Role of magnetic resonance imaging in the diagnosis of primary central nervous system angiitis

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Abstract. The present study reported on the use of magnetic resonance imaging (MRI) in the diagnosis of primary angiitis of the central nervous system (PACNS). A total of 19 consecutive patients with a clinical diagnosis of PACNS confirmed by clinical follow-up were enrolled in the present study. All patients underwent unenhanced and enhanced MRI prior to and after steroids or steroids plus immunosuppressive therapy. At baseline, all patients showed lesions on MRI in the grey and white matter. Lesions presented as slightly hypointense on T1-weighted images (T1WI), slightly hyperintense on T2WI, hyperintense on fluid-attenuated inversion recovery, iso- or slightly hyperintense on diffusion-weighted images (DWI) and hyperintense on apparent diffusion coefficient (ADC) mapping. After contrast injection, the lesions showed patchy, cord-like or goral enhancement. Seven cases had unilateral lesions and the other 12 cases had bilateral lesions. On all sequences, indistinct margins characterised most of the lesions, and certain lesions were oedematous. Treatment with steroids or steroids plus immunosuppressive agents resulted in improvement or disappearance of symptoms, and seventeen patients had evidently improved according to MRI. In conclusion, PACNS has unique characteristics on MRI; DWI, ADC mapping and enhanced images are of great importance for the diagnosis and clinical management of early-stage PACNS.

Introduction

Primary angiitis of the central nervous system (PACNS) is a rare idiopathic disorder that results in multifocal inflammation of the small and medium-sized blood vessels in the brain, which causes focal or diffuse neurological symptoms (1,2). PACNS may occur at any age, but is predominantly observed in children aged between 4 and 6 years old, with no clear gender predilection (3). PACNS is a rare disease, with incidences of 1-2.4 per million per year reported in Europe and America (4). Although PACNS is extremely rare, the number of reported cases has gradually increased since the late 1970s and after the diagnostic criteria had been devised (5). Viral infections increase the possibility of PACNS, particularly in immunocompromised patients (5). It is important to diagnose it promptly, since results on a small case series have suggested a favourable response to corticosteroids and immunosuppressive therapy (6). However, the diagnosis is often difficult due to its rarity and nonspecific clinical presentation (7). The range of differential diagnosis is broad, including infection, connective tissue diseases and systemic vasculitis, which require careful exclusion (8). Magnetic resonance imaging (MRI) is the primary neuroimaging modality for patients with suspected PACNS (9). Most PACNS patients have abnormal findings on MRI. Therapy comprises of immunosuppressants, including corticosteroids alone or, preferably, in combination with cyclophosphamide (10).

The present study performed a retrospective analysis of 19 cases of PACNS from Suqian City People's Hospital (Suqian, China) to characterise the MRI features of PACNS and to evaluate the diagnostic value and clinical significance of MRI.

Materials and methods

Patients. The Institutional Review Boards of Nanjing First Hospital (Nanjing, China) as well as the Nanjing Medical University local Ethics Committees approved this investigation. Written consent was obtained from all patients. A total of 19 PACNS patients consecutively hospitalized at Suqian City People's Hospital from February 2009 to January 2015 (7 males and 12 females; mean age, 42 years; age range, 34-52 years) were included. Regarding the mode of disease onset, 9 cases presented with sudden or progressive limb weakness, 14 with cephalalgia, 6 with apathy and cognitive disorder, 5 with physical convulsion and 7 with distortion of commissure. These patients were diagnosed by clinical criteria, which included i) Symptoms of cephalalgia and multifocal nervous system

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disorder, lasting for >6 months, or severe initial symptoms; ii) angiographic findings of involvement of multiple segmental arterial structures; iii) exclusion of systemic inflammation or infectious diseases; and iv) vascular inflammatory lesions identified on biopsy of pia mater and brain parenchyma (Table I).

After diagnosis, the patients underwent treatment with steroids or steroids plus immunosuppressive agents, which resulted in improvement or disappearance of symptoms and partial or complete disappearance of the lesions.

Examination procedure. All patients underwent an MRI examination on a 1.5 T scanner (Avanto®; Siemens, Erlangen, Germany). The MRI scan protocol included the following: T1-weighted imaging [T1WI; response time (TR), 448 msec; echo time (TE), 8.7 msec; field of view, 230 mm], T2WI (TR, 4,500 msec; TE, 91 msec), fluid-attenuated inversion recovery (FLAIR; TR, 8,000 msec; TE, 106 msec), diffusion-weighted imaging (DWI; b=1,000 sec/mm^2), apparent diffusion coefficient (ADC) mapping (TR, 3,400 msec; TE, 102 msec) and susceptibility-weighted imaging (SWI; TR, 49 msec; TE, 40 msec). All enhanced scanning procedures used T1WI, 5-mm section thickness and a 1.5-mm gap with gadopentate dimeglumine (0.1 mmol/kg) as the contrast medium.

Results

Cases. MRI findings showed 7 cases with unilateral lesions and 12 cases with bilateral lesions involving grey and white matter, often with indistinct margins (Figs. 1 and 2; Table I). Oedema was seen bordering six lesions. Nine cases showed bilateral asymmetrical involvement of frontal, temporal and parietal lobes, and three cases showed bilateral asymmetrical basal ganglia involvement. One case of brainstem, one case of left cerebellar hemisphere, two cases of right temporal lobe, two cases of frontal lobe and one case of left parietal lobe involvement were also identified, the involvement or location of lesions were shown in Table I.

All lesions were slightly hypointense on T1WI, slightly hyperintense on T2WI, markedly hyperintense on FLAIR, iso- or slightly hyperintense on DWI and hyperintense on ADC mapping. On SWI, distortion and thickening of vessels was identified (Fig. 2F). After contrast injection, all lesions showed focal, cord-like or goral enhancement (Figs. 1 and 2).

The first case was a 45-year-old female who experienced initially headache and fatigue in early 2009. She developed bilateral limb weakness. Neurological examination revealed dysarthria, ataxia and quardriparesis. Brain MRI showed the left frontal and parietal lobes as well as bilateral basal ganglia regions appeared hypointense on T1WI and slightly hyperintense on T2WI. The lesion appeared slightly hyperintense on DWI and ADC. On contrast-enhanced T1WI, left frontal and bilateral basal ganglia regions showed patchy enhancement (Fig. 1).

The second case was a 37-year-old female who presented with sustained treatment-responsive headache that had been begun February 2009. She was admitted to hospital with severe diffuse headache, limb weakness and distortion of commissure a few months later. There was no history of drug abuse. Routine laboratory evaluation, serum immunoprotein electrophoresis, ryoglobulins, coagulation studies, urine analysis, chest x-ray

and echocardiography revealed no abnormalities. Brain MRI indicated patchy lesions with isointense T1 and hyperintense T2 signal in right temporal lobe (Fig. 2).

Treatment and outcome. Among the 19 PACNS patients, less severely ill patients were treated with prednisone (1-2 mg/kg/day), while eight patients with a severe condition were administered intravenous pulse therapy of 1 g methylprednisolone for three days plus intravenous cyclophosphamide (CTX; 10 mg/kg) every two weeks for three months. In a total of 17 patients, clinical symptoms and MRI appearance had apparently improved (Figs. 1G and 2E), and only two patients relapsed.

Discussion

In 1959, Cravioto and Feigin (11) were the first to recognize the entity of PACNS after examination of brains on autopsy. PACNS attracted more attention when instances of successful treatment were reported in the 1980s (12). It was then referred to as 'granulomatous angiitis of the CNS', with the lesions mainly consisting of granulomas. In 1983, the term 'isolated angiitis of the central nervous system' (IACNS) was adopted for the disease. However, as certain patients presented with extracranial involvement, the term IACNS had limitations, and in recent years, the term PACNS has therefore been used in common practice (13).

According to Kelley (14), PACNS may be due to direct damage to blood vessels from infection or an immunoreaction mediated by immune complex deposits from auto-antibodies. PACNS may occur at any age. The mean age of the cohort of the present study was 42 years. The mode of onset may be acute or insidious. The prodrome usually lasts for half a year or longer, featuring chronic processes and easy recurrence. PACNS has varied clinical symptoms with headache being most common one (15), which occurred in 14 cases of the present study. Symptoms may correspond to focal or diffuse CNS involvement. Focal symptoms include hemiparesis and seizures; diffuse symptoms are headache, apathy, cognitive abnormalities and psychosis (16).

The histopathologic features of PACNS include inflammatory infiltrates composed mainly of lymphocytes accompanied by histiocytes and plasma cells, particularly involving small leptomeningeal and intracerebral arteries (17,18). Small vessels can be distinguished by bleeding of small vessels in brain parenchyma. At the acute stage, the vascular wall is infiltrated by lymphocytes, plasmatocytes, monocytes and giant cells. In the chronic stage, achroacytes and multinucleate giant cells with focal fibrosis of the vascular wall are observed. Langerhans cells are found in granulomatous arterial angiitis. At the stable stage, scar tissues develop (19).

A confirmed diagnosis of PACNS generally requires digital subtraction angiography (DSA) or biopsy, but none of them shows a high diagnostic rate (20,21). This is due to clinically suspected PACNS having a low detectability on DSA and biopsy results being subject to sampling errors and showing a variation depending on the course of the disease (22). The high proportion of negative biopsies in patients with clinical and radiographic features of PACNS may be explained as follows: i) The larger-diameter vessels of lesions may not extend to the

Table I. Clinical features, treatment and clinical course.

Case number	Age (years)/ sex	Symptoms	Location of lesions	Magnetic resonance imaging findings (contrast-enhanced pattern)	Treatment	Follow-up period	Clinical course
1	48/M	Limb weakness, cognitive abnormalities	Bilateral frontal, temporal and parietal lobes	Patchy, cord-like	Steroids, CTX	6 months	Stable
2	42/M	Headache, limb weakness, seizures	Bilateral frontal, temporal and parietal lobes	Patchy	Steroids	12 months	Stable
3	37/F	Headache, limb weakness, distortion of commissure	Right temporal lobe	Patchy	Steroids, CTX	3 months	Stable
4	50/F	Headache, cognitive abnormalities	Bilateral frontal, temporal and parietal lobes	Patchy, goral	Steroids	24 months	Stable
5	42/M	Headache, distortion of commissure	Brainstem	Goral	Steroids, CTX	2 months	Relapse
6	34/F	Limb weakness, seizures	Left parietal lobe	Patchy	Steroids	36 months	Stable
7	52/F	Headache, distortion of commissure	Bilateral frontal, temporal and parietal lobes	Patchy	Steroids	3 months	Stable
8	37/F	Headache, cognitive abnormalities, seizures	Right temporal lobe	Goral	Steroids, CTX	14 months	Stable
9	39/M	Headache, distortion of commissure	Bilateral frontal, temporal and parietal lobes	Patchy, cord-like, goral	Steroids, CTX	24 months	Stable
10	51/F	Limb weakness	Bilateral basal ganglia	Patchy, cord-like, goral	Steroids	7 months	Stable
11	39/F	Headache, distortion of commissure	Bilateral frontal, temporal and parietal lobes	Patchy	Steroids, CTX	12 months	Stable
12	45/F	Headache, limb weakness	Left frontal lobe	Patchy, goral	Steroids, CTX	24 months	Stable
13	46/M	Headache, cognitive abnormalities, seizures	Bilateral basal ganglia	Patchy	Steroids	18 months	Stable
14	39/M	Headache, limb weakness	Bilateral frontal, temporal and parietal lobes	Goral	Steroids	12 months	Stable
15	41/F	Headache, distortion of commissure	Bilateral frontal, temporal and parietal lobes	Cord-like,	Steroids	24 months	Stable
16	42/F	Limb weakness, cognitive abnormalities	Left cerebellar hemisphere	Patchy	Steroids	8 months	Stable
17	36/F	Headache, limb weakness	Bilateral basal ganglia	Goral	Steroids	12 months	Stable
18	35/F	Headache, distortion of commissure	Left frontal lobe	Patchy	Steroids	6 months	Stable
19	40/M	Cognitive abnormalities, seizures	Bilateral frontal, temporal and parietal lobes	Patchy, cord-like, goral contrast-enhanced	Steroids, CTX	3 months	Relapse

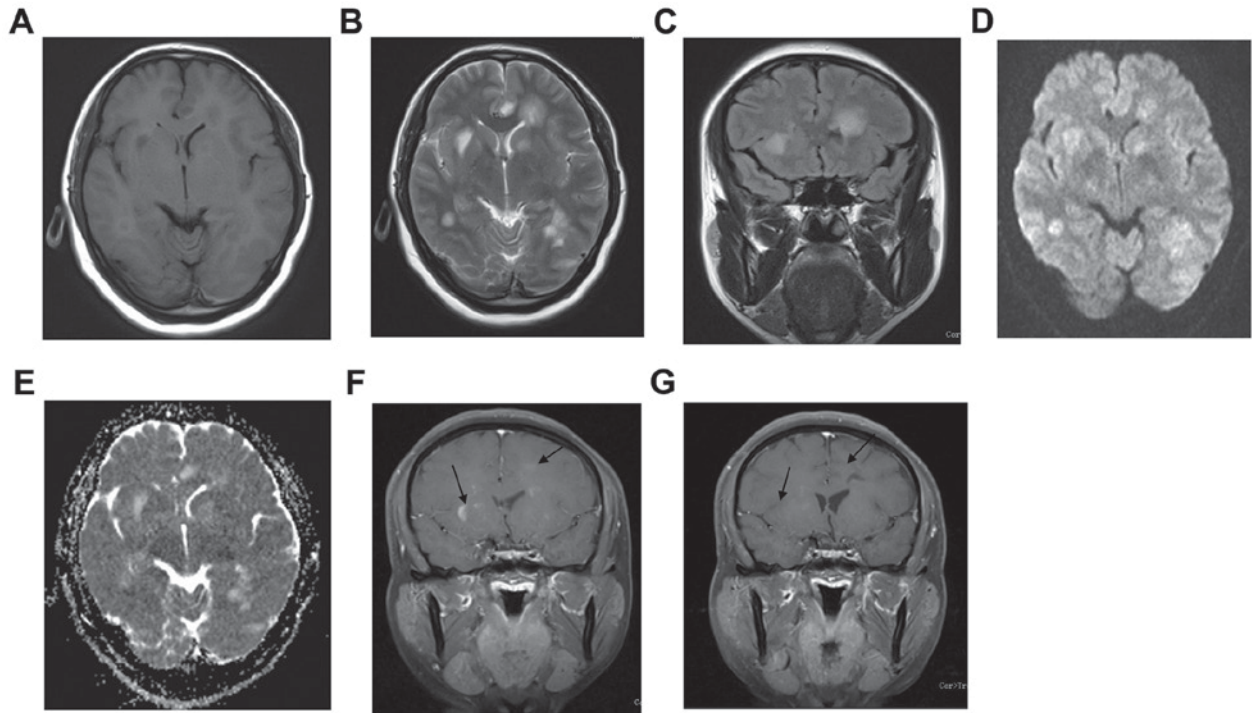CTX, cyclophosphamide; M, male; F, female.

Figure 1. MRI appearance in a 45-year-old female patient with primary central nervous system angiitis. (A and B). Left frontal and parietal lobe as well as bilateral basal ganglia regions appeared as hypointense on T1WI and slightly hyperintense on T2WI. (C) Coronal fluid-attenuated inversion recovery image showing hyperintense lesions in the left frontal and bilateral basal ganglia. (D and E) The lesion appeared slightly hyperintense on (D) diffusion-weighted imaging and (E) apparent diffusion coefficient mapping. (F) On coronal contrast-enhanced T1WI, left frontal and bilateral basal ganglia regions showed patchy enhancement. (G) Coronal contrast-enhanced MRI at two and a half months after treatment; all lesions on MRI in F (arrows) as well as symptoms had resolved. T1WI, T1-weighted imaging; MRI, magnetic resonance imaging.
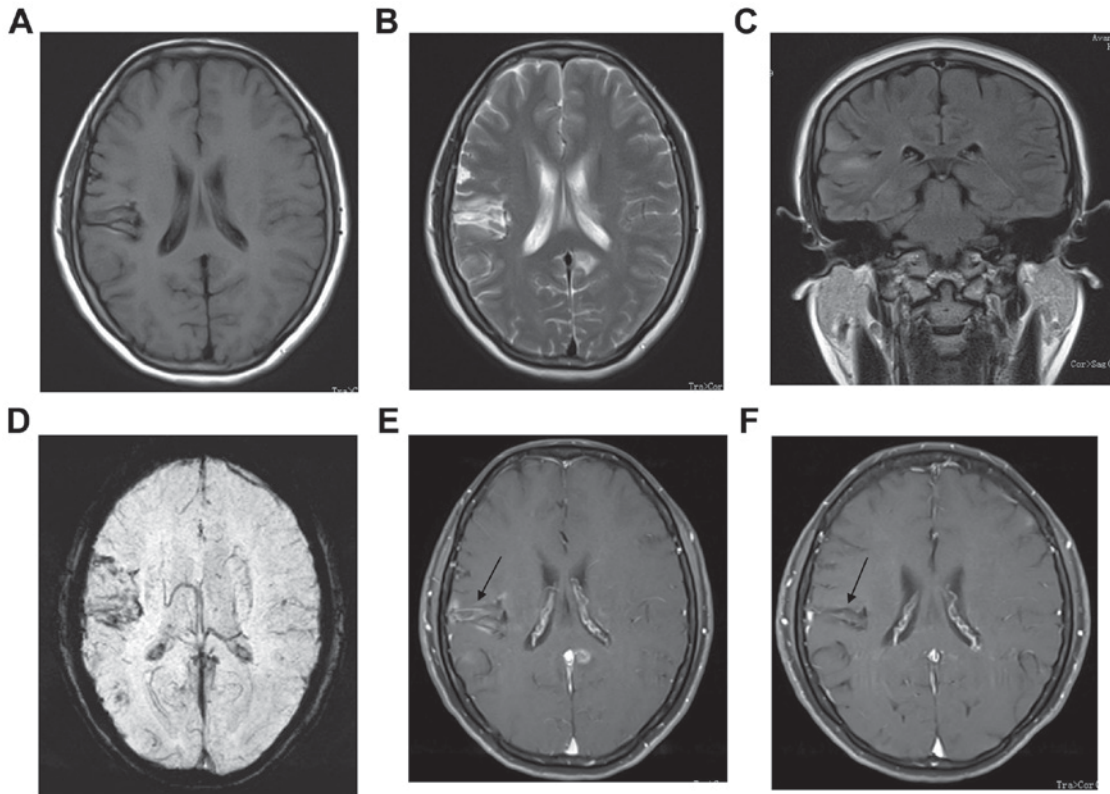

Figure 2. Magnetic resonance imaging appearance of a 37-year-old female patient with primary central nervous system angiitis. (A and B) Right temporal cortex appeared patchy with isointense T1 and hyperintense T2 signal. (C) Coronal fluid-attenuated inversion recovery image showing patchy hyperintensity involving the right temporal cortex. (D) Susceptibility-weighted imaging axial scan showing distorted blood vessels in the right temporal lobe. (E) Right temporal cortex showing focal contrast-enhanced on T1WI axial scan. (F) T1WI axial scan three months after treatment showing evidently decreased lesions compared with E (arrows). T1WI, T1-weighted imaging.

superficial parenchyma and leptomeninges, and biopsy may not be possible and ii) vessels of lesions in the potential biopsy field may be excluded by sampling errors due to their focality (23).

The MRI manifestations of PACNS are highly varied, with a sensitivity of 90-100% (3,5). Lesions are mostly located in the subcortical and deep white matter, while they are less common below the tentorium and occasionally occur in the spinal cord (5%) (9). The lesions in the present case series presented with slightly low intensity on T1WI, slight hyperintensity on T2WI, hyperintensity on FLAIR, isointensity or slight hyperintensity on DWI and hyperintensity on ADC mapping. Restricted or normal ADC values were found in the majority of acute and sub-acute phase PACNS lesions in the present study. Lesions with restricted ADC values are thought to be ischemic (6).

Infarcted lesions had cytotoxic oedema. The lesions with normal ADC values may reflect persistence of cytotoxic oedema and development of simultaneous vasogenic oedema (24).

PACNS mainly involves small and medium-sized vessels, and most lesions do not present as a wedge shape and do not conform to the typical distribution region of a vascular territory; MRI detection has a fairly high sensitivity. DWI has been recommended for the diagnosis of PACNS (3,25), and is capable of detecting early or small-sized lesions, particularly for identifying additional lesions in different vascular distribution regions or in different stages (26). Cytotoxic oedema is thought to be one characteristic of PACNS (27). DWI is helpful in increasing the diagnostic accuracy (28). Occasionally, since microhaemorrhages may occur, petechial hypointense lesions are seen on SWI, as in our patients.

SWI is an advantageous sequence for diagnosing PACNS. SWI is a technology with generates images by using magnetic susceptibility, including phase images and magnitude images, which are blended through reprocessing and made into SWI images. Vascular imaging on SWI relies on magnetic susceptibility deviation in oxygen saturation; it is free from interference by blood flow velocity and is thus particularly advantageous for imaging of small vessels around angiitis.

Lesions may be multiple, bilateral, unilateral, symmetrical, asymmetrical and even tumour-mimicking, and may show heterogeneous, cord-like and gyral enhancement patterns (4,28). MRI contrast-enhanced scanning has a significant meaning for diagnosing PACNS through diversified enhancement of the lesion. The vascular walls of acute inflammatory lesions are thickened and enhanced, which may be regarded as a direct sign of angiitis. Enhanced scanning serves as a basis for judging old and new lesions.

With regard to differential diagnoses, PACNS requires to be differentiated from the following diseases: i) Cerebral infarction: This disease tends to appear in patients with a medical history of hypertension, arteriosclerosis or diabetes mellitus. DWI and ADC mapping are useful for diagnosing infarction. ii) Multiple sclerosis: It mostly has an acute onset and a deferred course of disease. Multiple sclerosis is generally present in the white matter. iii) Infectious lesions. Onset may be acute or sub-acute and the disease course is comparatively short. Common signs of disease include fever, cephalalgia and meningeal irritation. Cerebrospinal fluid examination may provide evidence for intracranial infection. iv) Mitochondrial encephalomyopathy: This disease mainly features epileptic seizures and increased lactic acid, presenting as a disorder of energy metabolism and more pronounced damage to the cortex.

For the treatment of PACNS, glucocorticoids are the first choice for treating PACNS. In cases of resistant disease, CTX may be added. The period of treatment is 1-2 years in general. Within the cohort of the present study, 17 patients showed evident improvement of their clinical symptoms and imaging performance. Two patients had a relapse and progression of the symptoms during ongoing steroid therapy but responded to subsequent combination treatment with CTX. Furthermore, combination of steroids with CTX produced clinical stabilization in 8 patients with severe PACNS. Analysis of the cases of the present study as well as evidence from other cases from the literature suggested that long-term remission or cure is possible, particularly when therapy is combined with CTX (29,30).

Acknowledgements

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