Advanced Magnetic Resonance Imaging (MRI) Characterization in Bickerstaff's Brainstem Encephalitis

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Research Article

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Abstract

Purpose Bickerstaff's brainstem encephalitis(BBE) is considered a scarce variant of Miller-Fisher syndrome(MFS) and Guillain–Barré syndrome (GBS) but accounts for a significant proportion of brainstem encephalitis.Detailed knowledge of their neuroimaging manifestations is of paramount importance for a correct early diagnosis and proper management of the affected patients.In this study,We sought to characterize neuroimaging findings,including the morphology and manifestation of advanced MR imaging and differential diagnosis.

Methods Seven BBE patients (5 males,2 females; mean age 42.5 ± 5.7 years,range 17 to 63 years) were retrospectively studied using conventional MRI (T1- and T2- weighted,FLAIR sequences,postcontrast T1-weighted images) and advanced MRI such as diffusion-weighted imaging (DWI) and proton magnetic resonance spectroscopy (MRS).The apparent diffusion coefficient (ADC) values and the MRS ratio were calculated in lesion regions.

Results

1. The distribution of these lesions typically include bilateral and symmetrical involvement of the mesencephalon,thalamus,tegmentum,infratentorial periaqueductal region,and the periventricular region surrounding the third and fourth ventricles involving white and gray matter; additional supratentorial white matter is not involved.

2. MRI axial T2-weighted images and FLAIR sequences showed nearly symmetrical hyperintense signal changes with slightly spotty,patchy,or confluent homogeneous enhancement on postcontrast T1-weighted images without necrosis or hemorrhage.

3. DWI signal was enhanced,and the apparent diffusion coefficient (ADC) map signal was slightly increased.ADC values of BBE lesions were in the range of 1.21 to 1.67 × 10^{-3} mm/s^2 (mean 1.38 ± 0.66 × 10^{-3} mm/s^2).

4. Proton MR spectrum showed a slight increase in choline and a relative decrease in NAA peak,while Lipid and Lac doublet were not detected.

Conclusion Advanced MRI imaging can provide important physiological and metabolic information of BBE and complement the morphological findings of the clinical conventional MRI.

1. Introduction

BBE,MFS,and GBS are considered anti-GQ1B antibody syndrome due to their sharing of autoantibodies to the ganglioside complex GQ1b and their overlapping clinical spectrums after the detection of serum immunoglobulin G (IgG) antibody to ganglioside GQ1b[1].BBE is characterized by the clinical triad of progressive ophthalmoplegia,ataxia,and impaired consciousness[2].The annual incidence of BBE is approximately 0.078/100 000 and is more common in males than females[3].It is believed that the

immune response induced by antecedent Campylobacter jejuni or Haemophilus influenza is involved in the pathogenesis of BBE.Patients should be treated within 4 weeks of symptom onset,although it takes about 10 days from symptom onset to maximum symptom[4].

The BBE diagnosis usually depends on the typical clinical presentation and seropositivity of the anti-GQ1b IgG antibody.Cerebrospinal fluid analysis usually reveals albuminocytological dissociation.It is important to note that not all cases of BBE are anti-GQ1b positive.Serum anti-GQ1b IgG antibody positive in BBE patients accounted for 70%,and MRI showed brain abnormalities in 30% of patients[5].Abnormal MRI results are helpful to make an accurate diagnosis.Advanced imaging techniques,such as diffusion-weighted and MR spectrum,could provide more valuable information than conventional MRI.Therefore,the application of advanced MR imaging is expected to reflect more biological mechanisms of BBE and help to improve the accuracy of differential diagnosis from other brainstem diseases.This study aimed to evaluate the diagnostic performance of BBE by combining conventional MR imaging with advanced MR imaging.

2. Materials And Methods

2.1. Subjects

The study included seven patients (5 male,2 female; mean age 42.5 years,range 17 to 63 years).All patients underwent conventional MRI,DWI,and MRS during the acute phase of the disease.

2.2. Imaging protocols

All patients underwent MRI examination using a 12-channel head coil on Siemens 3.0 T Verio systems (Erlangen,Germany).The MRI protocol included T1-weighted imaging (TR,200–300 ms; TE,2–3 ms),T2-weighted imaging (TR,4200–4500 ms; TE,90–100 ms),fluid attenuated inversion recovery (FLAIR),diffusion-weighted imaging (DWI),proton magnetic resonance spectroscopy (MRS).

2.3. Diffusion-weighted imaging

DWI was performed using an EPI-based sequence.Two b-values of 0 and 1000 s/mm^2 were acquired in all three orthogonal directions.Acquisition of main parameters: 5400 ms TR,98 ms TE,100×110 matrix size,230×230 mm^2 FOV,0.16 mm × 0.16 mm in-plane resolution,5.0 mm slice thickness,2 averages,and 4 EPI image segments.

2.4. Magnetic resonance spectroscopy

Single-voxel spectroscopy using a point resolved spectroscopy sequence (PRESS) was performed with long TE (TR 1,700 ms;TE 135 ms).Appropriate automatic shimming and water suppression were achieved.Acquisition time was approximately 3.5 min per spectrum.

2.6. Image processing and analysis

The lesion region of interest (ROI) was drawn manually,and the ADC maps were automatically calculated by the processing tool contained in the Siemens Syngo MMWP(Syngo Multi-Modality Workplace).Spectroscopic data,including NAA/Cr,Cho/Cr,and Cho/NAA,were obtained from the cubic volumes (2 cm^3) of the lesions.

3. Results

All seven patients underwent serial neurological examinations.The clinical characteristics of the subjects were summarized in Table 1.

Conventional T2-weighted and FLAIR images showed hyperintense,multiple confluent lesions with limited,bilateral mesencephalon and thalamus involvement in 2 patients,and tegmentum involvement in 2 patients,as shown in Fig. 1.Patchy lesions were observed in 1 patient and the infratentorial periaqueductal region and the periventricular region surrounding the third and fourth ventricles were involved in 3 patients,as shown in Fig.2.

All patients with different types of enhanced lesions (spotty,patchy,confluent,or cloud-like).The conventional MRI manifestations were also summarized in Table 1.

The ADC values of BBE lesions in patients imaged within 7 days (acute stage) ranged from 1.21 to 1.67×10^{-3} mm/s^2 (mean $1.38 \pm 0.66 \times 10^{-3}$ mm/s^2),and were summarized in Table 2.Table 2 shows the mean ratios of metabolites obtained from lesions.The NAA/Cr ratio ranged from 0.75 to 1.69 (mean 1.30 ± 0.04),the Cho/Cr ratio ranged from 1.28 to 1.84 (mean 1.67 ± 0.05),the Cho/NAA ratio ranged from 1.01 to 2.41 (mean 1.37 ± 0.04) in the lesions.No lipid and lactate peaks were detected in all subjects (Table 2).A reduction in the NAA/Cr ratio was detected in the case of a slightly higher Cho/Cr ratio,as shown in Fig.3.

Discussion

BBE is an acute immune-mediated neurological disease usually associated with antecedent infection,specifically upper respiratory or gastrointestinal infection[6].The diagnosis of BBE is based mainly on clinical features,although additional examinations,such as anti-Gq1b antibody seropositivity and MRI abnormalities,may contribute to an accurate diagnosis.

Ophthalmoplegia is a core clinical feature of BBE,representing as central nervous system (CNS) involvement in anti-GQ1b antibody syndrome.Gq1b is predominantly expressed at the juxtaparanodes,neuromuscular injections,sensory nerves,and proximal segments of cranial nerves,such as the oculomotor,trochlear,and abducens nerves[7].T2WI and FLAIR images often have high signals,specific localization in bilateral ventromedial nucleus of the thalamus and superior cerebellar peduncle,and also contain a high concentration of GQ1b ganglioside.Neuromuscular block and conduction block caused by autoantibodies against anti-GQ1b binding at these sites can explain

ophthalmoplegia,ptosis,and ataxia in BBE.Abnormal signals at specific sites with high anti-GQ1b expression reflected tissue selection specificity.

BBE Patients present varying degrees of consciousness disturbance,suggesting impaired brainstem reticular activating system[8].Besides,the detachment of terminal myelin loops may cause the disorder of electrical conduction [9].In our study,MRI showed significant abnormalities involving the bilateral thalamus,mesencephalon tegmentum,and periventricular region surrounding the third and fourth ventricles manifesting hyperintensity on T2-weighted and fluid-attenuated inversion recovery(FLAIR) images.These midline structures are infratentorial sensory circumventricular organs where typical tight junctions among endothelial cells composing the blood-brain barrier (BBB) are anatomically deficient and relatively permeable[10].Similarly,these periventricular endothelial cells that form BBB contain a certain amount of GQ1b,which binding to these sites through circulating macromolecules such as anti-GQ1b antibodies,increasing permeability and allowing macromolecules by inducing BBB breakdown.Electrolytes and free water penetrate the brainstem parenchyma through the endothelial gaps[11].In our study,DWI showed isointense or slightly hypointense,and ADC increase reflected free water in the expanded extracellular space,consistent with vasogenic edema.Diffuse dilatation of extracellular space in the brainstem white matter and leakage of plasma from the vessel alter the brainstem reticular activating system,leading to the development of impaired consciousness.DW images and ADC maps are more sensitive than conventional MRI to determine the extent and degree of vasogenic edema in gray and white matter.

The histopathological process of BBE is associated with the breakdown of BBB which is characterized by dense inflammatory infiltration around the vessels,leading to demyelination and axonal damage[12].Antibody-mediated attacks in the nodes,activating the immunological cascade,and paranode,occurring independently of complement,both results in detachment of terminal myelin loops and disruption of the ion channels and membrane potential[13].In this study,MRS demonstrated that the Cho peak increased and the NAA peak decreased slightly.Cho/NAA values of BBE lesions were within the range.1.01 to 2.41 slight elevation of Cho may result from gliosis or ischemic damage to myelin,while NAA decreases are probably the result of vasogenic edema and neuron cell loss.The increase in Cho/Cr ratio detected in our study indicates that inflammation alone can lead to an increase in Cho levels,which may be secondary to choline oxidase's input in infiltrating macrophages and lymphocytes.Moreover,the reduced NAA/Cr ratio showed slight axonal degeneration and a reduction in axonal density associated with a decreased NAA values.MRS provides an evaluation of inflammatory demyelinating processes and is a non-invasive means of studying BBE biochemistry.These findings would support a primary demyelinating pathology in the BBE.

However,the exclusion of other disorders may need to be considered,including Wernicke encephalopathy and neuromyelitis optica spectrum disorders.

The distinct MR features of Wernicke encephalopathy are the symmetrical T2WI-hyperintense areas around the third ventricle,the mamillary bodies,and the tectal plate.Mammillary body,periaqueductal gray

necrosis were seen in Wernicke encephalopathy.MR demonstrated pronounced cerebellar atrophy with the fourth ventricle's expansion and marked dilation of the cerebellar fissure[14].

It was found that the longitudinally extensive transverse myelitis (LETM) spinal cord lesion associated with acute myelitis was the most specific neuroimaging feature of neuromyelitis optical spectrum disorders (NMOSD).Other neuroimaging features of

NMOSD shows characteristic periependymal lesions surrounding the third ventricle,involving the thalamus and hypothalamus.Brain lesions in NMOSD are typically localized in the periependymal regions with high expression of aquaporin-4[15].

Conclusion

Useful MR tips can guide the diagnosis of BBE.They included the location and morphology of lesions,distribution of lesions in gray and white matter,tissue-selective specificity,and imaging characteristics of DWI and MRS.Further,advanced imaging techniques,such as DWI and MRS,can better differentiatte BBE from other neurological diseases than conventional imaging techniques.Combining conventional MR imaging and advanced MRI techniques have acquired a better understanding of BBE as an inflammatory demyelination disease,and improving sensitivity and specificity of the neuro-diagnosis of BBE.

Declarations

Ethics approval and consent to participate

All experimental protocols were approved by the Human Ethics Committee of The First Affiliated Hospital of Guangxi Medical University.All methods were carried out in accordance with relevant guidelines and regulations.Written informed consent was obtained from individual or guardian participants.

Availability of data and material:

All data generated or analysed during this study are included in this published article.

Consent for publication:

Written informed consent for publication was obtained from all participants.

Competing interests:

The authors declare that they have no competing interests.No other author has reported a potential conflict of interest relevant to this article.

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Author Contribution:

Mao Yipu performed the data analyses,and was a major contributor in writing the manuscript.Jiang Muliang contributed significantly to analysis and manuscript preparation.Long Liling helped perform the analysis with constructive discussions.All authors read and approved the final manuscript.

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References

1. Shahrizaila N,Yuki N.(2013)Bickerstaff brainstem encephalitis and Fisher syndrome:anti-GQ1b antibody syndrome.J Neurol Neurosurg Psychiatry 84:576-583.
2. Shahrizaila N,Yuki N(2010)Guillain-Barré syndrome,Fisher syndrome and Bickerstaff brainstem encephalitis:Understanding the pathogenesis.Neurology Asia 15:203-209
3. Koga M,Kusunoki S,Kaida K(2012)Nationwide survey of patients in Japan with Bickerstaff brainstem encephalitis:epidemiological and clinical characteristics.J Neurology Neurosurgery Psychiatry 83:1210-1215.
4. A Merwick,J Dalmau,N Delanty(2013)Insights into antibody-associated encephalitis- Bickerstaff's 1950's papers revisited.J Neurol Sci 334:167-168.
5. Odaka M,Yuki N,Yamada M(2003)Bickerstaff's brainstem encephalitis:clinical features of 62 cases and a subgroup associated with Guillain-Barre syndrome.Brain 126:2279– 2290.
6. Ito M,Kuwabara S,Odaka M(2008)Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum:clinical analysis of 581 cases.Journal of Neurology 255:674–682.
7. Chiba A,Kusunoki S,Obata H(1997).Ganglioside composition of the human cranial nerves,with special reference to pathophysiology of Miller Fisher syndrome.Brain Res 745:32–36.
8. Koga M(2013)Bickerstaff brainstem encephalitis:epidemiology,diagnosis,and therapy.Nihon Rinsho 71:898–903.
9. Samira Y,Shahriar N,Neda K(2014)Comparison of electrophysiological findings in axonal and demyelinating Guillain-Barre syndrome.Iran J Neurol 13:138-143.
10. Wang QP,Guan JL,Pan WH(2008)A Diffusion Barrier Between the Area Postrema and Nucleus Tractus Solitarius Neurochem 33:2035-2043
11. Christopher JP,Ted DH,Alastair VF(2008)The area postrema:a brain monitor and integrator of systemic autonomic state.Neuroscientist 14:182-194
12. Thierry K,Jean CA,Andreas JS(2004)Clinical features and pathophysiological basis of sensory neuronopathies (ganglionopathies).Muscle Nerve 30:255-68.
13. Janev F,Steven SS,Hugh JW(2018)Nodes,paranodes and neuropathies.J Neurol Neurosurg Psychiatry 89:61-71.
14. Weidauer S,Nichtweiss M,Ianfermann H(2003)Wernicke encephalopathy:MR findings and clinical presentation.Eur Radiol 13:1001–1009.

15. Dean MW,Brenda B,Jeffrey LB(2015)International consensus diagnostic criteria for neuromyelitis optica spectrum disorders 85(2):177-189

Tables

Due to technical limitations, table 1,2 is only available as a download in the Supplemental Files section.

Figures

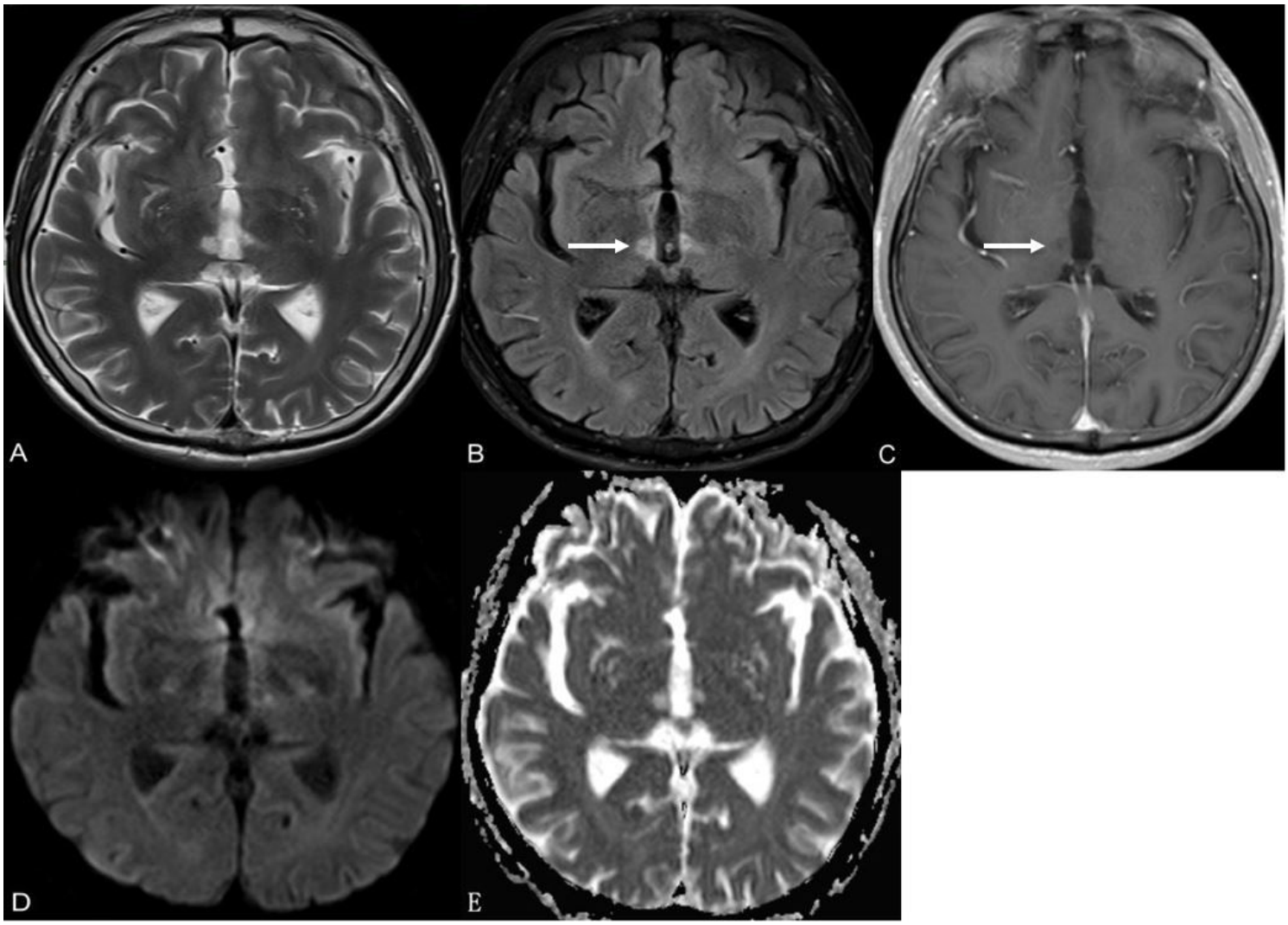

Figure 1

A 63-year-old male with BBE suffering from progressive ophthalmoplegia,ataxia and impaired consciousness.a,b Axial T2WI and FLAIR MR shows bilaterally symmetric high signal intensity in the thalami (arrow,b).c Axial post-contrast T1WI show slight enhancement(arrow,c).d,e Axial DWI and ADC shows slightly increased signal.

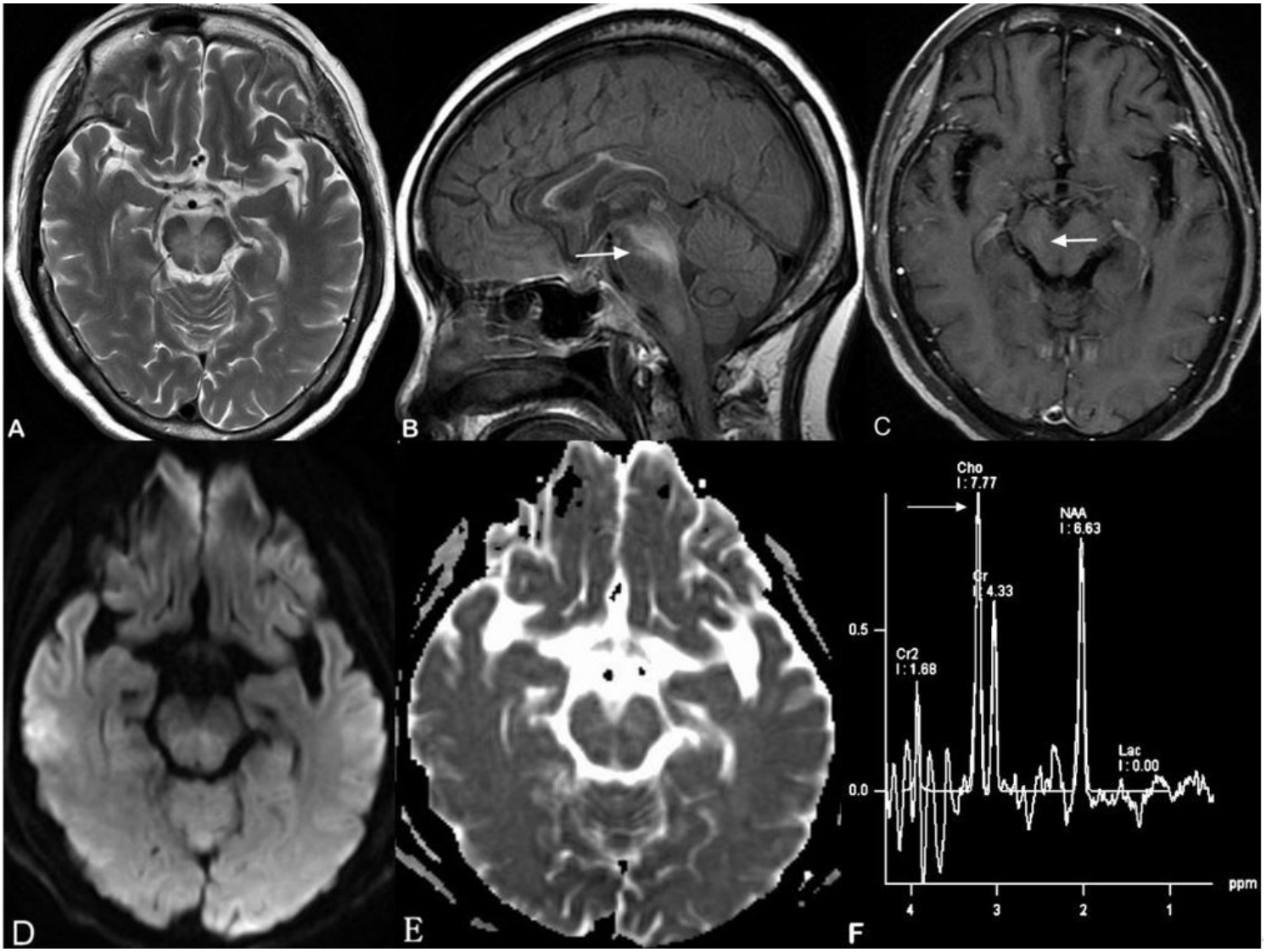

Figure 2

A 51-year-old female suffering from progressive double vision,cranial nerve palsies,and gait ataxia.a,b Axial T2WI and sagittal FLAIR MRshowing nearly symmetrical hyperintense signal changes of the mesencephalon and tegmentum (arrow,b).c Axial post-contrast T1WI show homogeneous patchy enhancement (arrow,c).d,e Axial DWI and ADC shows slightly increased signal.f MRS show a slight increase of the Cho peak and a slight decrease of the NAA peak (arrow,f).

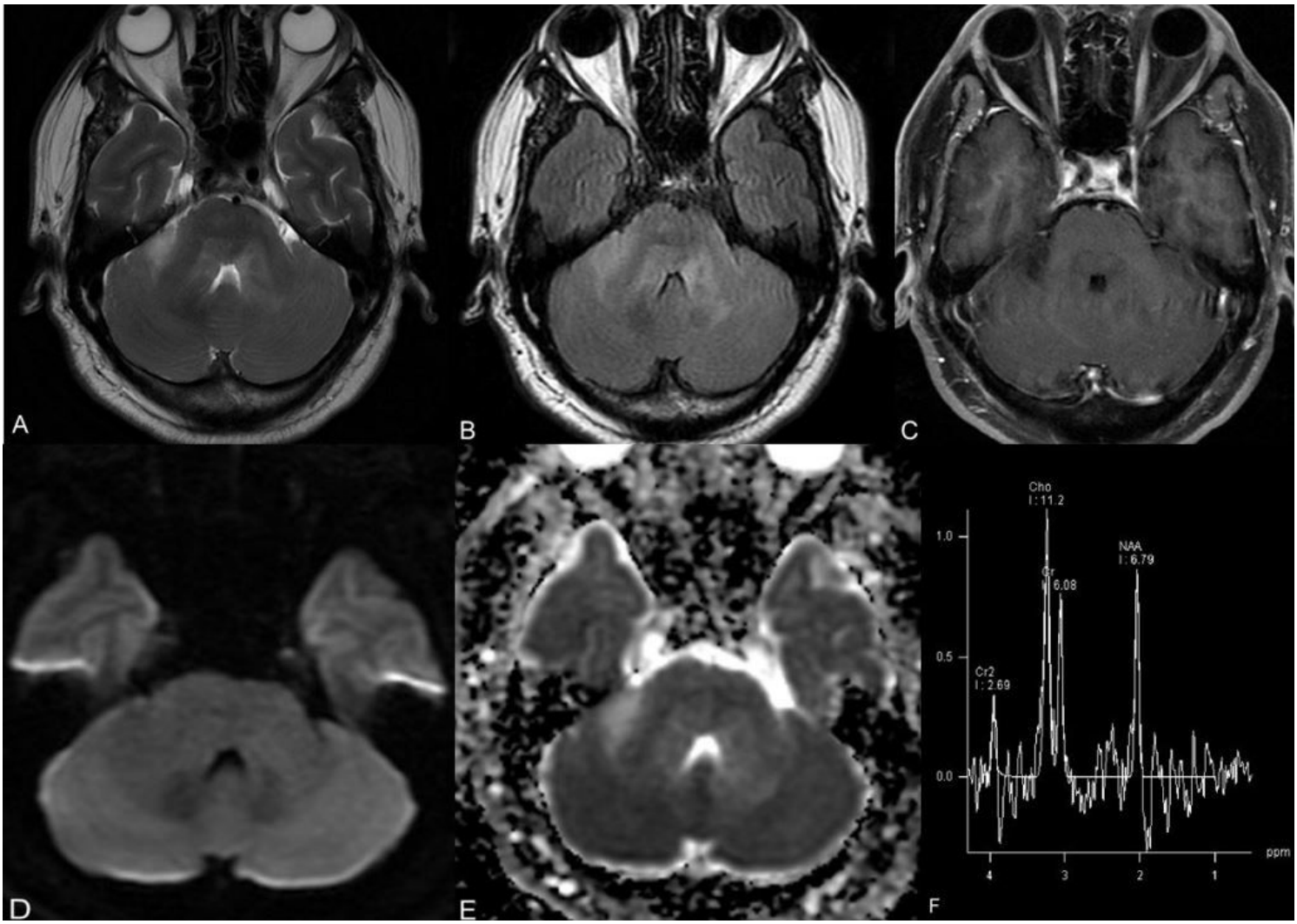

Figure 3

A 17-year-old male patient with history of progressive double vision,cranial nerve palsies,and gait ataxia.a,b Axial T2WI and FLAIR MRdemonstrates bilaterally symmetrical hyperintensities in the inferior cerebellar peduncle deep white matter.c The lesion was not enhanced with gadolinium enhancement on a T1-weighted image. d,e Axial DWI show isointensity and ADC show slightly increased signal.f MRS demonstrates a slight increase of the Cho/NAA ratio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.jpg
- Table2.jpg