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AJNR Am J Neuroradiol 2005, 26 (9) 2238-2242
<http://www.ajnr.org/content/26/9/2238>

This information is current as
of May 4, 2025.

Hyperintense Putaminal Rim Sign Is Not a Hallmark of Multiple System Atrophy at 3T

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BACKGROUND AND PURPOSE: Hyperintense putaminal rim (HPR) on the T2-weighted imaging, which has been observed in our daily practice while reading 3T brain images, has been described as a finding typical of multiple system atrophy (MSA). We hypothesized that the HPR sign is not an exclusive hallmark of MSA at a high magnetic field strength, but rather may be a normal finding.

METHODS: Ten consecutive clinically healthy age-matched adults who showed recognizable HPR at 3T were subsequently examined on a 1.5T imaging system within 2 hours. MR examination included axial T2-weighted fast spin-echo (FSE), fluid attenuated inversion recovery (FLAIR) on a 3T scanner, and equivalent T2-weighted FSE at 1.5T. MR images were obtained parallel to the intercommissural plane. All the images were interpreted by 2 experienced neuroradiologists.

RESULTS: All 10 subjects (3 men and 7 women; aged 52 ± 6.1 years [range, 44–61 years], expressed as mean \pm SD) with the positive HPR sign on axial T2-weighted FSE at 3T had negative findings at 1.5T. Such hyperintense rim was also vague or absent on the 3T-FLAIR images.

CONCLUSION: Our data suggest that the HPR at 3T scans is a nonspecific, normal finding. FLAIR may be helpful in discriminating between normal subjects and patients with MSA in case of isolated HPR at 3T.

Multiple system atrophy (MSA) is a sporadic, progressive neurodegenerative disorder of adult onset characterized by any combination of Parkinsonism, autonomic, cerebellar, and pyramidal symptoms and signs. Median intervals from onset to requirement of aid to walk, confinement to a wheelchair, bedridden state, and death are 3, 5, 8 and 9 years, respectively (1). In the most frequent type of MSA, referred to as MSA-P, patients have mostly Parkinsonism and few, if any, cerebellar signs (2). Clinical diagnostic end points for MSA, such as autonomic dysfunction or cerebellar signs, may not appear until later in the disease process. Some characteristic clinical features for Parkinson disease (PD) overlap in MSA patients (3). In addition, the clinical differentiation of other atypical Parkinsonian syndromes—such as progres-

sive supranuclear palsy (PSP), and corticobasal degeneration (CBD)—from MSA is also difficult, leading to misdiagnosis even up to the time of death (4, 5).

Brain routine MR imaging in MSA patients has disclosed several characteristic findings including putaminal and infratentorial signal intensity changes or atrophy that were determined as the specific parameters for MSA-P (6–8). Among these MR parameters, the most specific sign in MSA-P is the putaminal hyperintense rim (HPR) on the T2-weighted images, which has shown high specificity and positive predictive value with relatively suboptimal sensitivity and negative predictive value in MSA-P patients (9, 10), though a few studies have reported that the hyperintense rim can be encountered occasionally in cases of PSP, CBD, and old-age PD and even in healthy subjects (11–13).

HPR has been seen so frequently in our daily practice while reading 3T brain imaging as to be regarded as a normal finding. We present our investigation comparing the putaminal signal intensity changes at different magnetic field strengths and sequences in healthy subjects for evaluation of this radiologic sign and its underlying pathophysiology. We hypothesized that the HPR sign is not an exclusive hallmark of MSA at a high magnetic field strength, but rather is a normal finding.

Received December 25, 2004; accepted after revision March 11, 2005.

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Methods

Selection of Subjects

Inclusion criteria for this prospective study were clinically healthy adults matched for age with Parkinsonism patients (1) with the recognizable HPR at 3T scans. The enrolled subjects had to be healthy without neurologic symptoms and signs on examination (by W.C.S. and S.Z.L.). None of the subjects had experienced episodes of neurologic dysfunction. Subjects who had cerebrovascular disease, epilepsy, migraines, hypertension, diabetes, and other disorders that potentially could affect the central nervous system—such as chronic alcohol intake, endocrine or metabolic disease, coagulopathy, or other thromboembolic disorders—were not eligible to participate in the study. Most important, the absence of Parkinsonism or cerebellar features was the highlight of a clinical history and a neurologic work-up. Subjects with intracranial pathologic findings except Parkinsonian signs identified on 3T MR imaging (eg, infarction, posttraumatic process, demyelinating disease, significant brain atrophy, hydrocephalus, tumors, and so on) were excluded.

None had undergone or was undergoing any therapeutic treatment. Between August 5 and September 9, 2004, we selected 10 consecutive subjects who fulfilled these inclusion criteria. Written informed consent was obtained from all participants and approved by the local committee on ethics. These subjects who had acquired 3T images first consulted experienced neuroradiologists (W.H.L. and P.N.C.) and sought medical advice immediately after the 3T scanning. They were informed of the positive findings of HPR sign on the PACS monitor and agreed to undergo subsequent 1.5T MR imaging within 2 hours for complete imaging information.

MR Protocol

Brain MR examination included axial T2-weighted fast spin-echo (FSE), fluid attenuated inversion recovery (FLAIR) sequence on a 3T scanner and equivalent T2-weighted FSE at 1.5T. We did not perform FLAIR imaging on the 1.5T system because, if T2-weighted imaging at 1.5T showed hypo-/isointensities in the region of interest, FLAIR imaging would expect the similar signals as well. In addition, the 3T system has higher

signal intensity-to-noise ratio (SNR) and better T2 contrast than 1.5T. If the HPR sign was vague or absent on the FLAIR imaging at 3T, FLAIR imaging at 1.5T would be destined for negative findings. FLAIR imaging at 1.5T is redundant in our study. MR images were obtained parallel to the intercommisural plane. Section thickness was 5 mm and interslice gap was 1.5 mm. On the T2-weighted FSE at 3T, repetition times (TR) were 4000 ms and echo times (TE) were 105 ms. Number of excitations (NEX) was 1. Field of view (FOV)/matrix was 24×18 cm/ 384×256 . FLAIR images were obtained with the following parameters: TR, 6902 ms; TE, 90 ms; inversion time (TI), 2100 ms; NEX, 1; FOV, 24 cm; matrix, 384×192 . MR studies were performed on a 1.5T scanner by using a T2-weighted FSE technique. TR was between 4300 and 4700 ms, and TE was from 90 to 100 ms. FOV/matrix was 24×18 cm/ 288×192 with the number of signal intensity acquisitions of 2. We used a quadrature head coil on 3T scanner and an 8-channel neurovascular coil on a 1.5T scanner.

Image Evaluation

All images were transferred to our PACS station and analyzed by 2 experienced neuroradiologists (W.H.L. and C.C.L.) independently. In cases where there were differing opinions, the scans were re-evaluated and a consensus was reached. The brain MR images were systematically reviewed and special attention was given to the changes previously described in MR images of patients with MSA. These parameters included (1) dorsolateral hypointensity of the putamen relative to the globus pallidus, (2) linear slitlike hyperintensity in the lateral margin of the putamen on T2-weighted images (ie, hyperintense putaminal rim [HPR]), (3) putaminal atrophy, (4) fourth ventricle dilation, (5) brain stem atrophy (midbrain, pons, and medulla), (6) cerebellar atrophy (vermis and cerebellar hemispheres), (7) atrophy of the middle cerebellar peduncles, (8) hyperintensity of the middle cerebellar peduncles, (9) hyperintensity of the pons (including “hot cross bun” sign), and (10) hyperintensity of the cerebellum (7–10). Images were visually rated on a scale from 0 to 3, where 0 represented normal; 1, mild; 2, moderate; and 3, severe abnormalities. Participants with negative findings at ensuing 1.5T scans were regarded as definitely normal sub-

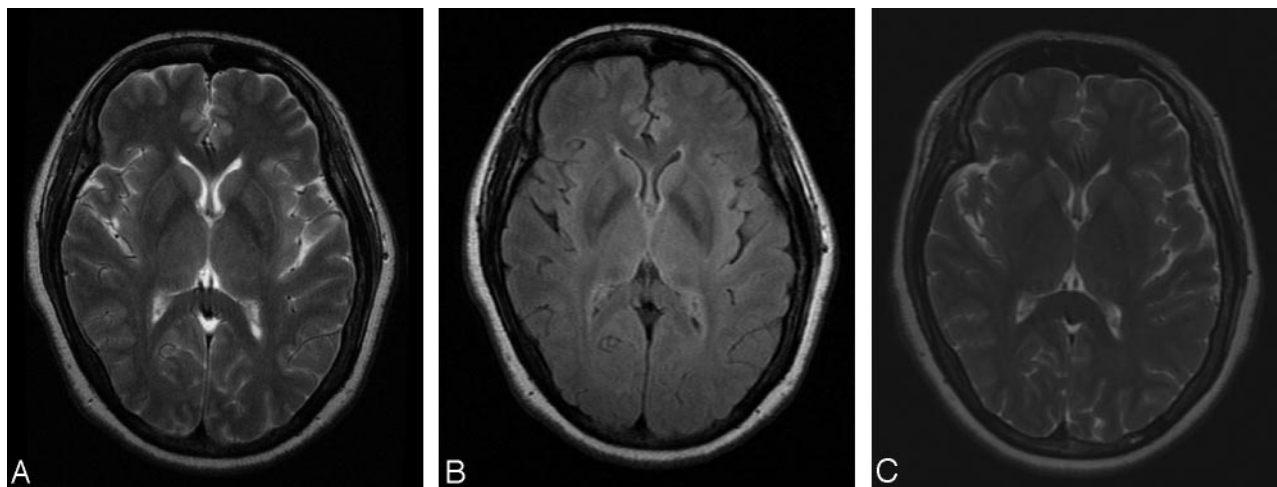


FIG 1. Concomitant axial T2-weighted imaging (TR, 4000 ms; TE, 105 ms) (A) and FLAIR imaging (TR, 6902 ms; TE, 90 ms; TI, 2100 ms) (B) of a healthy 46-year-old woman (case 10) are performed at the striatal level on the 3T scanner; (C) equivalent T2-weighted image (TR, 4400 ms; TE, 95 ms) is acquired at 1.5T.

A, There are bilateral slitlike signal intensity changes (grade 1 on right side and grade 2 on left side), consisting of a lateral hyperintense rim at the lateral border of the putamen (HPR) and a grade 1 hypointense area medial to this rim.

B, FLAIR image demonstrates vague hyperintensities of the putaminal outer margin.

C, The hyperintense rim is absent on T2-weighted image at 1.5T. Note grade 0 putaminal signal intensity hypointensity relative to the globus pallidus.

Basic data and 3T MR findings in 10 subjects with hyperintense putaminal rim

Patient No./ Age (y)/Sex	T2WI		FLAIR	
	Right	Left	Right	Left
1/61/M	1	1	0	0
2/60/F	1	1	0	0
3/46/F	2	3	0	1
4/49/F	2	2	1	1
5/48/F	2	2	1	1
6/55/F	1	2	1	0
7/56/F	1	2	0	0
8/44/M	1	1	0	0
9/54/M	1	1	1	0
10/46/F	1	2	1	1

Note.—T2WI indicates T2-weighted images; FLAIR, fluid-attenuated inversion recovery. Patient number is in order of examination date. With regard to the scale, 0 indicates normal; 1, mild; 2, moderate; and 3, severe abnormalities.

jects according to previous data obtained at 1.5T or lower scans.

Results

There were 3 men and 7 women, aged 44–61 years, enrolled in this study. Mean age at examination was 52 (SD, 6.1) years. We focused on signal intensity changes in the putamen on T2-weighted and FLAIR sequences. All 10 subjects showed bilateral mild to severe hyperintense rim in the outer margin of the putamen on T2-weighted images at 3T (Fig 1). There were 4 subjects whose left HPR appeared to be a higher degree than the right. The rest of the subjects had symmetric HPR. The HPR sign was vague or absent (ie, grades 0–1) on the FLAIR images. The basic data and 3T MR findings are summarized in the Table. Meanwhile, all the patients revealed grade 1–2 dorsolateral putaminal hypointensity at 3T, and this hypointensity became brighter signal intensity at 1.5T

(ie, degraded into grade 0–1). There were no other evident MR signs to suggest MSA in these subjects, such as putaminal atrophy, fourth ventricle dilation, and infratentorial signal intensity changes or atrophy. One subject had nonspecific T2-hyperintense foci in the central pons, probably because of ischemic change or capillary telangiectasia (images were not shown). All 10 subjects with the positive HPR sign on T2-weighted FSE at 3T displayed a normal appearance on T2-weighted FSE obtained on 1.5T scans, regardless of the grading (Fig 2).

Discussion

MSA is a sporadic and relentless neurodegenerative disorder with a relatively high rate of clinical misdiagnosis. HPR on T2-weighted MR imaging has been described as a diagnostic of MSA. HPR was reported as having 100% specificity and positive predictive value in MSA-P versus PD and controls at 1.5T (7). We observed that HPR is a common finding at 3T, in the 10 healthy subjects we studied. They showed positive HPR sign on T2-weighted imaging at 3T and displayed a normal appearance on T2-weighted imaging at 1.5T.

Because a 3T scanner was installed in our department as the current routine field strength for clinical MR imaging, the HPR sign was so frequent that the impression initially was that it was an artifact in healthy subjects. Moreover, most of the features revealing perfectly bilateral symmetric, smooth arc signals seemed to increase the likelihood of artifacts.

From the basic MR viewpoint, the chemical shift and truncation artifact (Gibbs phenomenon) are possible candidates for the alternating bands of dark and bright signal intensity (14). A stronger magnetic field strength will increase the chemical shift artifact, with chemical shift artifact occurring only in the frequency-encoding direction. The HPR in our cases is demonstrated in the phase-encoded (transverse) direc-

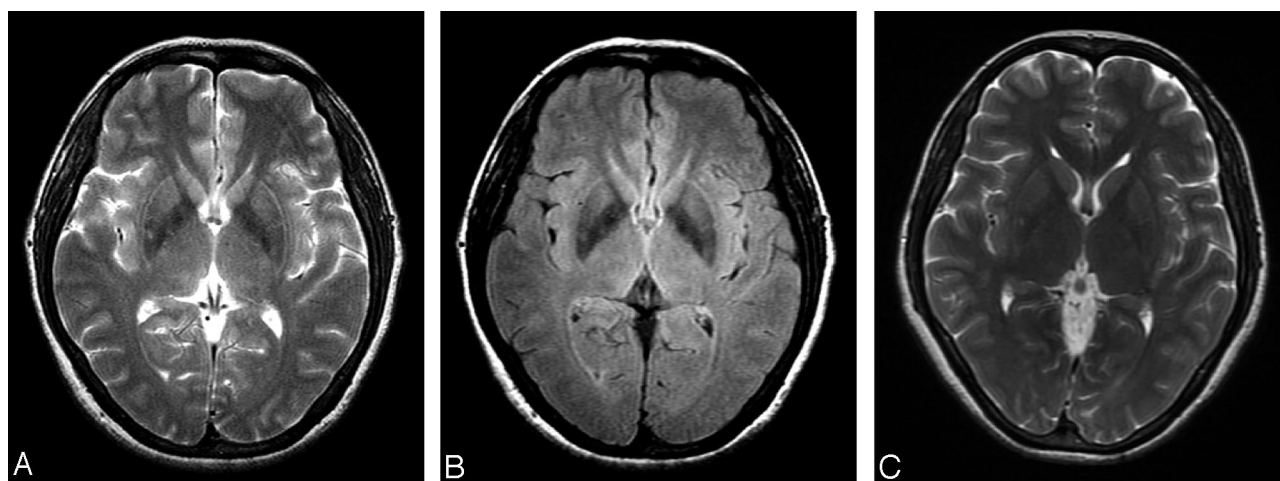


FIG 2. Brain MR imaging of a healthy 46-year-old woman (case 3) uses the same scanning protocol as that of Fig 1.

A, There are grade 2 HPRs on the right and grade 3 on the left and grade 2 dorsolateral putaminal hypointensities.

B, FLAIR image demonstrates grade 1 HPR on left side only.

C, Signal intensity changes of bilateral HPR in A turn to negative findings. The dorsolateral putaminal hypointensities become brighter signals than those in A.

tion. In this direction, a truncation artifact is favored. Nevertheless, this artifact appears at high contrast interfaces (eg, skull/brain, cord/cerebrospinal fluid). Furthermore, there was no significant difference when we decreased pixel size (images not shown). An artifact seems unlikely to be the cause of the signal intensity changes observed in the present study. In such a case, it would be better to think about a normal variant or sign of incipient MSA. MSA is a rare neurodegenerative disorder. We believe that it is a normal finding rather than an early sign of presymptomatic MSA in light of relatively high negative predictive value (73%) of the HPR for MSA-P at 1.5T, which has been used widely for diagnosis of MSA (10).

The pathophysiologic process underlying the hyperintense signal intensity changes remains uncertain. In a clinicopathologic study, the area with the most pronounced microgliosis and astrogliosis corresponded to the area of hyperintense signal intensity changes on MR imaging (15). Changes in glial cells—namely, glial cytoplasmic inclusions—have been recognized as pathognomonic for the neuropathologic diagnosis of MSA (16). Glial changes may play a part in the pathogenesis of MSA and, at least in part, contribute to the HPR of patients with MSA (15); however, many factors seem to induce MR signal intensity changes. Bhattacharya et al found that all their patients with MSA-P with pronounced putaminal rim hyperintensity had concomitant putaminal atrophy, which suggests that marked HPR may be partially due to extracellular fluid accumulation in the putaminal capsule secondary to atrophy of the nucleus (12).

Increased signal intensity in the lateral rim has been correlated with putaminal atrophy and reactive gliosis and with an enlargement of the space between the putamen and the external capsule. In brief, neuronal loss and gliosis result in putaminal atrophy and in consequent increase in the intertissue space between the putamen and the external capsule. In a recent clinicopathologic case report, the authors confirmed that the putaminal atrophy gave rise to the formation of this intertissue space, which produces the slitlike void on MR imaging in patients with MSA (17). In other words, with a 3T system with its higher SNR, this intertissue space in a normal subject who had no pathologic gliosis nor detectable atrophy may show hyperintense signal intensity changes.

Although we have no histologic proof, the HPR sign became vague or absent on the FLAIR images, because of its fluid nulling. This phenomenon indicates that the hyperintense rim of a normal subject represents the extracellular fluid accumulation in the CSF-equivalent space. That also explains why our findings contrasted with Block and Bakshi's report that suggested better depiction of hyperintense rim on FLAIR as compared with T2-weighted images in patients with MSA (18); in the first case, because fluid-containing space in a healthy subject tends to be negative on FLAIR images and, in the second case, because abnormal gliosis in MSA is depicted easily

with the conspicuous hyperintensity on FLAIR. It suggests that water-suppressed sequences like FLAIR images are useful in evaluation of clinically doubtful MSA to eliminate false-positive findings on T2-weighted images at 3T. It would be expected reasonably that positive findings in the lateral putaminal margin on FLAIR reflect real gliosis rather than only fluid-containing intertissue space, because the fraction of the signal intensity due to a partial volume of water in the area is reduced by FLAIR preparation.

Another point is that, in our experience, the slitlike changes on 3T-MR imaging were rarely found in younger subjects. There is a hint of age-related shrinkage of the putamen potentially producing the HPR as a consequence of ongoing enlargement of the intertissue space by the aging process. Raz et al (19) reported that a steady lifespan decline in the neostriatal volume was not confined to the adult age span, but also occurred in younger adults and even in adolescents. It implies that age-related differences of the intertissue space appear to be linear and uniform across the examined age range up to a threshold detected at 3T. Finally, in a recent 3T MR study, the authors presented 2-fold SNR gain over 1.5T in CSF better than that in other semisolid tissues (ie, white matter, gray matter, putamen, globus pallidus) in which the measured SNR increase was between 30% and 60% only (20).

Moreover, it is well known that the higher sensitivity to paramagnetic effects of iron accumulation in the putamen, especially in the dorsolateral portion, can provide the more frequent and stronger hypointensity at higher magnetic field strength scans. The 3T scanner is sensitive to the demonstration of the dorsolateral putaminal hypointensity by the normal aging process because of higher susceptibility effect, as indicated by our results. The combination of putaminal hypointense and hyperintense signal intensity changes on T2-weighted images is not a useful marker for MSA at 3T in light of high prevalence of coincidence in our series (9). Therefore, the standard 3T MR imaging protocol for diagnosis of MSA should be established in the future to avoid diagnosing an unaffected person as having the disease.

The major limitation of the present study is lack of correlating the findings with histopathologic or functional imaging observations. It is necessary to enroll more patients spread over a broader age distribution for the sake of confirmation of relationship to aging process. There were no patients with definite MSA showing the HPR sign at 3T to compare with healthy subjects. Whether there are differences in the detection of HPR sign in these 2 groups by using the 2 image-acquisition methods (T2-weighted FSE versus FLAIR at 3T) is the subject of an ongoing study.

Conclusion

With MR at different magnetic field strengths, different SNRs and susceptibility effects are capable of significantly affecting MR findings and consequently influencing interpretation of the images. Our data

support the hypothesis that the HPR at 3T, whether combined putaminal hypointensity or not, is a non-specific, normal finding. We believe that the hyperintense slitlike change of the putamen in normal subjects correlated with the fluid-filled intertissue space is apt to be depicted on a high-resolution machine such as the 3T scanner.

From a practical perspective, observation of the 3T-HPR alone should not necessarily lead to a suspicion of abnormality. FLAIR may be helpful to discriminate between normal subjects and patients with MSA in case of isolated HPR at 3T.

Acknowledgments

We are grateful to Miss Li-Chuan Huang, a radiographer, for data acquisition and MR technical support.

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