was observed that 57.65% of the patients had greater involvement of the left striate nucleus.

When trying to find associations between the predominant hemisphere with other variables (qualitative SPECT assessment, MSA subtype and diagnostic classification), no significant differences were obtained (Table 4).

Table 4. Relations between the dominant hemisphere and other variables.

Variables		Cerebral Dominance		*p* Value
		Right	Left	
SPECT qualitative assessment	Pathological	34 (69.4%)	26 (72.2%)	$p > 0.05$
	Non-pathological	15 (30.6%)	10 (27.8%)	
MSA type	MSA-C	19 (38.8%)	17 (47.2%)	$p > 0.05$
	MSA-P	30 (61.2%)	19 (52.8%)	
Clinical diagnosis	MSA-possible	12 (24.5%)	9 (25%)	$p > 0.05$
	MSA-probable	37 (75.5%)	27 (75%)	

MSA: Multiple System Atrophy; MSA-P: Multiple System Atrophy Parkinsonian Type; MSA-C: Multiple System Atrophy Cerebellar Type.

3.8. Response to Levodopa

We analyzed the responsiveness to levodopa in MSA as a diagnostic resource and compared it with other diagnostic or classification strategies. We found no association between the response to this treatment and the different variables used (diagnostic classification, SPECT categorizations and type of MSA) (Table 5).

Table 5. Relations between response to levodopa treatment and other variables.

Variables		Response to Levodopa		*p* Value
		NO	YES	
Diagnosis	Probable	97 (74%)	7 (87.5%)	$p > 0.05$
	Possible	34 (25.9%)	1 (12.5%)	
SPECT qualitative assessment	Pathological	104 (79.4%)	5 (62.5%)	$p > 0.05$
	Non-pathological	27 (20.6%)	3 (37.5%)	

Table 5. *Cont.*

Variables		Response to Levodopa		*p* Value
		NO	YES	
SPECT quantitative assessment	Global S/O	1.345 (0.175)	1.407 (0.174)	$p > 0.05$
	Right S/O	1.352 (0.180)	1.424 (0.188)	$p > 0.05$
	Left S/O	1.337 (0.175)	1.390 (0.162)	$p > 0.05$
MSA type	MSA-C	49 (37.4%)	3 (37.5%)	$p > 0.05$
	MSA-P	82 (62.6%)	5 (62.5%)	

S/O: Striatum/Occipital; MSA: Multiple System Atrophy; MSA-P: Multiple System Atrophy Parkinsonian Type; MSA-C: Multiple System Atrophy Cerebellar Type.

3.9. Relationship between Parkinsonian Clinic, SPECT Findings and MSA Subtype

Significant differences were found between the presence of clinical parkinsonism and the SPECT result (for both qualitative and quantitative assessments), as well as with the MSA subtype (MSA-C or MSA-P). Significant differences were found in all of them, except for clinical diagnosis (Table 6).

Table 6. Relations between presence of parkinsonian symptoms and other variables.

Variables		Parkinsonian Symptoms		*p* Value
		NO	YES	
Diagnosis	Probable	15 (68.2%)	89 (76.1%)	$p > 0.05$
	Possible	7 (31.8%)	28 (23.9%)	
SPECT qualitative assessment	Pathological	9 (40.9%)	100 (85.5%)	***
	Non-pathological	13 (59.1%)	17 (14.5%)	
SPECT quantitative assessment	Global S/O	1.522 (0.153)	1.301 (0.149)	***
	Right S/O	1.529 (0.162)	1.309 (0.155)	***
	Left S/O	1.515 (0.147)	1.293 (0.150)	***
MSA type	MSA-C	22 (100%)	30 (25.6%)	***
	MSA-P	0	87 (74.4%)	

S/O: Striatum/Occipital; MSA: Multiple System Atrophy; MSA-P: Multiple System Atrophy Parkinsonian Type; MSA-C: Multiple System Atrophy Cerebellar Type; *** $p < 0.001$.

4. Discussion

According to our study, we can observe a high reliability of the diagnosis issued by the nuclear medicine physician at initial clinical suspicion of MSA. This is demonstrated when we analyze the relationships between the visual (qualitative) diagnostic classification of [^{123}I]Ioflupane SPECT and quantitative assessment (with predefined ROIs method). There is a parallelism between this visual assessment and the quantitative value of SPECT. Currently there is a multitude of specific software to quantitatively assess the SPECT image, but there is no diagnostic standardization. This fact, in conjunction with the results of our study, allows us to propose our semi-quantification method because of its simplicity and high reproducibility.

The SPECT result (qualitative and quantitative) was related to the MSA subtype. This is to be expected from a pathophysiological point of view, given that SPECT detects nigrostriatal pathway involvement even in the prodromal phase of the disease [7,8]. This affectation is the origin of the parkinsonian clinic (which is mostly present in the MSA-P form) [1,2]. In any case, it should be noted that SPECT abnormalities in a patient with parkinsonism are not specific of MSA.

However, there was no relationship between the presence of parkinsonian symptoms and the diagnostic classification of the disease (probable or possible), the closest to a true MSA without postmortem confirmatory study (according to diagnostic criteria) [5]. Nevertheless, the previous clinical diagnostic classification (probable/possible) does not fully correspond with the SPECT assessment (both qualitative and quantitative), despite the fact that most of our patients (74%) were probable MSA [4,5]. Additionally, for cases

not confirmed by autopsy (possible MSA/probable MSA), [^{123}I]Ioflupane SPECT can be an accurate and non-invasive in vivo study.

Since there is still no clear consensus within quantitative assessment to establish a cut-off to consider a study normal or pathological, we propose, based on our results (probably the first study with such a large number of patients), that this cut-off can be set at 1.4, since it provides good values of sensitivity (80%) and specificity (86%).

On the other hand, we have not been able to establish a useful cut-off in the diagnostic classification (probable/possible). For a cut-off of 1.5, we obtained a good specificity (90.6%), although with a low sensitivity and area under the curve (28.6% and 50.4%, respectively). Therefore, it does not appear that clinical classification has an impact on the SPECT quantitative assessment.

In the present study, the proportion of patients with MSA was similar in men and women, which is consistent with the scientific literature [22]. However, initially, a higher percentage of males may present for consultation due to the clinical manifestations of erectile dysfunction [23].

The age distribution of the patients is also consistent with the literature [3,24–27]. It should be added that the age of our patients does not refer to the clinical onset, but to the timing of SPECT, which is usually requested after a first or second consultation in the movement disorders unit. The time elapsed between the clinical debut and the performance of the imaging test could be of importance in older subjects, as it could be due to a delay in clinical suspicion. We recommend further studies with this subgroup of patients, as it would be interesting to analyze their clinical particularities (coexistence of multiple signs and symptoms, other concomitant pathologies, greater difficulty in using current diagnostic criteria, etc.) [20]. Such particularities may mean that these elderly patients with suspected MSA require earlier care and/or closer follow-up.

The most frequent subtype of MSA was MSA-P, with a 3:1 ratio with respect to MSA-C. These data coincide with those published by the European MSA study group (EMSA group) where, although a higher percentage of MSA-C was obtained in Spain, the overall results show a predominance of MSA-P in Europe, with a homogeneous distribution [26,28–30].

In this aspect, [^{123}I]Ioflupane SPECT is useful to diagnose both subtypes, since we found significant differences for both qualitative and quantitative assessment. This finding is interesting, since the vast majority of our patients had parkinsonian syndrome and less than half of them had cerebellar symptomatology. Another important element seems to be the manifestation of dysautonomia, also very frequent in our patients, but not the presence of corticospinal symptoms. These results are in agreement with the diagnostic criteria regarding the clinical characteristics of this disease and their impact on establishing the diagnosis [5,6].

The scarce or null response to levodopa treatment in practically all of our patients coincides with that previously described by other authors [1,31]. In this context and given that there does not seem to be a clear association between the response to levodopa and the SPECT result (qualitative or quantitative), we questioned whether, in the presence of a pathological SPECT result in suspected MSA, we could dispense with this drug. This would imply a reduction in costs and would avoid potential adverse effects for patients [32,33].

Similarly, conventional MRI did not prove useful in the diagnosis of MSA in the majority of patients (89.2%). Since SPECT is performed at the same time as MRI upon initial suspicion of MSA, perhaps its usefulness lies in the detection of other pathologies that could be confused with MSA. It has been reported that this imaging technique usually shows nonspecific signs in atypical parkinsonism, with structural alterations appearing when the disease is advanced [34,35].

In contrast, [^{123}I]Ioflupane SPECT was positive in most patients (78.45%). This is similar to previously published studies, given that there may be integrity of the nigrostriatal pathway in early cases of MSA, especially in the MSA-C subtype [17]. In this context, it would be interesting to perform an evolutionary study in this subgroup of patients, since the rapidly progressive deterioration of the disease could confirm or rule out the

existence of MSA at a later stage. In the literature, we found hardly any research on this aspect [16,19,36,37].

We can confirm the high sensitivity of SPECT for the diagnosis of MSA (82%), especially in patients with MSA-P (97%) with respect to MSA-C. On the other hand, it has a high positive predictive value (PPV > 85%) in both subtypes, so we believe that in the clinical suspicion of MSA, SPECT is a very useful tool. These results correspond to those of other authors [9]. This tool could be considered for those incipient cases, perhaps even as diagnostic support in the prodromal phases (as the new category published) [6]. Furthermore, it is a widely available technique in our setting compared to others, such as PET-CT, for example, which is not available in all hospitals. For all these reasons, we propose that the role of [^{123}I]Ioflupane SPECT can be considered in the current diagnostic criteria.

Quantitative SPECT analysis showed that both striatal nuclei were significantly impaired, being more frequent the initial involvement of the left striatal nucleus. This lateralization has not been previously described, so we believe it is a finding that should be taken into account when diagnosing the disease. Moreover, it could be a distinctive feature to differentiate MSA from other entities. Therefore, it would be interesting to know how this condition evolves, by means of follow-up studies. In this regard, a baseline study could be performed (either at the onset of the disease or at any stage of the disease), in order to corroborate this deterioration at a later time. Previous publications point out the usefulness of [^{123}I]Ioflupane SPECT to monitor the evolution of this disease [16,19].

5. Conclusions

In conclusion, we could state: (i) [^{123}I]Ioflupane SPECT is a useful and reliable tool in the diagnosis of MSA (especially upon initial suspicion), with higher sensitivity and accuracy than other conventional imaging techniques. (ii) The qualitative assessment shows a net superiority in discerning between healthy–sick categories, as well as between MSA-P and MSA-C subtypes, which denotes that the assessment of the nuclear medicine physician has a relevant point in the diagnosis. There is also a good correspondence between the nuclear medicine physician's assessment and the quantitative assessment of [^{123}I]Ioflupane SPECT using predefined ROIs and our proposed cut-off. (iii) Treatment with levodopa does not seem to provide benefits in the diagnosis of patients with MSA, so in the presence of a positive [^{123}I]Ioflupane SPECT study, we believe that this drug could be omitted in terms of cost-effectiveness and cost-efficiency. (iv) Most of our patients showed an initial predominant involvement of the left striatal nucleus. This finding could be interesting for its possible usefulness in the diagnosis of MSA, especially to identify incipient cases of this disease.

Author Contributions: Concept and study design: J.V.-S., S.J.O.-L. and J.C.-V. Qualitative assessment of brain images and data acquisition: J.V.-S., S.J.O.-L. and T.A.-R. Drafting the manuscript and figures: J.V.-S. and J.C.-V. Supervision and correction of the manuscript: E.A. All authors have read and agreed to the published version of the manuscript.

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ARTÍCULO 2

TÍTULO:

Follow-Up Findings in Multiple System Atrophy from [^{123}I]Ioflupane Single-Photon Emission Computed Tomography (SPECT): A Prospective Study

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Follow-Up Findings in Multiple System Atrophy from [^{123}I]Ioflupane Single-Photon Emission Computed Tomography (SPECT): A Prospective Study

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Abstract: Background: Multiple system atrophy (MSA) is subdivided into two types: MSA-P (parkinsonian) and MSA-C (cerebellar). Brain SPECT allows for the detection of nigrostriatal involvement, even in the early stages. To date, the scientific literature does not show a consensus on how to follow-up MSA, especially MSA-C. Our aim was to analyze the diagnostic effectiveness of repeat [^{123}I]Ioflupane SPECT for the follow-up of MSA. Methods: A longitudinal observational study on 22 MSA patients (11 males and 11 females). Results: Significant changes were obtained in the quantitative SPECT assessments in the three Striatum/Occipital indices. The qualitative SPECT diagnosis did not show differences between the initial and evolving SPECT, but the neurologist's clinical suspicion did. Our results showed a brain deterioration of around 31% at 12 months, this being the optimal cut-off for differentiating a diseased subject (capable of solving diagnostic error rate). Previous imaging tests were inconclusive, as they showed less deterioration in the SPECT and quantitative assessments with respect to the group of confirmed patients. Repeated SPECT increased the diagnostic sensitivity (50% vs. 75%) and positive predictive value (72.73% vs. 77%). In addition, repeated SPECT proved decisive in the diagnosis of initial inconclusive cases. Conclusion: Repeat SPECT at 12 months proves useful in the diagnosis and follow-up of MSA.

Keywords: multiple system atrophy; dysautonomia; follow-up study; diagnostic accuracy; functional neuroimaging testing; Ioflupane-123

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1. Introduction

Multiple system atrophy (MSA) is a neurodegenerative disease with a fatal course that occurs sporadically in adults older than 30 years [1,2]. This entity is subdivided into MSA-P if parkinsonian symptoms predominate or MSA-C when cerebellar involvement predominates. This categorization varies depending on the clinical course of the patient [3]. There is a predominance of MSA-P in Europe and the USA and MSA-C in Asia. However, in Spain, there is a majority of MSA-C [4–7].

Following the revision of the diagnostic criteria for MSA in 2008, a positive SPECT result with [^{123}I]Ioflupane [3] was included as possible support for MSA-C. This test allows for the detection of nigrostriatal pathway involvement in vivo and noninvasively. However, it seems that it was not taken into account in the recent revision of its diagnostic criteria [8].

MSA cases show an asymmetric loss of putamen nucleus function, similar to idiopathic Parkinson's disease (PD) but with a greater involvement of the head of the caudate

nucleus [9]. Other studies have shown a greater decrease in presynaptic dopaminergic function in both striatal nuclei, rapidly and symmetrically in MSA compared to PD [10]. In studies performed using PET (Positron Emission Tomography) with another similar radiotracer, it was observed that MSA-P patients showed a greater involvement of the nigrostriatal pathway compared to MSA-C patients (who had a more uniform pattern). In addition, in some cases of MSA-C, the test was normal [11]. This coincides with early survival studies, which have postulated a more rapid functional deterioration in MSA-P patients compared to MSA-C patients [4].

Recently, a meta-analysis was performed that included 35 studies with a total of 701 patients: 356 with MSA-P, 62 with MSA-C, 204 with PSP (progressive supranuclear palsy), and 79 with DCB (corticobasal degeneration). A greater striatal involvement was observed in the PSP cases than in the PD and MSA-P cases, as well as in MSA-P patients with respect to MSA-C patients [12]. In an evaluation of 30 patients with MSA-C (possible or probable) without parkinsonism, signs of subclinical nigrostriatal dopaminergic deficit were found in [^{123}I]Ioflupane SPECT. No relationship was established between such involvement and the duration of the disease, either with cerebellar dysfunction or pontine atrophy on MRI [13].

Given that a normal study cannot exclude a diagnosis of MSA and that, in addition, MSA-C can show an apparent normality in the density of presynaptic dopamine transporters in a visual analysis and/or borderline values in a semiquantitative analysis, it is particularly relevant to perform follow-up studies in both cases. All this, added to the rapid progression of MSA, would allow for its evolution to be monitored using [^{123}I]Ioflupane SPECT [14]. In this regard, while serial studies on patients with PD do not seem to be justified, they would be on patients with suspected MSA, and especially those with MSA-C in its early stages [13,15], although these proposals have not been sufficiently contrasted. In fact, a recent article studied 7 patients with MSA-C, 5 with MSA-P, and 18 with PD, concluding that [^{123}I]Ioflupane SPECT and a semiquantitative analysis with SBR (Specific Binding Ratio) constitutes a specific biomarker of the progression of this disease, as well as of the subtype of dopaminergic degeneration in both MSA and PD [16].

To date, the scientific literature has not shown a consensus on how to follow-up MSA, especially MSA-C. Our aim is to understand the variations shown by these neuroimaging studies on MSA patients as time progresses. This way, the identification of possible changes typical of the progression of this disease could reveal the diagnostic effectiveness of [^{123}I]Ioflupane SPECT for the follow-up of MSA, and therefore the appropriateness of performing an evolutionary neuroimaging study on these patients.

2. Materials and Methods

This was a single-center longitudinal prospective observational study. Data were collected from 22 patients with MSA (11 males and 11 females) who underwent a second [^{123}I]Ioflupane SPECT during the follow-up period.

The SPECT study was performed with a Siemens® gamma camera, (Erlangen, Germany) model SymbiaTM, Symbia® model, equipped with a dual head. A low-energy, high-resolution collimator was used. The results were evaluated qualitatively with a visual analysis and quantitatively by using predefined Regions of Interest (ROIs) to obtain Striatum/Occipital indices for each striatal nucleus (right S/O and left S/O) and globally (global S/O), the latter being the arithmetic mean of both [17]. The reference area of non-specific uptake was the occipital lobe [18].

2.1. Ethical Considerations

The authorization for this study was obtained from our reference Biomedical Research Ethics Committee. For inclusion in the study, informed consent was obtained from each patient.

2.2. Statistical Study

In the descriptive study, qualitative variables were collected as absolute and percentage frequencies, as well as the mean and standard deviation in the quantitative variables, since they presented a normal distribution after applying the Shapiro–Wilks test. To calculate the association between the qualitative variables, the Chi-square test with Fisher's correction was applied. To analyze the baseline and final differences in the quantitative variables, the paired Student's *t*-test (parametric) or Wilcoxon's *t*-test (nonparametric) were used. Spearman's correlation coefficient was applied between the continuous quantitative variables. A value of $p < 0.05$ was considered to be significant.

3. Results

The demographic, clinical, and diagnostic variables are shown in Table 1. The mean age was 65 ± 9 years (ranging from 47 to 77 years). The mean time under study was 26 months.

Table 1. Demographic, clinical, and diagnostic characteristics.

N = 22 (100%)	
Subjects	▪ M 11 (50%) ▪ W 11 (50%)
Diagnosis	▪ MSA-probable 19 (86.36%) ▪ MSA-possible 3 (13.64%)
MSA type	▪ MSA-C 12 (54.55%) ▪ MSA-P 10 (45.46%)
Initial clinical suspicion	▪ MSA 18.2%, ▪ MSA-C 40.9% ▪ MSA-P 27.3%. ▪ Atypical parkinsonism 13.6%
Final clinical suspicion	▪ MSA-C 50% ▪ MSA-P 22.7% ▪ Atypical parkinsonism 18.2% ▪ Non-established 9.1%
Basal SPECT	▪ Pathological 50% ▪ Normal 31.8% ▪ Inconclusive 18.2%
Evolutionary SPECT	▪ Pathological 72.7% ▪ Normal 27.3% ▪ Inconclusive 0

N: Number of patients; M: Men; W: Women; MSA: Multiple System Atrophy; MSA-P: Multiple System Atrophy Parkinsonian Type; and MSA-C: Multiple System Atrophy Cerebellar Type.

The quantitative results of the baseline SPECT and repeated (or evolving) SPECT are shown in Table 2. While in the baseline SPECT there were 18.2% inconclusive results, in the evolving SPECT, there were no inconclusive cases.

Table 2. Quantitative analysis of both SPECT studies (basal and evolutionary).

S/O Indices	Basal SPECT	Evolutionary SPECT
Global S/O	$\bar{x}$ 1.43 (SD 0.25) [0.9–1.88]	$\bar{x}$ 1.29 (SD 0.2) [0.94–1.7]
Right S/O	$\bar{x}$ 1.437 (SD 0.26) [0.89–1.86]	$\bar{x}$ 1.29 (SD 0.21) [0.92–1.73]
Left S/O	$\bar{x}$ 1.43 (SD 0.25) [0.91–1.9]	$\bar{x}$ 1.28 (SD 0.2) [0.96–1.68]

S/O: Striatum/Occipital; $\bar{x}$: Average score; and SD: Standard deviation. The minimum and maximum scores are shown in square brackets.

Diagnostic accuracy values were calculated for both scans (baseline and evolving), taking as a reference the diagnosis at the end of the study period, since no postmortem confirmatory study was available (Table 3). When performing the second SPECT during the patients' follow-ups, it could be observed how the diagnostic performance increased, especially in terms of sensitivity and predictive values.

Table 3. Diagnostic accuracy of basal and evolutionary SPECT.

	Basal SPECT	Evolutionary SPECT
S	50% (22.38–77.62)	75% (50.66–99.34)
E	50% (1.66–98.34)	33.33% (0–79.39)
PPV	72.73% (41.86–100)	75% (50.66–99.34)
PNV	27.27% (0–58.14)	33.33% (0–79.39)

S: Sensitivity; E: Specificity; PPV: Positive predictive value; and PNV: Negative predictive value. The 95% confidence interval is shown in parentheses.

When looking for quantitative changes in [^{123}I]Ioflupane uptake over time (baseline and final), significant differences were observed in the three S/O indices. Global S/O (Striatum/Occipital): $\bar{x}$ = 1.4 (SD = 0.3) vs. $\bar{x}$ = 1.3 (SD = 0.2), p = 0.025); right S/O: $\bar{x}$ = 1.4 (SD = 0.3) vs. $\bar{x}$ = 1.3 (SD = 0.2), p = 0.031); and left S/O: $\bar{x}$ = 1.4 (SD = 0.2) vs. $\bar{x}$ = 1.3 (SD = 0.2), p = 0.021.

To determine the possible differences between cerebral hemispheres (possible changes in dominance according to evolution), the degrees of deterioration of both the right and left striatal nuclei were calculated. The basal versus final differences in each of the striatal nuclei were compared. The results showed that both striate nuclei deteriorated statistically significantly over time ($p < 0.05$). When comparing the degrees of deterioration of both hemispheres to find out if one of them deteriorated faster than the other, no significant differences were found.

Similarly, in order to detect the possible changes in the qualitative (visual) interpretations of the [^{123}I]Ioflupane SPECT results over time, we analyzed the possible changes in the qualitative diagnoses established by the nuclear medicine physicians according to the baseline study and evolutionary study, and found no significant differences (p = 0.188). Likewise, there was a significant association between the initial and final diagnostic suspicion ($p < 0.001$).

In 13 patients (59.09%), the baseline diagnosis was correct (which we call the "accurate diagnosis group"). However, in nine patients (40.91%), there was an erroneous baseline diagnosis (which we refer to as the "misdiagnosis group"). This initial mistake could be corrected during the evolutionary study.

We looked for baseline changes in the neuroimaging between the "misdiagnosis" and "accurate diagnosis" groups (Table 4) and found significant differences in the quantitative SPECT values between the two groups. In fact, we found significantly lower values in the "misdiagnosis group" with respect to the "accurate diagnosis group". No significant differences were observed when comparing the means of the interstudy months of both groups (26.2 vs. 21.3, p = 0.5).

Table 4. Changes between both quantitative SPECT assessments (basal–evolutionary) in relation to inter-study months for "misdiagnosis group" and "accurate diagnosis group".

	Misdiagnosis Group	Accurate Diagnosis Group	*p* Value
Global S/O	0.155	0.505	*
Right S/O	0.131	0.511	**
Left S/O	0.150	0.508	*
Inter-study months	26.206	21.333	$p > 0.05$

S/O: Striatum/Occipital index; * $p < 0.05$; and ** $p < 0.01$.

To quantify the effect in relation to time, we calculated the percentage of inter-study change, which was 31% at 12 months and 28–29% overall (Table 5). To determine whether, in cases of diagnostic error, there were greater or lesser changes in the images (i.e., a faster or slower progression of the MSA), the amount of net change between the two images (baseline versus evolutionary) was determined. This was performed globally and at 12 months for both groups ("misdiagnosis group" vs. "accurate diagnosis group"). In the "misdiagnosis group", the progression of deterioration was less, and, therefore, less evident in their SPECT than that in the "accurate diagnosis group". Moreover, a period of 12 months between the baseline and evolutionary study seemed to be very adequate for detecting possible changes.

Table 5. Amount of net deterioration according to SPECT: overall and 12-month assessment.

	Misdiagnosis Group N = 9		Accurate Diagnosis Group N = 13	
	Overall	12 Months	Overall	12 Months
Deterioration (%) Global S/O	21.5%	28.9%	34.1%	33.5%
Deterioration (%) Right S/O	22.7%	30.4%	33.7%	32.2%
Deterioration (%) Left S/O	20.3%	27.4%	34.5%	34.9%

N: Number of patients; and S/O: Striatum/Occipital index.

We searched for the possible impact of asymmetry on the involvement of both striatal nuclei (as a reflection of asymmetry between cerebral hemispheres), with respect to the total change that occurred, the speed of the disease progression, and the possible emission of an erroneous diagnosis. We could not correlate the asymmetry in the involvement of both striatal nuclei with the total change experienced in the baseline (r = 0.39, $p = 0.135$) and final studies (r = 0.028, $p = 0.927$). Neither did they differ with respect to the speed of the disease progression for the baseline (r = 0.094, $p = 0.728$), final (r = 0.09, $p = 0.758$), or the difference between the two (r = 0.11, $p = 0.696$). Finally, we found no significant differences in issuing a misdiagnosis in terms of the mean scores for the baseline skewness (0.009 "accurate diagnosis group" vs. 0.001 "misdiagnosis group", $p > 0.05$), final skewness (0.017 "accurate diagnosis group" vs. −0.008 "misdiagnosis group", $p > 0.05$), and baseline–final difference (−0.013 "accurate diagnosis group" vs. 0.005 "misdiagnosis group", $p > 0.05$).

4. Discussion

Our purpose was to describe and analyze the diagnostic effectiveness of performing serial brain SPECT studies of presynaptic dopamine transporters with [^{123}I]Ioflupane for MSA.

Based on the results presented, we can affirm that performing repeated SPECT with [^{123}I]Ioflupane was useful and effective in the diagnosis and follow-up of MSA. In our experience, instead of performing a single SPECT for the study of MSA, performing an evolving SPECT study improved both sensitivity (increasing from 50% to 75%) and PPV

(increasing from 72.7% to 75%). Moreover, in those cases of initial (or baseline) MSA with an inconclusive SPECT study, 100% of them were diagnosed.

Based on the overall S/O index change, we calculated the progression of the MSA. Consequently, we were able to determine the amount of global striatal deterioration for the first time, which was 28–29% on average overall and 31% after one year of follow-up. These findings are consistent with the characteristic evolution of this disease, whose rapidly progressive course triggers severe patient deterioration and poor survival [1,2,4,19]. Knowing this amount of functional loss can help to understand the pathochrony of this disease, as already pointed out in some studies where SPECT was considered as a biomarker of progression [14,16].

In a previous cross-sectional study by our group, we observed that there was asymmetry in the initial involvement of both striatal nuclei, with the left one being greater [20]. However, in the present work, we were able to verify that, although both striatal nuclei significantly worsened over time, the speed of deterioration was similar in both nuclei. This was another first for the present study. However, the analysis of the degree of asymmetry (lateralization) in the striatal involvement did not seem to play an important role in MSA, since we could not establish an association of this asymmetry with the impact on the total changes undergone, either with the speed of the progression of the disease or the possible emission of an erroneous diagnosis.

In our casuistry, the period in which the neurologists most frequently requested the evolutionary SPECT was 12 months. Based on our results, we believe it is appropriate to establish a cut-off of 12 months as the appropriate time to perform the evolutionary study for several reasons: (i) When analyzing the group of patients in which there was an initial misdiagnosis with respect to the group with a correct diagnosis, we found a greater diagnostic accuracy when using this cut-off. (ii) Given the percentage of functional loss mentioned above, this would allow us to distinguish it from other entities whose evolution is slower. (iii) When analyzing the changes in the SPECT, both qualitative and quantitative, there was a clear difference between the "misdiagnosis group" and the "accurate diagnosis group", which would allow for establishing an early accurate diagnosis and, consequently, an early initiation of treatment.

This is especially important for distinguishing between the MSA-P and MSA-C subtypes. In a previous cross-sectional study by our group, qualitative SPECT assessments were found to be accurate in differentiating between the two subtypes. Given that, in this disease, diagnostic errors can occur in the first SPECT assessment (especially in the MSA-C subtype), a serial study would allow for the detection of false negatives or doubtful results and correctly establish the diagnosis [11,15,16,21]. As an example of this, we found in our casuistry a 62-year-old woman with dysautonomic, parkinsonian, and cerebellar symptoms, unresponsive to treatment with levodopa, and it finally turned out to be a case of MSA-C with bilateral striatal involvement (Figure 1). Moreover, since a higher rate of progression has been demonstrated in the P form with respect to the C form, an evolutionary study would make it possible to establish this differentiation with a greater accuracy and confidence [4,11,12,14,22,23].

It should be noted that most of our patients had MSA-C, so the percentage of annual deterioration obtained could be higher in cases of MSA-P. In this regard, we recommend that future studies should not only analyze MSA as a whole, but also differentiate separately between the two subtypes of the disease, especially taking into account that SPECT may have a clear difference in its diagnostic effectiveness between MSA-P and MSA-C, as our group observed in a previous cross-sectional study.

After performing the evolutionary SPECT, it was observed that the diagnosis based on the qualitative assessment of SPECT (performed by the nuclear medicine physician) remained without differences in both time periods, whereas the quantitative analysis did show significant differences, reflecting the progressive deterioration characteristic of MSA. On the other hand, the diagnostic suspicion initially established by the neurologist did not always coincide with the confirmatory diagnosis obtained with the evolutionary SPECT, so

diagnostic reassignments had to be made. These reassignments were significantly related to the qualitative assessment of the SPECT, which provides greater value to the evolutionary or serial study.

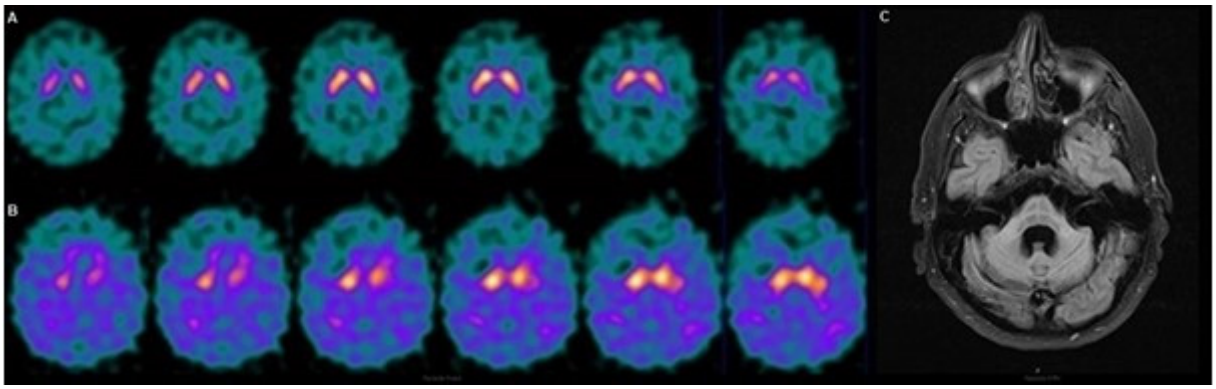

Figure 1. Follow-up of patient with MSA-C. A 62-year-old woman with MSA-C with dysautonomic, parkinsonian, and cerebellar symptoms, unresponsive to levodopa treatment. The evolutionary SPECT allowed the detection of bilateral striatal disease. (**A**) Anodyne basal SPECT. (**B**) Evolutionary SPECT at 12 months with noticeable bilateral striatal dysfunction. (**C**) MRI showed the characteristic "hot cross bun" sign in the cerebellum. The SPECT images are at 5 cm and the MRI image is at 10 cm.

When the changes between the baseline and evolutionary studies were studied, in the "misdiagnosis group", the progression of the deterioration was slower, so the progression of the disease was more insidious. We believe that this slower progression was related to the fact that, in the baseline study, the changes in the neuroimaging were more subtle in the "misdiagnosis group" and, therefore, more difficult to detect (which led to a greater probability of making an erroneous diagnosis). Therefore, in the event of initial diagnostic doubt, the evolutionary study would allow us to confirm or rule out the existence of involvement (Figure 2).

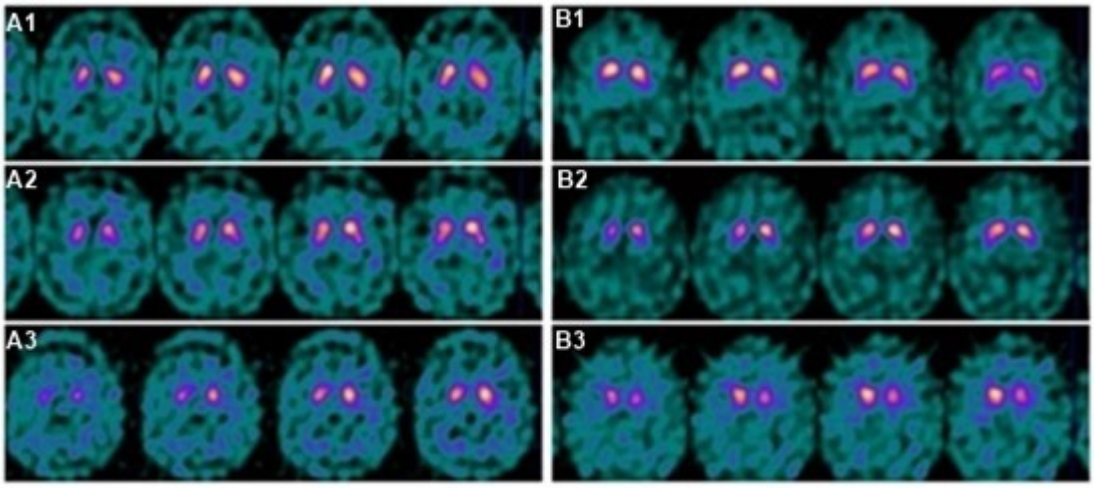

Figure 2. SPECT evolution of striatal involvement in two patients (**A**,**B**) with MSA. (**A**) Seventy-one-year-old male with MSA-P, studies performed at baseline (**A1**), 11 months (**A2**), and 3 years (**A3**). (**B**) Forty-eight-year-old male with MSA-C. SPECT at baseline (**B1**), 9 months (**B2**), and 2 years (**B3**). The SPECT images are at 5 cm.

The weaknesses and strengths of this study can be presented in parallel, as both are closely related. One weakness could be that it was a single-center study (which diminishes its external validity). However, this gives it a strength, as all the neuroimaging tests were

evaluated by the same physicians (two senior nuclear medicine specialists and one junior specialist, with the diagnosis being obtained by a group decision). If it had been carried out in several hospitals with different physicians, inter-observer bias would have to be considered. The sample size can be considered as a weakness, although we should not forget that MSA is a rare disease with a fatal prognosis. This makes patient recruitment very difficult and, above all, difficult to establish loyalty for a possible follow-up. For this reason, there are very few neuroimaging follow-up studies, with some being retrospective [15] or having a smaller sample size [13]. It could have been considered to recruit a cohort of healthy patients (as a control group) to study them comparatively with the MSA patients; however, no ethics committee could approve the administration of radionuclides in healthy patients. Undoubtedly, the greatest strength of this study is its longitudinal design, as this allowed for each subject to be his or her own comparison features. This lends a great robustness to the results, especially if we consider that the brain imaging studies were carried out under identical conditions, i.e., with the same SPECT device and the same physicians.

In our opinion, in order to obtain more information regarding the diagnostic effectiveness of [^{123}I]Ioflupane SPECT for MSA, studies based on a larger number of patients and with longer follow-up times would be necessary. With this, it would even be possible to perform repetitive SPECT (at shorter intervals), in order to know with a greater accuracy which would be the most appropriate cut-off for indicating the performance of a new SPECT.

5. Conclusions

In conclusion, we can say: (i) the evolving SPECT study is useful in the diagnosis of MSA, with a higher diagnostic yield with respect to baseline SPECT; (ii) one third of global striatal function deteriorates at 12 months, so we believe it is more appropriate to perform the evolutionary study at that time point; and (iii) striatal deterioration evolves unfavorably globally, without a clear lateralization of involvement.

Author Contributions: Concept and study design: J.V.-S., S.J.O.-L. and J.C.-V. Qualitative assessment of brain images and data acquisition: J.V.-S., S.J.O.-L. and T.A.-R. Drafting the manuscript and figures: J.V.-S. and J.C.-V. Supervision and correction of the manuscript: E.A. All authors have read and agreed to the published version of the manuscript.

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ARTÍCULO 3

TÍTULO:

Comparative Study between the Diagnostic Effectiveness of Brain SPECT with [^{123}I]Ioflupane and [^{123}I]MIBG Scintigraphy in Multiple System Atrophy

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Comparative Study between the Diagnostic Effectiveness of Brain SPECT with [^{123}I]Ioflupane and [^{123}I]MIBG Scintigraphy in Multiple System Atrophy

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Abstract: Background: Multiple system atrophy (MSA) is a neurodegenerative disease. It has a fast progression, so early diagnosis is decisive. Two functional imaging tests can be involved in its diagnosis: [^{123}I]Ioflupane SPECT and [^{123}I]MIBG scintigraphy. Our aim is to comparatively analyze the diagnostic performance of both techniques. Methods: 46 patients (24 males and 22 females) with MSA underwent [^{123}I]Ioflupane SPECT and [^{123}I]MIBG scintigraphy. In each of these techniques, qualitative assessment was compared with quantitative assessment. Results: SPECT visual assessment was positive in 93.5% of subjects (S = 95.24%; PPV = 93.02%). A cut-off of 1.363 was established for overall S/O index (S = 85.7%, E = 100%). Visual assessment of scintigraphy was positive in 73.1% (S = 78.57%, PPV = 94.29%). For the delayed heart/medistinum ratio (HMR) a cut-off of 1.43 (S = 85.3, E = 100%) was obtained. For each unit increase in delayed HMR, the suspicion of MSA increased by 1.58 (OR = 1.58, $p < 0.05$). The quantitative assessment showed an association with the visual assessment for each technique ($p < 0.05$). Conclusions: Both tests are useful in MSA diagnosis. Comparatively, we did not observe a clear superiority of either. Striatal and myocardial deterioration do not evolve in parallel. Qualitative assessment is crucial in both techniques, together with the support of quantitative analysis. Delayed HMR shows a direct relationship with the risk of MSA.

Keywords: multiple system atrophy; dysautonomia; diagnostic accuracy; Ioflupane-123; meta-iodobenzylguanidine-123

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1. Introduction

Multiple system atrophy (MSA) is a neurodegenerative disease belonging to the group of α-synucleinopathies. It is due to cytotoxicity induced by the accumulation of misfolded α-synuclein protein in the cytoplasm of oligodendrocytes and neurons of the central nervous system (CNS) and autonomic nervous system (ANS) [1,2].

At the CNS level, the substantia nigra, basal ganglia, inferior olivary nucleus, brainstem pons, and cerebellar Purkinje cells (striatonigral and olivopontocerebellar systems, respectively) are affected. The ANS is also involved at both the supraspinal (dorsal motor nucleus of the vagus nerve, locus coeruleus, and ventrolateral catecholaminergic neurons of the bulb) and medullary (intermediolateral columns and Onuf's nucleus) levels [3,4]. All this gives rise to a wide variety of symptoms and signs.

It has been considered that in MSA, two degenerative processes occurring in parallel coexist: (i) the accumulation of α-synucleins in the nucleus and cytosol of neurons, leading

to primary neurodegeneration; (ii) in turn, cytoplasmic inclusions in glial cells, leading to secondary neuronal degeneration [5]. Such changes at the cellular and tissue level would occur years before the onset of symptoms [6]. Furthermore, since there is no disease-modifying treatment available (much less curative), the disease progresses rapidly towards death, with a very poor survival rate [7,8].

The estimated global incidence of MSA is 0.6–0.7 cases per 100,000 individuals per year, with ranges varying from a minimum to a maximum of 0.1–3 cases per 100,000 people per year, respectively [9,10]. Data collected to date indicate that the incidence increases with the patients' age, with rates reaching 3 cases/100,000 population per year in those over 50 years and 12 cases/100,000 population per year in those over 70 years [10]. The prevalence ranges from 2 to 5 cases per 100,000 population and can reach 7.8 cases per 100,000 population in individuals over 40 years [10,11]. However, it is estimated that up to 10% of patients with parkinsonism symptoms may have an underlying MSA, potentially raising these numbers to 16.4 cases per 100,000 population [4]. Currently, there are no known risks or protective factors. The scientific literature reports dissimilar results without a clear relationship to reported environmental agents [12]. While it is primarily a sporadic disease, there are reported cases with a probable familial association of autosomal recessive inheritance [10,13–15]. The average age of onset ranges from 54 to 60 years old [16–20]. This condition affects males and females similarly, with no ethnic superiority. It is diagnosed 2 to 9 times more often in men than in women, believed to be due to their higher likelihood of seeking medical attention for erectile dysfunction, which is an early symptom of this disease [21,22].

MSA can be subdivided based on the predominant symptoms at the time of the initial diagnostic evaluation, into MSA-P if parkinsonian symptoms predominate, or MSA-C when cerebellar involvement is more pronounced. Currently, this entity is understood dynamically, meaning that this subdivision may change based on the patient's clinical evolution [23]. There is a predominance of MSA-P in Europe and the USA and MSA-C in Asia. In Spain, contrary to the rest of the studied European countries, there appears to be a majority of MSA-C [7,10,19,24]

The predominant tremor in MSA is action and postural, spasmodic, and irregular, with resting tremor observed less frequently [17]. The slowness in movements, to a greater or lesser extent (akinesia or bradykinesia), along with rigidity, worsens rapidly and progressively as the disease advances. Characteristics include falls due to postural instability, often preceding motor symptoms. Mid-term consequences include postural abnormalities such as severe trunk flexion (camptocormia) and anteriorization of the head (antecollis) [25–27]. Less frequently, orofacial dystonias or dyskinesias may occur, occasionally resembling sardonic laughter (a distorted facial expression due to involuntary spasms, typical in patients with *Clostridium tetani* infection) or Pisa syndrome, characterized by subacute axial dystonia causing severe lateral flexion of the head and neck, as well as axial trunk rotation. Moreover, the extension of degeneration at the putaminal level is directly associated with the lack of an adequate response to levodopa treatment [28]. The involvement of the olivopontocerebellar system is marked by gait and limb ataxia, ataxic dysarthria, dysdiadochokinesia, and scanning speech. Additionally, ocular abnormalities such as nystagmus with gaze-evoked and dysmetria may develop [25]. The neurodegeneration of the corticospinal system is also common in this disease, although its involvement is not considered a determining factor in current diagnostic criteria. Among the pyramidal signs specific to MSA patients is the extensor plantar response [23,29]. The mechanisms most frequently implicated in the development of autonomic symptoms (dysautonomia) are directly related to the pontine micturition center and the Onuf nucleus at the sacral spinal cord level. On the one hand, there is a loss of inhibitory signal input at the pontine micturition center, leading to detrusor muscle hyperreflexia. On the other hand, there is a loss of corticotropin-releasing factor neurons in the pontine micturition area and bladder. Consequently, urinary abnormalities such as incontinence, nocturia, urgency, and polyuria are typical. Severe damage to the Onuf nucleus in the sacral spinal cord causes bladder

atony and erectile dysfunction in men [30,31]. The loss of catecholaminergic neurons in the C1 area of the ventrolateral medulla manifests as severe variability in blood pressure and heart rate, potentially leading to orthostatic hypotension, syncope, or postprandial hypotension [30]. The loss of mesopontine cholinergic neurons, along with degeneration at the locus ceruleus (with preservation of those in the rostral raphe), may contribute to the development of REM Sleep Behavior Disorder, typically associated with prodromal phases of other α-synucleinopathies [32,33]. Other manifestations secondary to brainstem involvement include respiratory abnormalities such as laryngeal stridor and dysfunction in temperature regulation [25,30,34].

Because of these peculiarities, this entity can be difficult to diagnose. The diagnosis is made in relation to a series of items, known as Gilman's criteria [23,29], which were revised recently [35]. It is interesting to know which diagnostic tests would allow the identification and diagnosis of patients with MSA in the absence of post-mortem confirmatory histopathological study. In this context, currently available functional neuroimaging tests can help. In our work, we address two nuclear neuroimaging tests: SPECT of presynaptic dopamine transporters with [^{123}I]Ioflupane (previously included in the 2008 criteria for possible MSA-C, but not in the current criteria) and cardiac innervation scintigraphy with [^{123}I]MIBG (which is still included as diagnostic support).

The [^{123}I]Ioflupane SPECT test reflects the density of presynaptic dopamine transporters in the nigrostriatal pathway (substantia nigra and caudate and putamen nuclei). It consists of a qualitative assessment of the image (visually performed by the nuclear medicine physician) which can be assisted by the quantitative assessment performed by specific software. The result will typically show bilateral striatal hypocaptation, usually more symmetrical with respect to other entities such as Parkinson's disease (PD), and the presence of non-specific cortical activity (background) may also be observed [36]. In contrast, cardiac innervation scintigraphy with [^{123}I]MIBG reflects the state of the ANS by binding to the noradrenaline transporters expressed in the presynaptic terminals of postganglionic sympathetic neurons. Similar to SPECT, the result consists of a visual and a quantitative assessment, by means of the early heart/mediastinum ratio (HMR), delayed HMR, and washout percentage [37]. In MSA, scintigraphy usually shows normal myocardial uptake of the radiopharmaceutical or slightly decreased uptake [38]. This reduction is usually of a lesser extent since the development of dysautonomia in MSA is primarily due to presynaptic dysfunction, with postsynaptic adrenergic fibers being relatively unaffected [4,39,40]. On the contrary, in other diseases (as it happens in PD) the uptake is null [10,41]. The combination of these findings is shown in Figure 1.

Moreover, while in PD the nigrostriatal involvement occurs at the presynaptic terminal, in atypical parkinsonisms (such as MSA) the involvement also occurs at the postsynaptic terminal [42]. Currently, it is not known whether pre- or postsynaptic involvement occurs earlier in MSA [43]. In view of the above, both neuroimaging studies are recommended in the most recent guidelines for the diagnosis of atypical parkinsonism [44]. The aim of this study is to analyze the diagnostic performance of both tests in MSA.

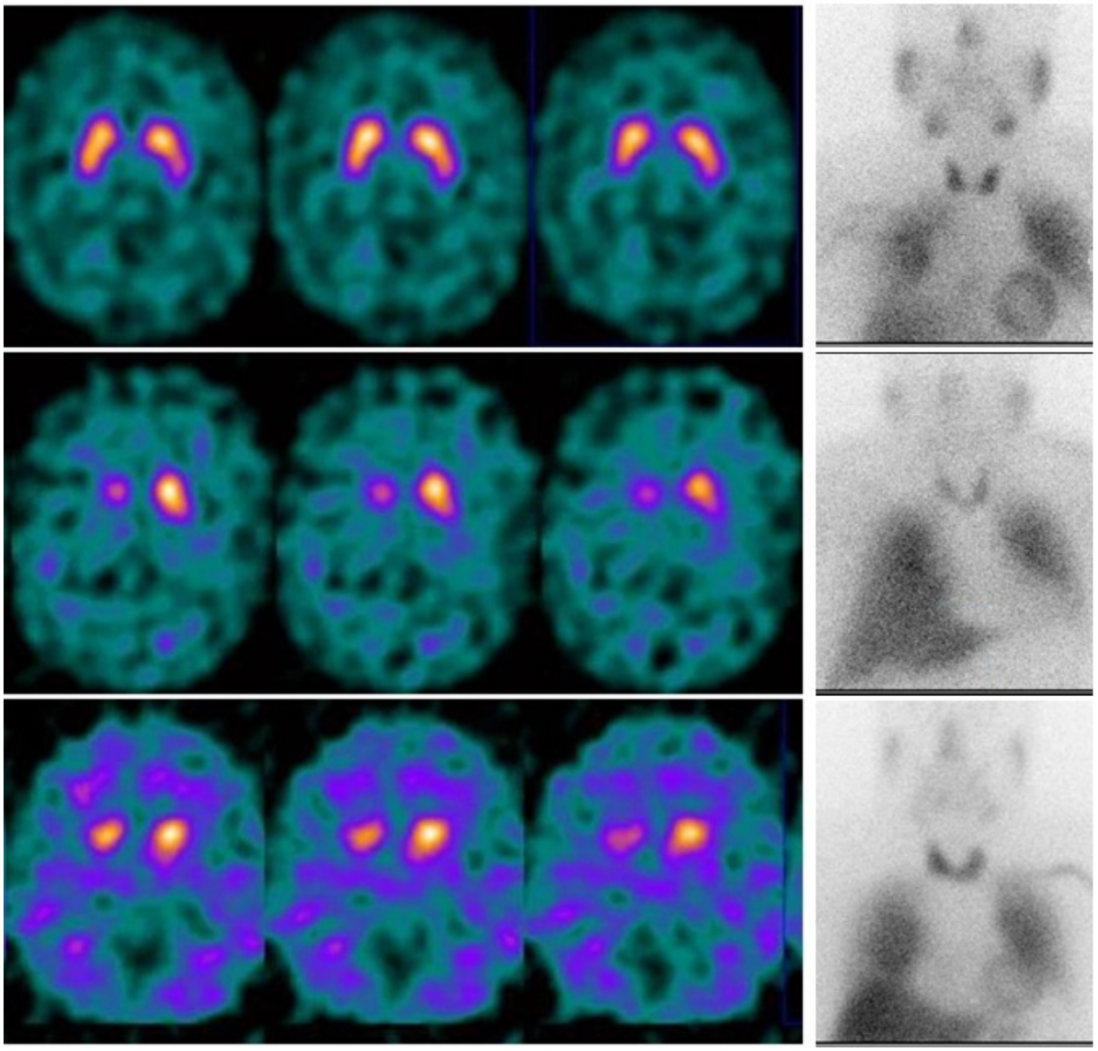

Figure 1. Combination of [^{123}I]Ioflupane SPECT and [^{123}I]MIBG scintigraphy in the study of parkinsonism. Top row: healthy patient: preserved uptake in both striatal nuclei and integrity of myocardial sympathetic function. Middle row: patient with PD: bilateral asymmetric striatal hypocaptation and absence of myocardial sympathetic function. Bottom row: patient with MSA-P: bilateral striatal hypocaptation (more symmetrical) with marked presence of cortical nonspecific activity and intact or slightly decreased myocardial sympathetic function.

2. Materials and Methods

Single-center retrospective observational study of patients diagnosed with MSA—by neurologists from the movement disorders unit—who underwent SPECT of presynaptic dopamine transporters with [^{123}I]Ioflupane and scintigraphy with [^{123}I]MIBG, between 2004 and 2020. Both studies were conducted with a maximum one-month difference, following the request from the referring physician, typically after the initial visit to the movement disorders unit, resulting in an early diagnosis for most patients. All imaging studies were individually and blindly analyzed by three medical nuclear medicine specialists dedicated to the field of neurology. The diagnostic performance of both imaging techniques in MSA is addressed comparatively. In turn, in each of them, the effectiveness of qualitative (visual) versus quantitative analysis is confronted.

Myocardial innervation scintigraphy was obtained using a Siemens® gamma camera, model Symbia® (Erlangen, Germany), equipped with a dual head and low-energy, high-resolution collimator. Two static planar images were acquired in anterior chest projection with a 256 × 256 matrix at 15 min and 4 h after intravenous administration of the

radiopharmaceutical [^{123}I]MIBG. Subsequently, a qualitative assessment (by the nuclear physician) of myocardial uptake was performed, as well as a quantitative analysis (according to the value emitted by the device). For the latter, myocardial uptake was compared with mediastinal uptake in the 4 h image, using regions of interest (ROIs), and the delayed heart/mediastinum ratio (HMR) was obtained [44].

$$\text{Heart/mediastinum ratio (HMR)} = \frac{\text{Mean counts per pixel in myocardium}}{\text{Mean counts per pixel in mediastinum}}.$$

The [^{123}I]Ioflupane SPECT was used with the same gamma camera and collimator described. Tomographic images of the skull were obtained 3–4 h after administration of the radiopharmaceutical and after thyroid block with Lugol's solution. A 360° circular orbit was performed around the skull, with 3° intervals, acquiring 60 images with a duration of 35 s per interval, with a matrix of 128 × 128. Subsequent reconstruction of the images was performed using filtered back projection algorithms without attenuation correction (Hanning filter with a frequency of 0.7). Images were analyzed according to transaxial slices and orbito-meatal orientation, consisting of a qualitative assessment of the same and a quantitative assessment using ROIs to compare the average number of striate nuclei counts with respect to the occipital lobe, known as the striate/occipital index (S/O).

2.1. Inclusion Criteria

Both techniques included patients with suspected or clinical diagnosis of MSA, referred to the nuclear medicine department.

2.2. Exclusion Criteria

Patients with factors that could affect both studies (qualitatively or quantitatively). (1) For [^{123}I]Ioflupane SPECT: patients with medication such as antidepressants or other substances (such as cocaine). (2) For [^{123}I]MIBG scintigraphy: drugs that interfere with the noradrenaline transporter and its vesicular storage, and diseases and common causes of small fiber neuropathies (such as diabetes mellitus) (Figure 2).

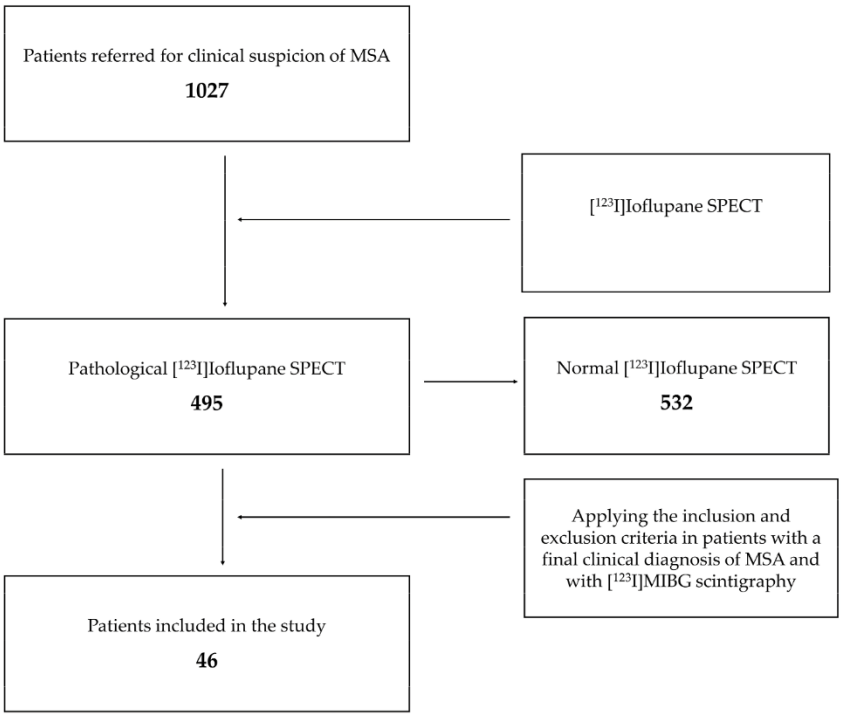

Figure 2. Flowchart of the patient inclusion process. SPECT: single-photon emission computed tomography; MSA: multiple system atrophy.

2.3. Ethical Considerations

Authorization was obtained from the Biomedical Research Ethics Committee of the province of Málaga. Prior to the performance of both neuroimaging tests, informed consent was obtained from each patient. The harmonized tripartite standards of the Helsinki declaration, the Organic Law on Biomedical Research of 15/2007 of 3 July, the Organic Law on Personal Data Protection (LOPD) of 13 December 2018, the code of ethics of the "Organización Médica Colegial" (OMC), the basic regulatory law 41/2002 on patient autonomy and rights and obligations regarding clinical information and documentation, of November 14, as well as the standards of good clinical practice, were respected.

2.4. Statistical Analysis

Within the descriptive study, qualitative variables were shown as absolute and percentage frequencies and quantitative variables as mean and standard deviation. The Shapiro–Wilk test was used to determine whether the values of each variable followed a normal distribution. To establish associations between quantitative variables, the Student *t*-test (parametric) and Mann–Whitney–Wilcoxon U test (nonparametric) were used, and for qualitative variables, the Chi-squared test was applied (with Fisher's correction when necessary). Spearman's correlation coefficient was used to analyze possible associations between continuous quantitative variables. ROC curves were constructed to establish an optimal cut-off point for these associations. A value of $p < 0.05$ was considered significant.

3. Results

A total of 46 patients were analyzed: 24 males (52.2%) and 22 females (47.8%). The mean age was 63 ± 9 years (range 47 to 79 years). They were classified according to Gilman's criteria into 33 MSA-probable (71.7%) and 13 MSA-possible (28.3%). The predominant MSA subtype was MSA-parkinsonian (MSA-P) (80.4%) versus MSA-cerebellar (MSA-C) (19.6%). In total, 30 patients (65.2%) showed dysautonomic symptoms, 42 (91.3%) had parkinsonism, 10 (21.7%) had cerebellar symptomatology, and 8 subjects (17.4%) had corticospinal involvement. Although all were treated with levodopa, 43 of them (93.5%) showed no response to this treatment.

The [^{123}I]Ioflupane SPECT test was performed on all subjects, with a result compatible with MSA in 93.5% of them and apparently normal in the remaining 6.5%. In the quantitative assessment of SPECT using the three S/O indices, the values obtained were: right S/O index $\bar{x}$ = 1.34, SD = 0.12, (range: 1.14–1.63); left S/O index $\bar{x}$ = 1.32, SD = 0.13, (range: 1.12–1.61); global S/O index $\bar{x}$ = 1.33, SD = 0.13, (range: 1.13–1.60).

Scintigraphy with [^{123}I]MIBG was also performed in all patients, 73.1% being compatible with MSA (normal uptake 58.7%; decreased uptake in 17.4%) and incompatible in the remaining 23.9% (absent uptake). The quantitative assessment of this test was performed using the delayed heart/mediastinum ratio, obtaining values of $\bar{x}$ = 1.58, SD = 0.32, (range: 1.12–2.27).

The diagnostic effectiveness of both neuroimaging techniques was analyzed in the 46 patients with MSA (Table 1).

Table 1. Diagnostic effectiveness of both techniques ([^{123}I]Ioflupane SPECT and [^{123}I]MIBG scintigraphy) in MSA.

	[^{123}I]Ioflupane SPECT	**[^{123}I]MIBG Scintigraphy**
Sensitivity	95.24% (87.61–100)	78.57% (64.97–92.17)
Specificity	25% (0.00–79.93)	50% (0.00–100)
PPV	93.02% (84.25–100)	94.29% (85.17–100)
PNV	33.33% (0.00–100)	18.18% (0.00–45.52)
Accuracy	89.13%	76.09%

Percentage values (%) ± 95% confidence interval; PPV: positive predictive value; PNV: negative predictive value.

In the [^{123}I]Ioflupane SPECT, the degree of agreement between the qualitative assessment (visual, performed by the nuclear physician) and the quantitative assessment (numerical, using the three S/O indices) was calculated (Table 2). Differences were found between both assessments when using the global S/O index to consider a patient as healthy or sick.

Table 2. Association between qualitative and quantitative SPECT assessments in two groups (healthy and sick).

S/O Indexes	Healthy	Sick	*p* Value
Global	$\bar{x}$ = 1.429 (S = 0.056)	$\bar{x}$ = 0.658 (S = 0.672)	*
Right	$\bar{x}$ = 1.421 (S = 0.063)	$\bar{x}$ = 1.329 (S = 0.127)	>0.05
Left	$\bar{x}$ = 1.437 (S = 0.056)	$\bar{x}$ = 1.304 (S = 0.133)	>0.05

$\bar{x}$: average scores; SD: standard deviation; * $p < 0.05$.

Similarly, in the [^{123}I]MIBG scintigraphy, the relationship between both the visual assessment and numerical assessment was studied. After this, the results obtained by both techniques (SPECT and scintigraphy) were compared. Two groups were established according to the visual classification of the scintigraphy: "not suggestive of MSA" (subjects with no cardiac uptake) and "suggestive of MSA" (patients with normal or decreased cardiac uptake). We found differences between the qualitative and quantitative assessments of [^{123}I]MIBG: "not suggestive of MSA" $\bar{x}$ = 5500, SD = 4.035 vs. "suggestive of MSA" $\bar{x}$ = 21.588, SD = 8.302; $p < 0.001$. However, we found no association between qualitative assessment of [^{123}I]MIBG scintigraphy and quantitative [^{123}I]Ioflupane SPECT by global S/O index: "not suggestive of MSA" $\bar{x}$ = 0.921, SD = 0.601 vs. "suggestive of MSA" $\bar{x}$ = 0.640, SD = 0.694; $p > 0.05$.

In addition, in order to determine the diagnostic performance of the [^{123}I]MIBG technique, a logistic regression was performed between visual classification, numerical classification, and introducing as an additional variable the clinical diagnostic classification according to Gilman's criteria (MSA-probable and MSA-possible). It was obtained that, for each unit increase in delayed HMR, the risk of suspected MSA increased by 1.58 units (OR = 1.58; CI (95%) [1.24–2.50]; $p < 0.007$).

Furthermore, the possible superiority of the visual assessment with each of the techniques (SPECT and scintigraphy) was analyzed. Two groups were formed: "suspected MSA" (when the scan result showed preserved or slightly diminished myocardial innervation), and "no suspected MSA" (when no/absent myocardial uptake was obtained on SPECT) (Table 3). Fisher's test took a value of 1, indicating that neither technique showed superiority as no statistically significant association was observed between the two variables. Similarly, when analyzing the possible relationship between the qualitative assessment of the scintigraphy and the diagnostic classification according to Gilman's criteria (Table 3), no significant differences were obtained ($p < 0.47$).

Table 3. Association of qualitative assessment of [^{123}I]Ioflupane SPECT or qualitative assessment of [^{123}I]MIBG scintigraphy in both groups: "suspected MSA" and "non-suspected MSA".

		Visual Scintigraphy *		
		Suspected MSA	**Non-Suspected MSA**	***p* Value**
Visual SPECT **	Negative 3 (6.5%)	3 (8.6%)	0	$p > 0.05$
	Positive 43 (93.5%)	32 (91.4%)	11 (100%)	
Diagnostic classification	Possible 13 (28.3%)	11 (31.4%)	2 (18.2%)	$p > 0.05$
	Probable 33 (71.7%)	24 (68.6%)	9 (81.8%)	

(*) Visual evaluation of [^{123}I]MIBG scintigraphy (qualitative classification); (**) visual evaluation of [^{123}I]Ioflupane SPECT (qualitative classification).

We wanted to know whether there was a possible correlation between the quantitative assessments of both studies ([^{123}I]Ioflupane SPECT and [^{123}I]MIBG scintigraphy). Spearman's correlation coefficient was applied, obtaining a non-significant coefficient of r = 0.06 ($p > 0.05$), which indicated a very low correlation.

We calculated the optimal cut-off point within the quantitative assessment of the study with [^{123}I]MIBG scintigraphy (delayed HMR). We obtained the ROC curve, whose graph showed an optimal cut-off of 1.43 with an S = 85.3% and E = 100% (Figure 3). The area under the curve (AUC) was 0.9647 (95% CI (0.918–1)).

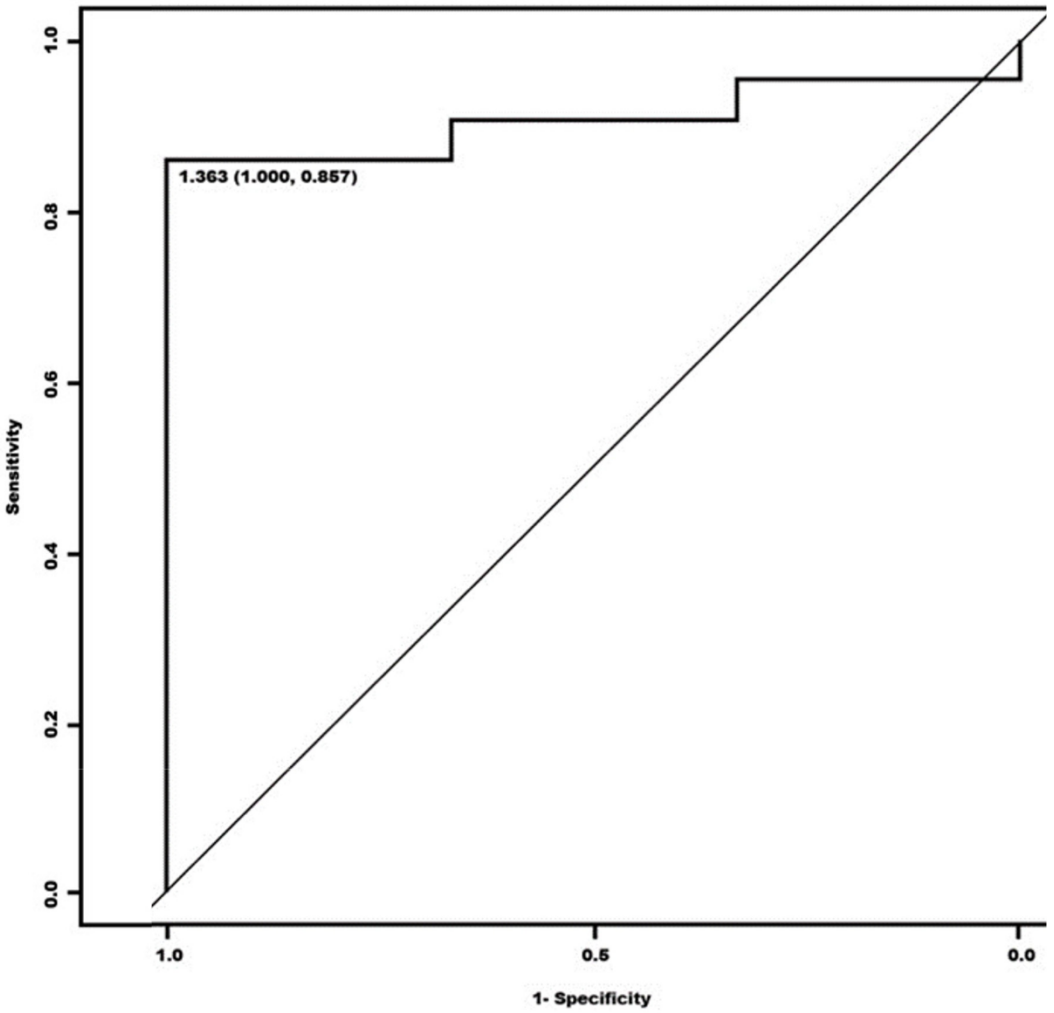

Figure 3. ROC curve of quantitative and visual assessment of the [^{123}I]MIBG scintigraphy test for two categories ("suspected MSA", "not suspected MSA").

Similar to a previous study by our group on the diagnostic effectiveness of [^{123}I]Ioflupane SPECT in 139 patients with MSA, we obtained an ROC curve for the calculation of the cut-off of the global S/O index as a function of the SPECT visual assessment, according to two categories ("pathological" and "non-pathological") (Figure 4). The optimal cut-off point was set at 1.363 (S = 85.7%, E = 100%) with an AUC of 0.9048 (95% CI (0.8099–0.9996)). This value is very close to that obtained in a study in which the cut-off was 1.401 (S = 86.7% and E = 80%). The AUC was 0.8951 (95% CI (0.8267–0.9635)).

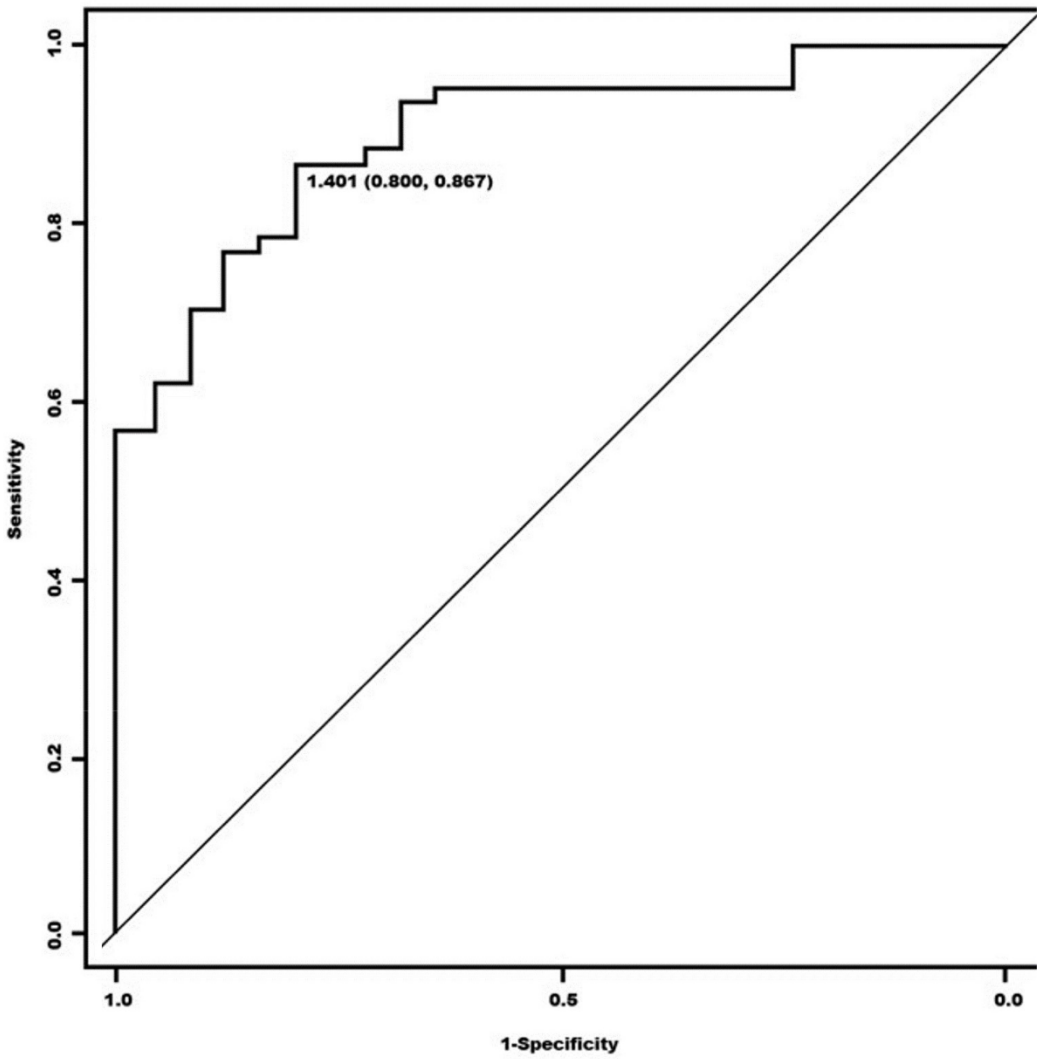

Figure 4. ROC curve of quantitative and visual assessment of the [^{123}I]Ioflupane SPECT test for two categories ("pathological" versus "not pathological").

4. Discussion

The present study analyzes the diagnostic performance of both neuroimaging tests in MSA, both independently and comparatively between them.

When analyzing the possible superiority of one technique over the other, we found no significant differences, so both techniques are equally useful in the diagnosis of MSA. In fact, no correlation could be established between the quantitative results of both tests. This may be since each of them evaluates different aspects affected in this pathology (dopaminergic nigrostriatal pathway and myocardial sympathetic innervation, respectively). However, it can also be deduced from this that, since they are not related, striatal and myocardial deterioration do not evolve in parallel, so we believe that both tests are necessary for an accurate diagnosis.

The [^{123}I]Ioflupane SPECT was positive in 93.5% of subjects (S = 95.24%; PPV = 93.02%). Given this sensitivity value, we believe it wiser to perform this neuroimaging test first. The [^{123}I]MIBG scintigraphy was compatible with MSA in 73.1% (S = 78.57%, PPV = 94.29%), which suggests that, together with the superior specificity (E = 50%) with respect to SPECT (E = 25%), performing this technique second would allow us to confirm selected patients and at the same time rule out possible false positives. Current guidelines recommend both techniques for the correct study of atypical parkinsonism [44]. In view of the above, we believe that the [^{123}I]Ioflupane SPECT technique could be reconsidered in the diagnostic

criteria for MSA, as it was in the previous review [10]. On the other hand, we also state the usefulness of [^{123}I]MIBG scintigraphy as a support tool (and for the differential diagnosis of Parkinson's disease) and the need for it to remain in the current criteria after the last revision [35]. In fact, once again when analyzing our variables with the previous diagnostic classification (when our study was performed), under the categories of MSA-probable and MSA-possible, we found no differences either in the final diagnosis or in the outcome of the neuroimaging tests. We think that with the creation/adaptation of the new categories after the last revision (Established and Clinically Probable MSA [35]), future studies will be able to check whether they are more accurate.

In this regard, the nuclear physician adequately classified a healthy subject from a diseased one in both neuroimaging techniques. Furthermore, in this study, we again confirm the relationship between the qualitative assessment of the nuclear physician and the quantitative assessment by means of specific uptake indexes as diagnostic support, in both tests. These findings are similar to previous research by our group [45].

As a first, we have shown that there is a direct relationship between the delayed HMR and the risk of MSA (for each unit increase in delayed HMR, the risk of suspected MSA increases by 1.58) (OR = 1.58, $p < 0.05$). In addition, we propose that the cut-off of this index could be set at 1.43 (S = 85.3, E = 100%), a value close to previous studies [46–48]. In addition, other neurodegenerative diseases such as PD show lower values with respect to this cut-off point, allowing us to differentiate between them [49,50].

As for the cut-off point in the [^{123}I]Ioflupane SPECT, the overall S/O index was again shown to be the most appropriate for discerning, together with the qualitative assessment of the nuclear physician, between a healthy patient and a patient with MSA. It is worth noting that the cut-off obtained of 1.363 (S = 85.7%, E = 100%), from a significantly smaller number of cases than in previous studies, barely differs by 0.038 with respect to our previous study: 1.401 (S = 86.7% and E = 80%) [45].

Based on the results obtained, it could be thought that [^{123}I]Ioflupane SPECT has a low specificity score and that the accuracy of [^{123}I]MIBG scintigraphy is also low. One explanation for this finding may be that the patient sample obtained has been selected with strict inclusion and exclusion criteria, so that almost all patients have clinically confirmed MSA at follow-up (rather than pathology confirmation when the patients died). We have taken as a gold standard the clinical diagnosis at the end of the study period, where many of these patients had already died, so this is the definitive diagnosis. Therefore, when analyzing the results retrospectively, the diagnostic tests as a whole do not stand out for their specificity, but for their ability to detect (sensitivity) patients with a specific diagnosis (positive predictive value).

Therefore, it was assessed whether one test might be superior in diagnosing MSA compared to the other one, but no statistically significant differences were obtained. This was expected, as both studies focus on different pathophysiological pathways affected in MSA. Consequently, neither test can replace the other; rather, they complement each other. In order to identify a movement disorder, neurologists usually first request [^{123}I]Ioflupane SPECT and can thus confirm that a degenerative process is present (instead of other forms of parkinsonisms, such as those with pharmacological causes). Secondly, they request [^{123}I]MIBG scintigraphy to make a differential diagnosis of PD or Lewy body dementia versus other atypical parkinsonisms (MSA, progressive supranuclear palsy, or corticobasal degeneration). These findings support the results obtained in our previous research, in which we advocated for the need to include both imaging studies in the diagnostic algorithm of MSA [36,45].

The novelty of this study lies in the direct comparison between both imaging tests in the specific case of multiple system atrophy, where the specific literature on the subject is lacking. In fact, in the field of nuclear medicine, data such as those provided by this study are necessary to establish a cut-off point in the quantitative analysis of [^{123}I]MIBG scintigraphy. For this reason, we point out what information is provided by each of the two neuroimaging tests in MSA.

Regarding the weaknesses and strengths of this research, we could denote the limitations of a cross-sectional study. If we had followed up with the recruited patients, then we could have verified whether the diagnostic effectiveness of both neuroimaging tests (in terms of sensitivity and specificity) was maintained over time, or whether, on the contrary, in subsequent analyses, errors in the diagnostic classifications were detected and the previous results would have to be reconsidered. For example, we could have known how many cases of MSA-probable and MSA-possible were confirmed in the long term. By following up with patients, we could have serially observed changes in both forms of multiple system atrophy (MSA-C and MSA-P), both with [^{123}I]Ioflupane SPECT and [^{123}I]MIBG scintigraphy. However, although the recruitment period was long, it was not feasible to perform an evolutionary study because MSA has a poor prognosis, and because of this, many of the patients (or their relatives) wished to drop out of the study when they were aware of the denouement of the disease; other patients died within a short period of time. Moreover, based on our hospital protocol, when the patient already has an established diagnosis of MSA, it is not appropriate to perform both neuroimaging techniques. Consequently, we were only able to follow up with a subsample of these patients with one of the two techniques, namely [^{123}I]Ioflupane SPECT [36].

Another possible limitation is that a stratified analysis by groups was not performed. For example, dividing by age and gender, to try to determine differences in the severity of MSA in the different groups. Another interesting possible subdivision would be based on the presence of dysautonomic symptoms, parkinsonism, cerebellar symptoms, or corticospinal involvement. However, when subdividing by groups, the size of each group was very small, and the statistical results were not reliable. In this regard, we must keep in mind that MSA has a very low prevalence, so achieving large sample sizes is very difficult.

It could be noted as a limitation of the present study that it is a single-center study. If a multicenter study had been carried out, then the results would have had a higher external validity. This would also have made a larger sample size possible. However, if a multihospital study had been performed, then we would have to take into account the possible inter-observer variability. In our investigation, all neuroimaging tests were evaluated by the same group of nuclear medicine physicians (all diagnostic reports were made by consensus among the three participating physicians). Consequently, there was no variability among the imaging assessments, which confers reliability to the results in this aspect.

5. Conclusions

Both imaging techniques ([^{123}I]Ioflupane SPECT and [^{123}I]MIBG scintigraphy) have been shown separately to be useful in the diagnosis of MSA, with optimal diagnostic performance. Comparatively, we observed no net superiority of either. This, together with the fact that striatal and myocardial deterioration do not seem to evolve in parallel, supports the need to consider both tests in the diagnosis of MSA. The qualitative assessment of the nuclear physician remains crucial in both techniques, together with the support of quantitative analysis using established indices and our proposed cut-off. Delayed HMR shows a direct relationship with the risk of MSA.

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Data Availability Statement: Data is contained within the article.

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Abbreviations

CI = Confidence Interval; E = Specificity; HMR = Heart/Mediastinum Ratio; MIBG = meta-iodobenzylguanidine; MSA = Multiple System Atrophy; MSA-P = Multiple System Atrophy Parkinsonian Type; MSA-C = Multiple System Atrophy Cerebellar Type; ROI = Region of Interest; S = Sensitivity; SD = Standard Deviation; S/O index = Striatum/Occipital index; SPECT = Single-Photon Emission Computed Tomography.

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IV. CONCLUSIONES

CONCLUSIONES

A tenor de los objetivos inicialmente demarcados y a la luz de los resultados obtenidos, podemos concluir que:

1) El SPECT cerebral con [^{123}I]Ioflupano es una herramienta útil y fiable en el diagnóstico de la AMS especialmente al inicio de la sospecha clínica, con mayor sensibilidad y precisión que otras técnicas de imagen convencionales.

2) La evaluación cualitativa de esta técnica muestra una superioridad clara para distinguir entre las categorías de sano–enfermo y entre los subtipos de AMS (forma parkinsoniana o cerebelosa), lo que indica que la valoración del médico nuclear es crucial en el diagnóstico. También hay una buena correspondencia entre dicha valoración cualitativa y la cuantitativa utilizando la metodología de las ROIs predefinidas y nuestro punto de corte propuesto (Índice E/O: 1,4).

3) El tratamiento con levodopa no parece ofrecer beneficios en el diagnóstico de pacientes con AMS, por lo que en presencia de un estudio positivo de SPECT con [^{123}I]Ioflupano, este fármaco podría omitirse en términos de coste-efectividad.

4) La mayoría de nuestros pacientes mostraron inicialmente un compromiso predominante del núcleo estriado izquierdo, lo cual podría ser de utilidad en el diagnóstico de casos incipientes de AMS.

5) El estudio evolutivo mediante SPECT es apropiado para el diagnóstico de AMS, con un mayor rendimiento con respecto a la SPECT basal.

6) Un tercio de la función estriatal global se deteriora a los 12 meses, por lo que sería más adecuado realizar el estudio evolutivo en ese momento.

7) La velocidad de deterioro estriatal evoluciona de forma bilateral y simultánea.

8) Ambas técnicas de imagen (SPECT con [^{123}I]Ioflupano y gammagrafía con [^{123}I]-MIBG) han demostrado ser útiles por separado en el diagnóstico de la AMS, con un rendimiento óptimo.

9) Comparativamente, no se observa superioridad neta en ninguna de ambas técnicas de imagen. Lo cual, unido a que el deterioro estriatal y miocárdico no evolucionan en paralelo, apoya la necesidad de considerar ambas pruebas en el diagnóstico de AMS.

10) La evaluación cualitativa del médico nuclear es determinante en ambas técnicas, junto al análisis cuantitativo mediante índices establecidos y el punto de corte propuesto (Índice corazón-mediastino tardío: 1,36).

11) El índice corazón-mediastino tardío en la cuantificación de la gammagrafía con [^{123}I]-MIBG muestra una relación directa con el riesgo de presentar AMS, de modo que, por cada unidad de incremento, el riesgo aumenta en 1,6 veces (OR = 1.58).

V. REFERENCIAS BIBLIOGRÁFICAS

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VI. ANEXOS

ANEXO 1. Autorización del Comité Ético de Investigación Provincial de Málaga.

Comité de Ética de la Investigación Provincial de Málaga

Servicio Andaluz de Salud
CONSEJERÍA DE SALUD

Dra. Dña. Gloria Luque Fernández, Secretaria del CEI Provincial de Málaga

CERTICA:

Que en la sesión de CEI de fecha: 24/06/2021 ha evaluado la propuesta de D/Dña.: Javier Caballero Villarraso, referido al Proyecto de Investigación: "Efectividad diagnóstica del SPECT cerebral con I123 Ioflupano en la atrofia multisistémica".

Este Comité lo considera ética y metodológicamente correcto.

La composición del CEI en esta sesión es la siguiente:

Dra. Ana Alonso Torres (UGC Neurociencias)
Dra. Mª Victoria de la Torre Prados (UMA)
Dra. Marta Blasco Alonso (Obst. y Ginecología)
Dª. Ana Díaz Ruíz (Licenciada en Derecho)
Dª. Inmaculada Doña Díaz (Alergología)
Dr. Rafael Carvia Ponsaille (Anatomía Patológica)
Dr. José C. Fernández García (UGC Endocrinología y Nutrición)
Dr. Manuel Herrera Gutiérrez (UGC UCI)
Dr. Antonio López Téllez (Médico de Familia)
Dr. José Leiva Fernández (Médico Familia)
Dra. Mª Dolores López Carmona (Medicina Interna)
Dr. Jesús López del Peral (Esp.Protec.Datos)
Dña. Carmen López Gálvez del Postigo (Miembro Lego)
Dra. Elena Sánchez Yáñez
Dra. Gloria Luque Fernández (Investigación)
Dra. Leonor Ruíz Sicilia (UGC Salud Mental)
Dra. Mª Angeles Rosado Souvirón (UGC Farmacia)
Dr. José L. Guerrero Orriach (UGC Anestesia y Reanimación)
Dra. Cristobalina Mayorga Mayorga (Laboratorio)

Fdo.: Dra. Gloria Luque Fernández
Secretaria del CEI