“Hot cross bun” sign in multiple system atrophy with predominant cerebellar ataxia: a comparison between proton density-weighted imaging and T2-weighted imaging

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ABSTRACT

Objective: To investigate whether proton density-weighted imaging can detect the "hot cross bun" sign in the pons in multiple system atrophy with predominant cerebellar ataxia significantly better than T2-weighted imaging at 3 T.

Methods: Sixteen consecutive patients with multiple system atrophy with predominant cerebellar ataxia according to the Consensus Criteria were reviewed. Axial unenhanced proton density-weighted imaging and T2-weighted imaging were obtained using a dual-echo fast spin-echo sequence at 3 T. Two neuroradiologists independently evaluated visualisation of the abnormal pontine signal using a 4-point visual grade from Grade 0 (no "hot cross bun" sign) to Grade 3 (prominent "hot cross bun" sign on two or more sequential slices). Differences in grade between proton density-weighted imaging and T2-weighted imaging were statistically analysed using the Wilcoxon signed-rank test.

Results: In 11 patients (69%), a higher grade was given for proton density-weighted imaging than T2-weighted imaging. In 1 patient (6%), grades were the same (Grade 3) on both images. In the remaining 4 patients (25%), signal abnormalities were not detected on either image (Grade 0). The "hot cross bun" sign was thus observed significantly better on proton density-weighted imaging than on T2-weighted imaging ($P = 0.001$).

Conclusions: The "hot cross bun" sign considered diagnostic for multiple system atrophy with predominant cerebellar ataxia is significantly better visualised on proton density-weighted imaging than on T2-weighted imaging at 3 T.

Keywords: Multiple system atrophy; MSA-C; Proton density-weighted imaging; "Hot

cross bun” sign; Olivopontocerebellar atrophy; Magnetic resonance imaging

INTRODUCTION

Multiple system atrophy (MSA) is a rare and mainly sporadic adult-onset neurodegenerative disorder characterised by any combination of parkinsonian, autonomic, cerebellar, and pyramidal symptoms. MSA can be divided into the two clinical subtypes: MSA with predominant cerebellar ataxia (MSA-C) and MSA with predominant parkinsonism (MSA-P), previously described as olivopontocerebellar atrophy and striatonigral degeneration, respectively [1].

Magnetic resonance (MR) signal abnormalities have been reported to correspond to histopathological features in patients with MSA-C [2]. A cruciform hyperintensity in the pons on T2-weighted imaging (T2WI) is well known as the "hot cross bun" sign in patients with MSA-C [3, 4] and most previous studies of this "hot cross bun" sign have focused solely on T2WI [5, 6]. Some previous studies of MSA using both T2WI and proton density-weighted imaging (PDWI) have suggested that infratentorial signal changes were easily shown on PDWI [2, 4], but detailed statistical analyses have not been performed. PDWI can frequently offer additional information to T2WI, particularly for lesions in the posterior fossa. In multiple sclerosis, for example, additional PDWI is recommended by the Consortium of Multiple Sclerosis Centers Consensus Guidelines because of the greater sensitivity of PDWI to lesions in the posterior fossa [7]. However, to the best of our knowledge, no studies have yet investigated the clinical utility of PDWI at 3 T in patients with MSA-C.

The purpose of this study was to investigate whether PDWI can detect the "hot cross bun" sign in the pons in MSA-C significantly better than T2WI at 3 T.

MATERIALS AND METHODS

Patients

This retrospective study was approved by our institutional review board, and the requirement for informed consent was waived. Retrospective evaluations were performed for 16 consecutive patients (6 men, 10 women; mean age, 65 years; age range, 56-77 years) who had been clinically diagnosed with probable or possible MSA-C according to the Consensus Criteria [8] and had undergone brain MR examinations at our institution between July 2008 and November 2010.

Imaging Protocols

Brain MR examination was performed using a 3-T MR scanner (Magnetom Tim Trio; Siemens, Erlangen, Germany) with a 12- or 32-channel head coil (1 patient with a 12-channel head coil; 15 patients with a 32-channel head coil). The head of the patient was fixed with cotton stabilisers within the head coil, and the patient was instructed not to move the head during MR acquisition. Unenhanced PDWI and T2WI were obtained using a dual-echo fast spin-echo sequence parallel to the anterior commissure-posterior commissure line. Parameters of this sequence were as follows: repetition time (TR), 4000 ms; echo time (TE), 20/81 ms; slice number, 35; slice thickness, 3 mm; interslice gap, 1 mm; matrix size, 348 × 384 (12-channel) / 267 × 384 (32-channel); average, 1; total acquisition time, 192 s (12-channel) / 152 s (32-channel).

Image Analysis

Pontine signals were assigned a 4-point visual grade, as follows: Grade 0, no visualisation of "hot cross bun" sign; Grade 1, a relatively hyperintense anteroposterior line compared with the horizontal (left-to-right) line; Grade 2, definite "hot cross bun" sign on a single slice; Grade 3, prominent "hot cross bun" signs on two or more sequential slices. The "hot cross bun" sign was visually assessed by two independent, experienced neuroradiologists (with 9 and 16 years of experience in neuroradiology). If discrepancies existed between the two readers, consensus was obtained in discussion after both reading sessions were completed. Image evaluation procedures were performed on a PACS system (Centricity, PACS Workstation version 2.0; GE Medical Systems, Milwaukee, WI).

Statistical Analysis

The concordance rate for visual grades between the two readers was determined using quadratic-weighted κ statistics. Differences in the grade of "hot cross bun" signs between PDWI and T2WI were statistically assessed using the Wilcoxon signed-rank test. All statistical analyses were performed using MedCalc version 11.5 software (MedCalc Software, Mariakerke, Belgium). Values of $P < 0.05$ were considered statistically significant.

RESULTS

High concordance rates were observed between the two readers with κ values of .924 for PDWI and .765 for T2WI. Grades of the "hot cross bun" sign in each patient are

shown in Table 1. In 11 patients (69%), a higher grade was given for PDWI than for T2WI (Fig. 1, Fig. 2). In only 1 patient (6%), grades were the same (Grade 3) on both PDWI and T2WI (Fig. 3). In the remaining 4 patients (25%), no "hot cross bun" sign was detected on either PDWI or T2WI. The "hot cross bun" sign was thus visualised significantly better on PDWI than on T2WI (P= 0.001).

DISCUSSION

The present study confirmed that degenerative changes in the pons of patients with MSA-C are significantly better detected on PDWI than on T2WI. Even though infratentorial lesions in several central nervous system diseases are known to be better detected on PDWI than on T2WI [7, 9, 10], most previous studies of the "hot cross bun" sign have focused only on T2WI [5, 6]. Some previous reports of MSA using both T2WI and PDWI have briefly mentioned that MR signal changes in patients with MSA were more easily shown on PDWI than on T2WI [2, 4]. However, such differences have not previously been confirmed statistically.

In this study, long TR and short TE images were acquired, and were defined as PDWI. In spin-echo acquisition of PDWI, TR is usually between from 2000 ms to 3000 ms with suppressed cerebrospinal fluid (CSF) signal. It increases detectability of lesion at the vicinity of the CSF, such as cerebral cortex. In fast spin-echo acquisition, however, TR is increased for more echo trains and slices in each excitation. It increases CSF signal [11], but it is not a problem in the present study, because the "hot cross bun" sign is observed at the center of the pons.

The reason PDWI is superior to T2WI for detecting infratentorial lesions is considered to be as follows. In general, contrast between a lesion and the surrounding normal structures depends on differences of the intrinsic parameters, including T1, T2 and proton density. In a previous study of multiple sclerosis, T1 and particularly T2 relaxation times of infratentorial lesions were found to be closer to the relaxation times of white matter than supratentorial lesions, and densely packed fibres or a rigid structure in infratentorial areas may result in less accumulation of extracellular water, both of which may contribute to reduced contrast between the lesion and background white matter in the posterior fossa [12]. MSA shows characteristic histological changes, such as neuronal loss and the presence of gliosis, in the middle cerebellar peduncle and transverse pontine tracts [13]. Whereas oedema fluid is mostly unbound to tissue macromolecules [14], intracellular water within gliosis is closely related to densely packed glial fibrils and other cytoplasmic structures, thereby resulting in a shortening of T2 relaxation relative to T1 relaxation [15, 16]. In previous clinical studies, PDWI clearly demonstrated neuropathological changes that were equivocal on T2WI in the inferior olives in palatal myoclonus [10] and in the pyramidal tracts in amyotrophic lateral sclerosis [17]. An experimental animal study showed the advantage of PDWI over T2WI in visualising astrocytic gliosis, displaying signal changes on PDWI without corresponding signal abnormalities on T2WI [15]. PDWI also offers a high signal-to-noise ratio because the signal intensity is only slightly attenuated by the T1 or T2 relaxation processes, resulting in improved anatomical detail. PDWI is usually obtained and is useful for interpretation of areas of high signal intensity observed on T2WI in which anatomical detail is obscured [18]. PDWI thus plays a

relatively more important role in the visualisation of infratentorial lesions than T2WI, resulting in better detectability of the infratentorial "hot cross bun" sign in MSA-C on PDWI than on T2WI.

The "hot cross bun" sign is seen not only in patients with MSA, but also in some patients with other diseases, such as spinocerebellar ataxia, variant Creutzfeldt-Jakob disease, and selective Wallerian degeneration of transverse pontocerebellar fibres due to vasculitis [19-21]. Nevertheless, the "hot cross bun" sign is highly specific for MSA [3], and is a hallmark of disease progression in general [5, 6]. The "hot cross bun" sign is attributable to neuronal loss and astrocytic gliosis in areas of transverse pontine tracts with relative preservation of the pontine tegmentum and corticospinal tracts, which run craniocaudally into the dorsal pons [4, 13]. The second consensus statement on the diagnosis of MSA noted that MR imaging could assist diagnosis, and that T2-signal changes on 1.5-T MR imaging in the brainstem could be helpful, including the "hot cross bun" sign [8]. On T2WI, Horimoto et al. [6] reported that the pontine "cross sign" is useful to distinguish clinical subtypes of MSA, as this sign becomes evident about 5 years earlier in MSA-C than in MSA-P. The present results suggest that even when abnormal signal intensity in the pons is not detected or is detected with low confidence on T2WI, PDWI would better visualise the "hot cross bun" sign, facilitating the diagnosis of MSA and providing useful information for differential diagnosis in early stages of this disease.

This study has several limitations. No neuropathological evaluations were performed. Hence, no patients with definite MSA-C were examined because definite MSA requires neuropathological demonstration of α-synuclein-positive glial cytoplasmic

inclusions with neurodegenerative changes in striatonigral or olivopontocerebellar structures. A fluid-attenuated inversion recovery (FLAIR) sequence was not acquired. A FLAIR sequence nowadays tends to be used on the routine clinical examinations of central nervous system, however, it is known that PDWI is sensitive to detect infratentorial lesions that may be missed by FLAIR images [7]. On the basis of knowledge of the above, in the present study, PDWI was used to evaluate infratentorial signal changes, such as in the pons in MSA-C.

CONCLUSIONS

The current study confirms that the “hot cross bun” sign that is considered diagnostic for MSA-C is visualised significantly better on PDWI than on T2WI at 3 T. The addition of PDWI is considered beneficial to depict the “hot cross bun” sign of MSA-C.

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Table 1 Grading scores for the “hot cross bun” sign

Patient	Sex	Age (years)	Category of MSA-C	Grade	
				PDWI	T2WI
1	F	61	possible	3	2
2	F	65	possible	3	2
3	F	68	possible	0	0
4	F	66	possible	3	1
5	F	77	possible	0	0
6	F	67	probable	2	1
7	F	72	probable	0	0
8	M	65	probable	3	1
9	F	65	possible	3	3
10	M	70	probable	3	1
11	M	66	possible	0	0
12	F	57	probable	3	1
13	F	60	possible	3	1
14	M	56	possible	3	2
15	M	64	possible	3	1
16	M	68	probable	2	1

MSA-C: multiple system atrophy with predominant cerebellar ataxia, PDWI: proton density-weighted imaging, T2WI: T2-weighted imaging, A 4-point visual grade of pontine signals: Grade 0, no visualisation of “hot cross bun” sign; Grade 1, a relatively hyperintense anteroposterior line compared with the horizontal (left-to-right) line; Grade 2, definite “hot cross bun” sign on a single slice; Grade 3,

prominent “hot cross bun” signs on two or more sequential slices.

FIGURE LEGENDS

Fig. 1: A 57-year-old woman diagnosed with probable MSA-C. **A)** PDWI demonstrates a prominent “hot cross bun” sign on two slices (Grade 3). **B)** T2WI demonstrates a relatively hyperintense anteroposterior line compared with the horizontal (left-to-right) line (Grade 1). This patient is classified as showing higher grade on PDWI than on T2WI.

Fig. 2: A 67-year-old woman diagnosed with probable MSA-C. **A)** PDWI demonstrates a definite “hot cross bun” sign on a single slice (Grade 2). **B)** T2WI demonstrates a relatively hyperintense anteroposterior line compared with the horizontal (left-to-right) line (Grade 1). This patient is classified as showing higher grade on PDWI than on T2WI.

Fig. 3: A 65-year-old woman diagnosed with possible MSA-C. PDWI **(A)** and T2WI **(B)** demonstrate a prominent “hot cross bun” sign on three slices. This patient is classified as showing the same grade on PDWI and T2WI (Grade 3).

Fig. 1

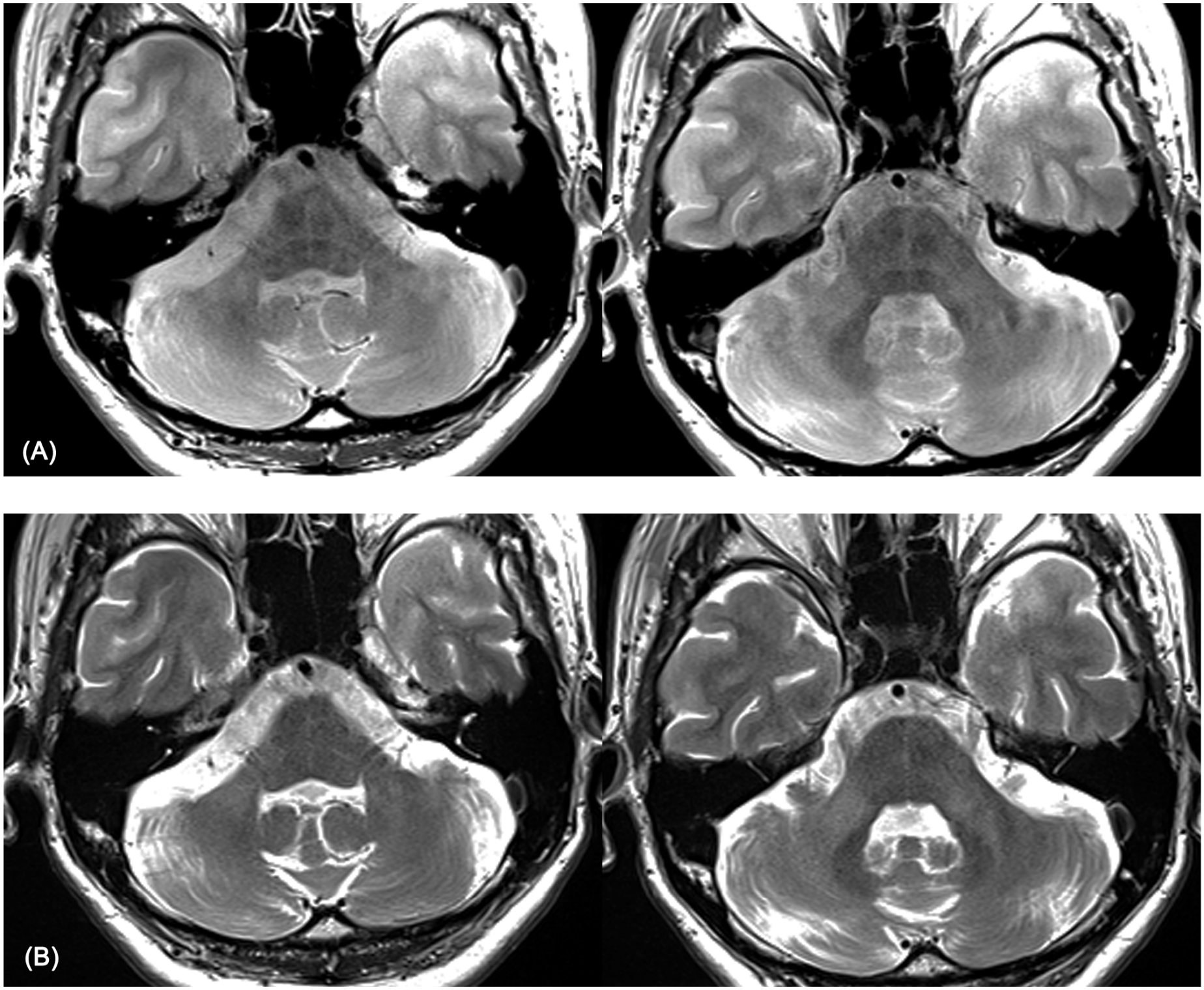

Fig. 2

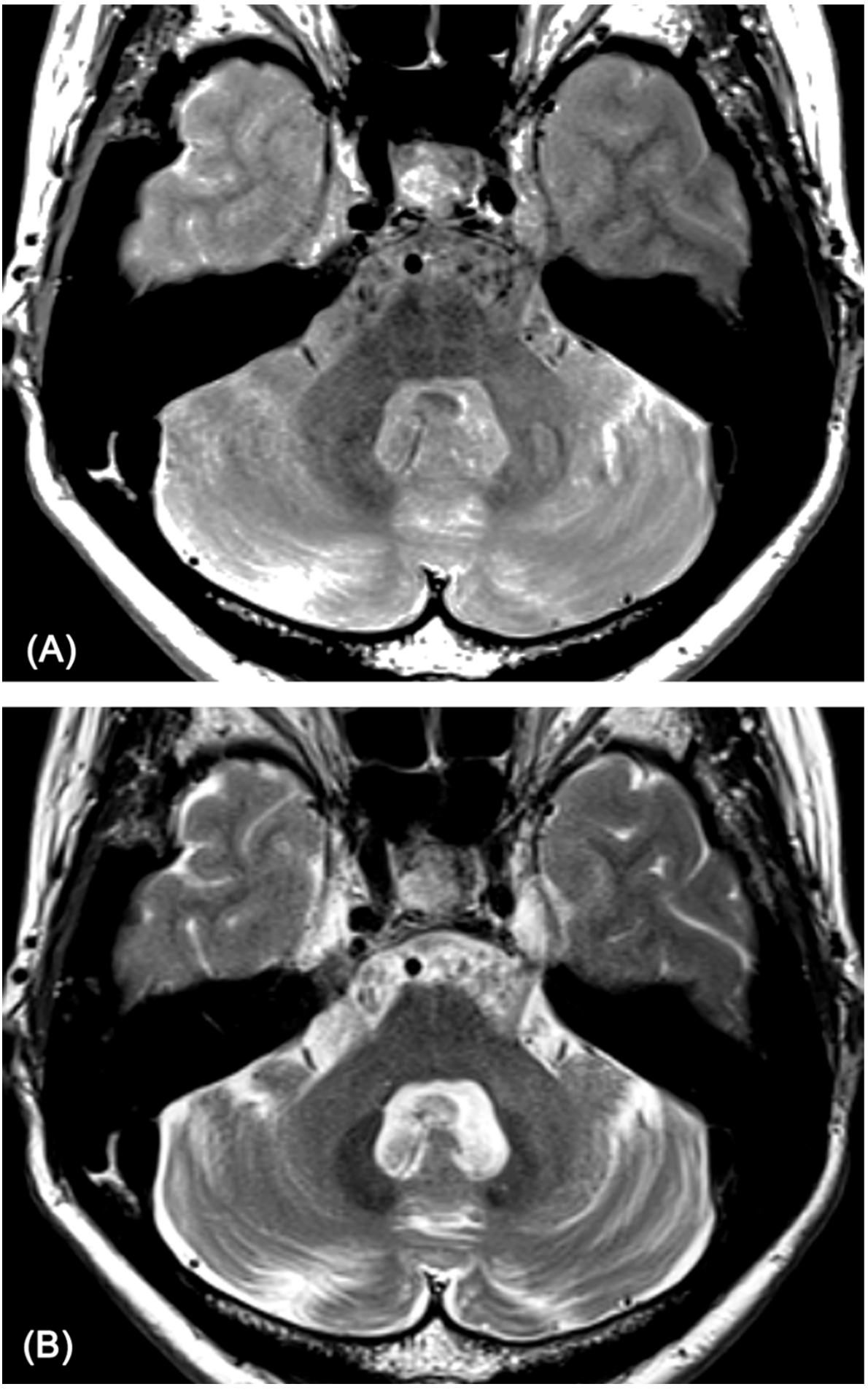

Fig. 3