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Original Article

ORIGINAL ARTICLE

Magnetic resonance imaging abnormalities as a marker of multiple system atrophy in isolated rapid eye movement sleep behavior disorder

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Abstract

Study Objectives: Patients with isolated rapid eye movement (REM) sleep behavior disorder (IRBD) develop Parkinson disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA). Magnetic resonance imaging (MRI) is abnormal in MSA showing abnormalities in the putamen, cerebellum, and brainstem. Our objective was to evaluate the usefulness of MRI to detect MRI abnormalities in IRBD and predict development of MSA and not PD and DLB.

Methods: In IRBD patients that eventually developed PD, DLB, and MSA, we looked for the specific structural MRI abnormalities described in manifest MSA (e.g. hot cross-bun sign, putaminal rim, and cerebellar atrophy). We compared the frequency of these MRI changes among groups of converters (PD, DLB, and MSA) and analyzed their ability to predict development of MSA. The clinical and radiological features of the IRBD patients that eventually converted to MSA are described in detail.

Results: A total of 61 IRBD patients who underwent MRI phenoconverted to PD (n = 30), DLB (n = 26), and MSA (n = 5) after a median follow-up of 2.4 years from neuroimaging. MRI changes typical of MSA were found in four of the five (80%) patients who converted to MSA and in three of the 56 (5.4%) patients who developed PD or DLB. MRI changes of MSA had sensitivity of 80.0%, specificity of 94.6%, positive likelihood ratio of 14.9 (95% CI 4.6–48.8), and negative likelihood ratio of 0.2 (95% CI 0.04–1.2) to predict MSA.

Conclusions: In IRBD, conventional brain MRI is helpful to predict conversion to MSA. The specific MRI abnormalities of manifest MSA may be detected in its premotor stage.

Statement of Significance

Patients with isolated rapid eye movement (REM) sleep behavior disorder (IRBD) develop Parkinson disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA). It is uncertain which of these three conditions a patient with IRBD will develop with time. We have found that the magnetic resonance imaging (MRI) abnormalities in the brain typically seen in established MSA (e.g. cerebellar atrophy and hot cross-bun sign) were commonly found in those IRBD that converted to MSA and not in those that developed PD and DLB. This finding indicates that in IRBD, conventional MRI is a promising tool that may be able to detect future development of MSA in subjects with IRBD.

Key words: isolated REM sleep behavior disorder; multiple system atrophy; magnetic resonance imaging

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Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is defined by excessive motor activity and dream-enacting behaviors in REM sleep. RBD is termed isolated (IRBD) when it cannot be attributed to any known cause [1, 2]. Longitudinal studies indicate that IRBD represents the prodromal manifestation of the synucleinopathies, as most individuals eventually develop motor, cognitive, and autonomic symptoms and are clinically diagnosed with Parkinson disease (PD), dementia with Lewy bodies (DLB) and, far less frequently, with multiple system atrophy (MSA) [3–6]. A recent multicenter study involving 1,280 IRBD patients showed that 352 (28%) developed a clinically defined synucleinopathy and among them 16 (4.5%) were diagnosed with MSA [6]. It is uncertain if there are highly specific clinical, laboratory, or imaging markers able to identify which of these neurodegenerative phenotypes will develop a patient diagnosed with IRBD. This is important since PD, DLB, and MSA have different management and prognosis [7–9].

In the general population, MSA is much less prevalent than PD and DLB. MSA is characterized by various combinations of parkinsonism, cerebellar syndrome, and dysautonomia [9–13]. MSA has a prodromal phase where non-motor features (e.g. RBD, impotence, urinary urgency, and laryngeal stridor) may precede the onset of parkinsonian and cerebellar manifestations [10]. At presentation, diagnosis of MSA can be challenging since parkinsonism and dysautonomia are also common in PD. Diagnostic accuracy is needed given the faster disease progression and shorter survival of MSA compared with PD [7–14]. Thus, it is important to identify biomarkers able to distinguish MSA from PD and other parkinsonisms, especially in the earliest stage.

Unlike PD and DLB, brain magnetic resonance imaging (MRI) in manifest MSA is frequently abnormal showing specific structural changes in the putamen, cerebellum, and brainstem [15–32]. Our aim was to analyze the usefulness of brain MRI to detect in IRBD the typical morphologic abnormalities seen in manifest MSA and their ability to predict the future development of MSA.

Methods

Patients' selection

We identified from our database all IRBD patients who underwent routine brain MRI at our institution in the Hospital Clínic de Barcelona, Spain. In all instances, diagnosis of IRBD was performed according to accepted criteria using video-polysomnography (V-PSG) [33, 34]. After the diagnosis of IRBD was made, patients had periodical follow-up visits at our Neurological Service every 3–12 months. At the time of the current study (November 2019), we noted the clinical status (remained disease-free or diagnosed with PD, DLB, and MSA) of the patients that had undergone brain MRI. For the present study, we selected only those IRBD patients who had an MRI and eventually developed PD, DLB, and MSA during the follow-up [7–9]. MSA patients were clinically classified into MSA-P and MSA-C subtypes when parkinsonism and cerebellar syndrome predominated, respectively [9].

MRI evaluation

Brain MRI studies were performed when the IRBD patients were free of motor and cognitive complaints and neurological examination was unremarkable. MRI was acquired with 1.0, 1.5, and 3.0 T scanners (1.0, 1.5, and 3 T Harmony, Symphony, Aera, Vida, Trio and Prisma, Siemens, Erlangen, Germany, and 1.5 T Signa HDxt and 3.0 T Signa Architect, GE Healthcare, Milwakee, WI, USA). All studies included T1 and T2-weighted sequences, diffusion-weighted imaging, T2 gradient echo weighted imaging, and SWI sequences with axial, coronal, and sagittal sections.

For this study, two experienced neuroradiologists (J.B. and T.P.) evaluated independently all the MRI studies looking for nine typical signs described in MSA, namely (1) putaminal atrophy, (2) putaminal hypointensity, (3) hyperintense lateral putaminal rim, (4) cerebellar atrophy, (5) hyperintensity of the cerebellum, (6) middle cerebellar peduncle atrophy, (7) middle cerebellar peduncle hyperintensity, (8) brainstem atrophy, and (9) the hot cross-bun sign in the pons [15–32]. The two neuroradiologists rated each sign on a scale from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) [24] independently and blindly to the status of the patients (remained disease-free or converted to PD, DLB, or MSA) at the time of this study. For the purpose of this study, an MRI was considered to be abnormal when the neuroradiologists scored either (1) one moderate or one severe radiological sign of MSA or (2) two or more mild radiological signs of MSA, that is, with total scores of 2 points or higher.

Statistical analysis

Data are given in medians, numbers, and percentages. We calculated the sensitivity (proportion of MSA patients with abnormal MRI before phenoconversion), specificity (proportion of patients with PD and DLB who had normal MRI before phenoconversion), positive likelihood ratio (increase of pretest probability in IRBD to develop MSA having an abnormal MRI), and negative likelihood ratio (decrease of pretest probability in IRBD to develop MSA having normal MRI) of abnormal MRI to predict phenoconversion to MSA. Patients were classified into "MSA" and "no-MSA" (PD and DLB) groups for descriptive comparisons. Interrater reliability was calculated with Cohen's kappa (<0.2 no agreement; >0.8 excellent agreement).

MRI data from the IRBD patients who remained disease-free at the time of this study (November 2019) were excluded, as we ignore if these individuals will develop PD, DLB, or MSA.

For this study, development of mild cognitive impairment was not considered as phenoconversion since the MRI abnormalities in patients with mild cognitive impairment who were initially diagnosed with IRBD have not been investigated in the medical literature to date.

The study was approved by the ethics committee at our institution and patients gave written informed consent.

Results

Of the 267 individuals diagnosed in our center with IRBD from 1990 to 2019, 129 (48.3%) underwent conventional brain MRI. Of these 129 subjects, 61 (47.3%) had developed a clinically defined synucleinopathy during follow-up, namely 30 (49.2%) PD, 26 (42.6%) DLB, and 5 (8.2%) MSA. The median interval

from neuroimaging to diagnosis of the clinically defined synucleinopathy was 2.4 years.

Seven MRI studies (11%) were acquired with a 1.0 T scan, 33 (59%) with 1.5 T a scan, and 18 (30%) with a 3.0 T scan. Positive signs (at least one; either mild, moderate, or severe) were detected in 14.3% of 1.0 T studies, 25.0% of 1.5 T studies, and 29.5% of 3.0 T studies, without significant differences among the three scans to detect study-related abnormalities ($p = 0.86$). Interrater reliability was excellent ($\kappa = 0.85$), with no major discrepancies, as the rates into normal MRI and abnormal MRI did not differ significantly between the two independent experienced neuroradiologists.

Of the five IRBD patients who developed MSA, MRI was abnormal in four subjects before phenoconversion (Table 1). Three patients developed MSA-C with an interval from MRI to MSA-C diagnosis of 6 months, 2 years, and 2.5 years. In another IRBD patient, MRI was abnormal 4 years before the diagnosis of MSA-P.

In these four IRBD patients who converted to MSA, the abnormalities detected were cerebellar atrophy ($n = 3$), brainstem atrophy ($n = 2$), hyperintense lateral putaminal rim ($n = 2$), the hot cross-bun sign ($n = 2$), middle cerebellar peduncle atrophy ($n = 2$), posterior putaminal hypointensity ($n = 1$), and middle cerebellar peduncle hyperintensity ($n = 1$). At least two MRI abnormalities were found in each MRI study.

Three of the five IRBD subjects that developed MSA underwent a second MRI study when they were diagnosed with this neurodegenerative disease. These MRI studies showed more marked abnormalities in the cerebellum and in the brainstem when compared with those detected at baseline, plus the addition of new radiological features such as the hyperintense lateral putaminal rim (Table 1).

The MRI was normal in the fifth MSA patient, who actually, never developed motor symptoms in life and only postmortem brain examination demonstrated definite MSA showing alpha-synuclein glial cytoplasmic inclusions in the cerebellum, brainstem, and spinal cord [35].

Three subjects with abnormal MRI at IRBD diagnosis phenoconverted to DLB ($n = 2$) and PD ($n = 1$). One of the patients who developed DLB had moderate cerebellar atrophy on MRI (in addition to global cortical-subcortical supratentorial atrophy) without other radiological signs suggestive of MSA. He was diagnosed with IRBD at the age of 75, had hyposmia and constipation, and developed rigid-akinetic parkinsonism plus dementia after 5 years of follow-up, with neuropsychological testing showing impairment of memory, visuospatial, and executive skills. The other patient who eventually developed DLB had mild hyperintense putaminal rim and mild cerebellar atrophy in MRI. IRBD was diagnosed at the age of 62 and she had hyposmia, constipation, depression, and orthostatic hypotension with abnormal cardiac scintigraphy. Four years later, she developed a dementia (with impaired visuospatial, language, and executive functions), visual hallucinations, delusional ideas, and bilateral

Table 1. Abnormal MRI findings in IRBD patients who converted to MSA, PD, and DLB

Patient	Age at IRBD diagnosis (y)	Age at MRI before conversion (y)	MRI findings before conversion	Age at conversion (y) and diagnosis	Age at MRI after conversion (y)	MRI findings after conversion
1	70	70	Putaminal rim; Cerebellar atrophy; Middle cerebellar peduncle atrophy; Middle cerebellar peduncle hyperintensity; Pontine atrophy; Cross-bun sign*	72/MSA-C	72	Middle cerebellar peduncular hyperintensity and cross-bun sign were more marked than in the previous study†
2	55	55	Putaminal rim; Cerebellar atrophy; Middle cerebellar peduncle atrophy; Pontine atrophy†	56/MSA-C	56	More marked atrophy of cerebellum, middle cerebellar peduncles and pons plus new appearance of middle cerebellar peduncles hyperintensity‡
3	60	60	Cerebellar atrophy; Brainstem atrophy; Cross-bun sign†	61/MSA-C	MRI not done	
4	64	64	Putaminal hypointensity Cerebellar atrophy†	68/MSA-P	68	New appearance of Middle cerebellar peduncles hyperintensity and the putaminal rim†
5	60	60	Normal†	61/MSA by postmortem evaluation	MRI not done	
6	62	65	Putaminal hypointensity; Cerebellar atrophy†	70/PD	MRI not done	
7	62	65	Putaminal hypointensity; Cerebellar atrophy†	67/DLB	MRI not done	
8	77	75	Cerebellar atrophy†	80/DLB	MRI not done	

IRBD, isolated REM sleep behavior disorder; MSA, multiple system atrophy; MRI, magnetic resonance imaging; MSA-C, multiple system atrophy with predominant cerebellar signs; MSA-P, multiple system atrophy with predominant parkinsonian signs.
*MRI studies performed at 1.0 T.
†MRI studies performed at 1.5 T.
‡MRI studies performed at 3.0 T.

rigid-akinetic syndrome. The patient who converted to PD had mild hyperintense putaminal rim and mild cerebellar atrophy in MRI. She was diagnosed with IRBD at the age 62, had chronic constipation and hyposmia, and 7 years later, she developed unilateral bradykinesia and rigidity, fulfilling criteria of PD. MRI studies were not repeated in these three patients at the time of phenoconversion or during follow up.

The specific MRI abnormalities of MSA had sensitivity of 80.0%, specificity of 94.6%, positive likelihood ratio of 14.9 (95% CI 4.6–48.8), and negative likelihood ratio of 0.2 (95% CI 0.04–1.2) to predict MSA in IRBD.

Case presentation of MSA patients

Patient 1

A 70-year-old woman was referred for a 15-year history of abnormal behaviors during sleep such as talking, shouting, groaning, crying, laughing, singing, clapping, and punching. The neurological exam was unremarkable and V-PSG showed increased EMG activity during REM sleep accompanied by excessive body jerking and kicking confirming the diagnosis of RBD [33]. Brain MRI showed mild hyperintense lateral putaminal rim, moderate cerebellar atrophy, severe middle cerebellar peduncular atrophy, mild middle cerebellar peduncular hyperintensity, mild pontine atrophy, and mild hot cross-bun (Figures 1, A and 2, A). Two years after IRBD diagnosis and MRI, she complained of gait instability and neurological exam revealed mild ataxia, slight limb dysmetria, dysarthria, and nystagmus. These cerebellar features progressed over the next year and she developed bladder incontinence, orthostatic hypotension, and constipation fulfilling MSA-C diagnostic criteria [9]. A second brain MRI performed after the diagnosis of MSA showed additional severe middle cerebellar peduncle hyperintensity and severe hot cross-bun sign (Figures 1, B and 2, B). Dopamine transporter single photon emission computerized tomography (DAT-SPECT), a neuroimaging tool that evaluates the integrity of the nigrostriatal dopaminergic system, demonstrated decreased binding of dopamine in the left putamen. Laryngoscopy discarded motor abnormalities of the vocal cords. Repeated V-PSG revealed persistence of RBD and ruled out stridor and sleep apnea. After 4 years from MSA diagnosis, she developed rigid-akinetic parkinsonism and became wheelchair dependent. She died 12 years after IRBD diagnosis due to respiratory failure. Postmortem neuropathological examination was refused.

Patient 2

A 55-year-old man consulted because of 1-year history of nightmares and dream-enacting behaviors. The neurological exam was normal and V-PSG showed RBD. MRI was abnormal showing mild hyperintense lateral putaminal rim and mild atrophy of the pons, mild cerebellum atrophy, and mild middle cerebellar peduncles atrophy (Figure 3, A). Six months later, the patient reported unstable gait and the neurological exam revealed gait ataxia, inability to walk in tandem, mild dysmetria, and nystagmus. An autonomic nervous system study revealed sympathetic and parasympathetic dysfunction. After 2 years of follow-up from baseline MRI, the cerebellar syndrome progressed and orthostatic hypotension, bladder incontinence and erectile dysfunction appeared fulfilling MSA-C diagnostic criteria [9]. Laryngoscopy showed flickering movements of the right vocal cord and a new V-PSG ruled out stridor and sleep apnea. Spanish version of UPSIT-40 showed a score of 27 indicating normal smell identification function. A second MRI study showed severe atrophy of the pons, cerebellum and middle cerebellar peduncles, and the appearance of severe cerebellar peduncles hyperintensity (Figure 3, B).

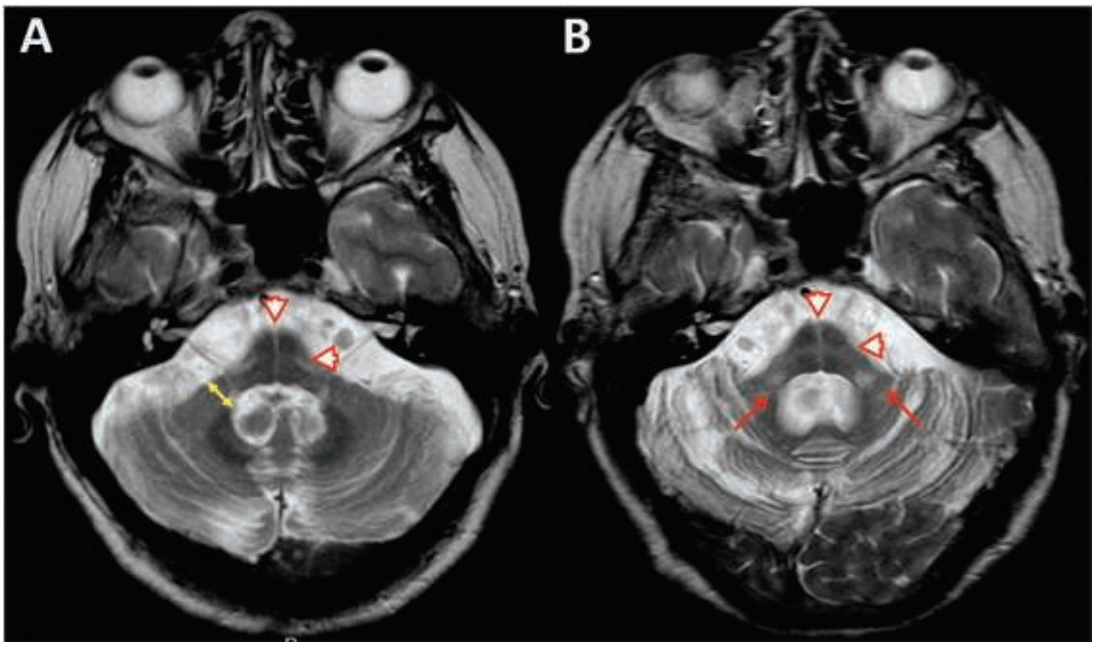

Figure 1. Patient 1. MRI changes at IRBD diagnosis (A) and after conversion to MSA-C (B). (A) Axial T2 weighted imaging (TE: 4,130 ms, ET: 103 ms, ST: 5 mm) shows bilateral severe middle cerebellar peduncle atrophy (yellow arrow) and moderate hot cross-bun sing (red arrowheads) at IRBD diagnosis. (B) Two and a half years later, axial T2-weighted (TE: 5,540 ms, ET: 78 ms, ST: 5 mm) revealed progression to severe hot cross-bun sign (red arrowheads) and new development of severe hyperintensity in both middle cerebellar peduncles (red arrows).

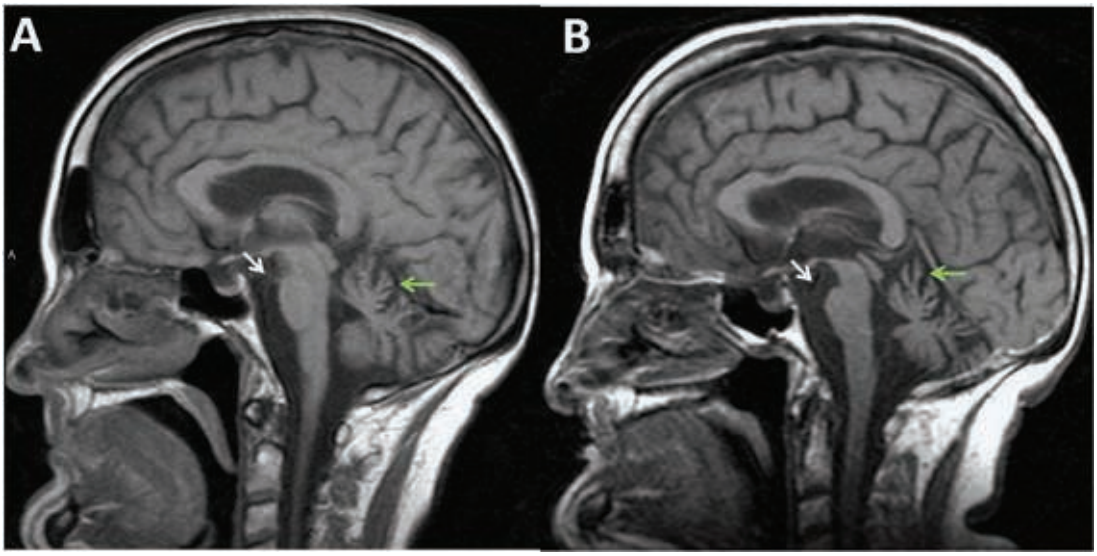

Figure 2. Patient 1. MRI changes at IRBD diagnosis (A) and after conversion to MSA-C (B). (A) Sagittal T1 weighted imaging (TE: 505 ms, ET: 12 ms, ST: 5 mm) shows moderate cerebellar atrophy (green arrow) and mild brainstem atrophy (white arrow) at IRBD diagnosis. (B) T1 weighted imaging (TE: 400 ms, ET: 8 ms, ST: 5 mm) reveals progression to severe cerebellar atrophy (green arrow) and severe brainstem atrophy (white arrow) at MSA-C diagnosis.

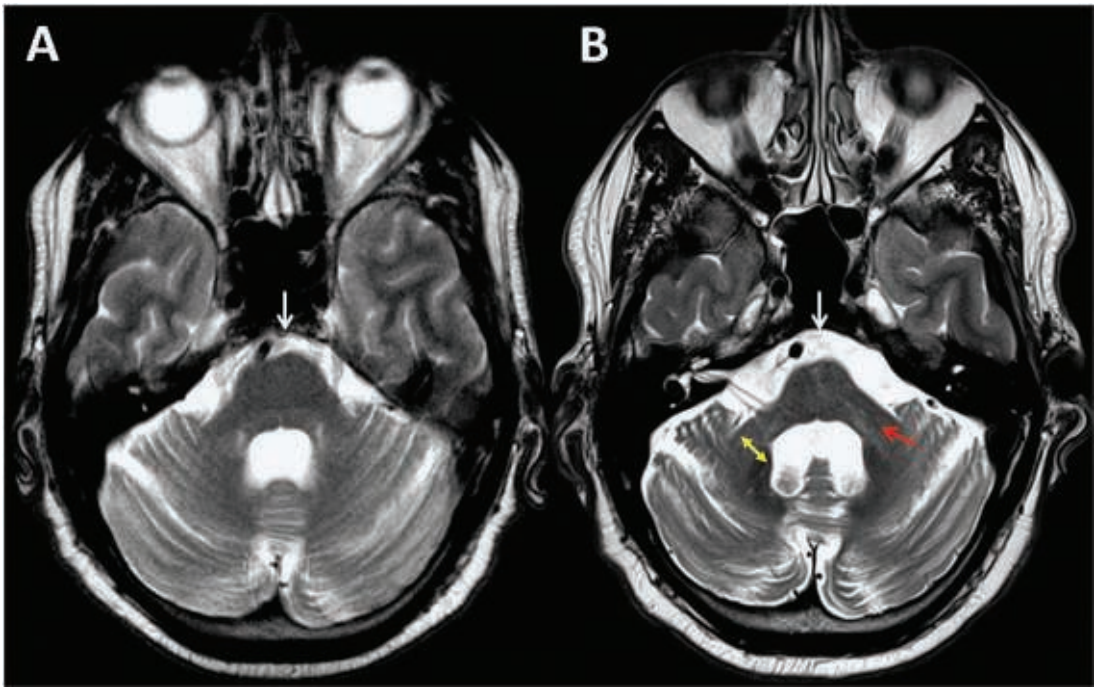

Figure 3. Patient 2. MRI changes at IRBD diagnosis (A) and after conversion to MSA-C (B). (A) Axial T2 weighted imaging (TE: 4,090 ms, ET: 103 ms, ST: 5 mm) shows mild cerebellar atrophy and mild brainstem atrophy (white arrow). (B) Two years later, axial T2 weighted imaging (TE: 5,840 ms, ET: 95 ms, ST: 5 mm) shows progression to severe cerebellar atrophy and severe brainstem atrophy (white arrow), moderate cerebellar peduncles atrophy (yellow double arrow), and moderate cerebellar peduncles hyperintensity (red arrows).

Patient 3

A 60-year-old man presented with a 2-year history of fearful nightmares and dream-enacting behaviors, and V-PSG showed RBD. Neurological assessment ruled out parkinsonism, cerebellar signs, and cognitive impairment. MRI showed moderate cerebellar atrophy, mild pontine atrophy, and mild hot cross-bun sign. One year later, he developed postural dizziness, urinary incontinence, and erectile dysfunction. The neurological exam showed gait ataxia, limb ataxia, and dysarthria and MSA-C was diagnosed [9]. A new V-PSG study detected the appearance of inspiratory stridor during all sleep stages, obstructive sleep apnea, while laryngoscopy demonstrated bilateral vocal cord abductor paresis. The patient was treated with continuous positive airway pressure which successfully eliminated stridor during sleep and the apneic events. During the next 3 years, the cerebellar syndrome worsened and made him wheelchair dependent. He developed stridor during wakefulness and tracheostomy was performed. MRI was not repeated after the diagnosis of

MSA-C. The patient was lost after 10 years of follow-up from IRBD diagnosis.

Patient 4

A 64-year-old woman was referred to our sleep center because of a 2-year history of dream-enacting behaviors. Neurological examination was normal and V-PSG demonstrated RBD. MRI showed mild posterior putaminal hypointensity and moderate cerebellar atrophy (Figures 4, A and 5, A). During the next 4 years, she developed orthostatic hypotension with syncopes, bladder incontinence, and unstable gait. DAT-SPECT demonstrated decreased dopaminergic binding in the left and right putamen. After 4 years from diagnosis of IRBD, clinical examination showed facial hypomimia, bradykinesia, rigidity, and polymioclonus fulfilling diagnostic criteria of MSA-P [9]. A second MRI showed, at the time of MSA-P diagnosis, the new appearance of both mild middle cerebellar peduncles hyperintensity and mild hyperintense lateral putaminal rim plus the abnormalities detected in the previous baseline MRI study when the patient had IRBD (Figures 4, B and 5, B).

Patient 5

A 60-year-old man was referred to the otorhinolaryngologist for therapeutic management of bilateral vocal cord abductor palsy. He had a 2-year history of inspiratory stridor that first appeared during sleep and evolved during wakefulness leading to episodes of respiratory failure. Detailed clinical history revealed a 10-year history of dream-enacting behaviors and nightmares, an 8-year history of erectile dysfunction, a 6-year history of urinary retention, and a 5-year history of syncopes. Neurological examination was normal. Orthostatic hypotension and anal sphincter denervation were evidenced. V-PSG demonstrated RBD, inspiratory stridor in all sleep stages, and obstructive sleep apnea. MRI was normal. The patient declined therapy for vocal cord paralysis with tracheostomy and continuous positive airway pressure mask. After 7 months of follow-up, he suffered sudden death during wakefulness. The neuropathological exam was diagnostic of MSA showing abundant alpha-synuclein positive glial cytoplasmic inclusions and neuronal loss with gliosis in the cerebellum, brainstem, and intermediolateral cell columns of the spinal cord [32].

Discussion

Our study shows that the typical MRI abnormalities of manifest MSA are frequently found in the IRBD patients that eventually develop MSA and not PD and DLB. The identification of these morphological changes in conventional MRI can help to predict the conversion to MSA in subjects initially diagnosed with IRBD. Our findings also indicate that MRI may be abnormal in the premotor stage of MSA.

Atrophy of the putamen, cerebellum and brainstem, hypointensity of the putamen, putaminal hyperintense rim, and the hot cross-bun sign are MRI changes highly specific for MSA [15–32]. These radiological signs reflect some neuropathological features of MSA, namely loss of Purkinje cells (reflected in MRI by cerebellar atrophy), degeneration of the myelinated transverse pontocerebellar tracts (represented by the hot cross-bun sign in the pons), and increased iron deposition in the putamen (reflected by putaminal hypointensity) [15, 16]. These radiological and pathological changes are frequent in MSA but not in PD and DLB [18, 20, 21, 24, 27]. Putaminal hyperintense rim can be observed in normal subjects and is the least specific of the MSA-associated radiological signs [29]. Overall, the combination of these supratentorial and infratentorial changes on conventional 1.5 T MRI have a high specificity (>90%) to distinguish manifest MSA from PD, atypical parkinsonian syndromes and healthy controls [15–18, 20, 21, 24, 27]. Sensitivity of these radiological signs in manifest MSA is moderate ranging from 20% to 80% [15–21, 24, 27], indicating that normal MRI does not exclude the clinical diagnosis of MSA [18, 20]. Of note, similar results were found in our current study in IRBD where specificity was

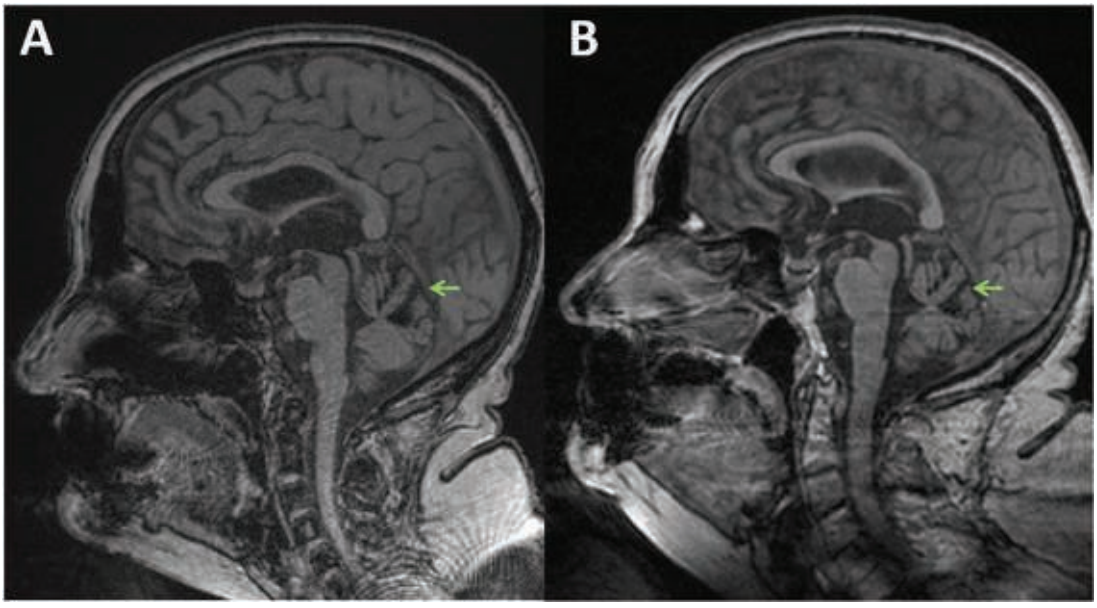

Figure 4. Patient 4. MRI changes at IRBD diagnosis (A) and after conversion to MSA-C (B). (A) Sagittal T1 imaging shows moderate cerebellar atrophy at IRBD diagnosis (green arrow). (B) No changes were detected in the cerebellar atrophy in a second MRI study performed 4 years later (green arrow).

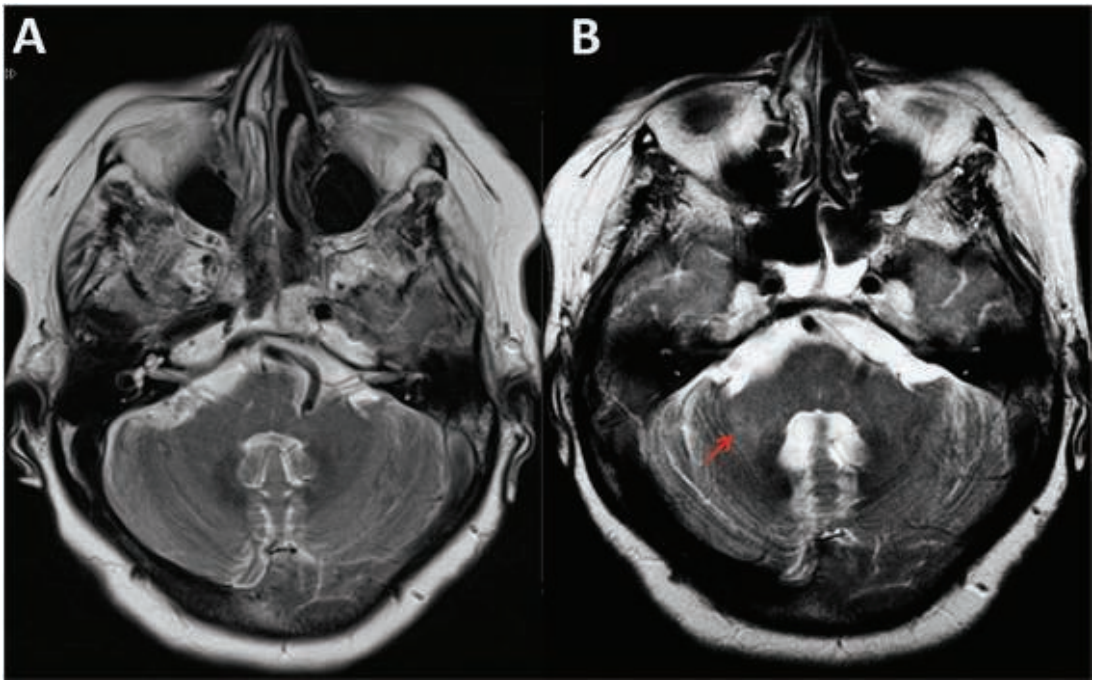

Figure 5. Patient 4. MRI changes at IRBD diagnosis (A) and after conversion to MSA-P (B). (A) Axial T2 weighted imaging (TE: 4,760 ms, ET: 89 ms, ST: 5 mm) shows normal middle cerebellar peduncles. (B) Four years later, T2 weighted imaging (TE: 4,090 ms, ET: 103 ms, ST: 5 mm) reveals mild hyperintensity in the right cerebellar peduncle (red arrow).

very high (94.4%) and sensitivity was moderately high (80.0%), resulting in an almost 15-times increased risk ratio to develop MSA once the MRI abnormalities typical of this disease are detected in patients with IRBD.

In MSA, serial MRI studies show that the pontine, cerebellar, and brainstem signs worsen over time as the disease advances [19, 22, 23, 25]. This is in line with our observation that the IRBD patients who developed MSA showed more marked and pronounced radiological changes when MSA was clinically diagnosed compared when the MRI is performed when neurological exam was unremarkable.

IRBD represents the prodromal stage of PD, DLB, and MSA [1, 2]. It is difficult, however, to predict which of these three synucleinopathies a patient with IRBD will develop. Subtle parkinsonian signs, presynaptic nigrostriatal dopaminergic denervation on DAT-SPECT, hyperechogenicity of the substantia nigra on transcranial sonography, depression and constipation are common features in IRBD but they do not indicate conversion to one of the three synucleinopathies (PD, DLB, or MSA) [1, 2]. In our current study, we showed that the abnormalities detected by conventional MRI are specific markers of underlying MSA, and not of PD and DLB. Although only a small proportion of IRBD patients develop MSA [1–6], our findings can be important since prognosis, management, and counseling in MSA is different from PD and DLB. An early orientation into MSA can be important for neuroprotective trials as this synucleinopathy shows different neuropathological features compared with PD and DLB. In the IRBD population other potential specific markers of latent MSA (and not of PD and DLB) might be the appearance of stridor during sleep, vocal cord abductor impairment demonstrated by laryngoscopy, normal sense of smell, normal cardiac scintigraphy, and abnormal spontaneous electromyographic activity of the anal, and urethral sphincters [7–14, 21, 22, 36].

Our study has limitations. First, information is limited to only five individuals who developed MSA. This is not surprising, as less than 5% of the IRBD patients convert to MSA, while the remaining 95% are diagnosed with PD and DLB [3–6]. This can be explained by the fact that in the general population MSA is much less frequent than PD and DLB [7–14]. Second, this is a retrospective study where conventional MRI was performed over a 30-year period using different MRI scanners. This heterogeneity reflects the technical improvements that have appeared in neuroimaging over this long period of time where very important scientific advances were made in MRI. Performing the MRI studies in a single timepoint with the same MRI device and adjustments would have been ideal, but this design would have reduced greatly the sample size and the follow-up period of our study. We realize that MRI scans with lower resolution (1.0 T) may be less sensitive to detect structural changes than those with higher resolutions. We are also aware that some features detected with 3.0 T scans may not be pathologic, as is the case of mild putaminal hyperintense rim. However, we found no differences in the proportion of 1.0, 1.5, and 3.0 T studies where radiological abnormalities were detectable, suggesting that this fact did not significantly influence the results and conclusions of our study. Third, MRI analyses were rated visually and quantification of parameters such as pontine atrophy could not be performed since in this retrospective study different MRI scanners were used and the slice positions varied from one study to another. Fourth, MRI studies of patients that remained disease-free at the end of the study were excluded

from the current study analysis, as we do not know whether they eventually will develop PD, DLB, or MSA. However, 3 of the 68 IRBD patients were rated as having abnormal MRI, with some changes typical of MSA. According to our current study, these three individuals seem to be at risk to develop MSA than PD or DLB and we are closely following them. In these cases, clinical follow-up should be targeted to looking for the presence of other features typical of MSA and not of PD or DLB (e.g. laryngeal palsy and normal sense of smell) and could be complemented with serial routine conventional MRI studies to address radiological progression. Finally, the definite diagnosis of MSA by postmortem examination was only done in one of the five individuals clinically diagnosed with this condition. Also, we do not have neuropathological confirmation of the three patients who had abnormal MRI and were diagnosed with PD and DLB.

Strengths of our study include the confirmation of RBD by V-PSG in all cases, the blind and independent review of MRI by two experienced neuroradiologists, and a large cohort of IRBD patients recruited in a long period of observation of 30 years.

In summary, our study shows that in IRBD conventional brain MRI may be useful to predict conversion to MSA and not to PD and DLB. The specific radiological morphological abnormalities observed in established MSA may be detected in the premotor stage of this disease with conventional brain MRI.

Disclosure statement

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