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Central nervous system aspergillosis in immunocompetent patients

Case series and literature review

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Abstract

The aim of this study was to investigate the clinical characteristics of central nervous system (CNS) aspergillosis in immunocompetent patients.

This study enrolled six immunocompetent patients diagnosed with CNS aspergillosis. Additionally, we reviewed the clinical profiles for 28 cases reported in the literature. The age, gender, etiology of *Aspergillus* infection, clinical manifestations, location of the lesion, treatment, and prognosis were analyzed.

There were 19 men (average age, 54.6 ± 14.3 years) and 15 women (average age, 47.0 ± 19.4 years). The clinical manifestations included headache (55.9%; n = 19), visual impairment (32.4%; n = 11), diplopia (32.4%; n = 11), hemiplegia (20.6%; n = 7), fever (17.6%; n = 6), and epilepsy (8.8%; n = 3). According to the radiological features, CNS aspergillosis lesions were divided into two subtypes: parenchymal lesions in the cerebral lobes (n = 11), and meningeal lesions in the meninges (n = 23). The patients with meningeal lesions are easy to be complicated with more serious cerebrovascular diseases, such as subarachnoid hemorrhage and massive infarction. Most of the lesions in brain parenchyma were abscess formation, and magnetic resonance imaging showed ring enhancement. The clinical diagnosis of *Aspergillus* infection was mainly based on brain biopsy (n = 14), autopsy (n = 8), pathological examination of adjacent brain tissues (n = 7), cerebrospinal fluid (CSF) or tissue culture (n = 3), and second-generation sequencing analysis of the CSF (n = 3). Clinical improvement was achieved in 23 cases, and 11 patients succumbed to the disease. Voriconazole treatment was effective in 24 (70.6%) cases.

Immunocompetent subjects are also at risk for *Aspergillus* infections. Concomitant cerebrovascular diseases are common in patients with CNS aspergillosis, especially in patients with meningeal aspergillosis. Parenchymal aspergillosis lesions are usually localized and manifest as brain abscesses with annular enhancement on magnetic resonance imaging. Biopsy, CSF culture, and next-generation sequencing are mainstream diagnostic modalities. Voriconazole is an effective treatment for *Aspergillus* infection, and early diagnosis and treatment should be highlighted.

Abbreviations: CNS = central nervous system, CSF = cerebrospinal fluid, CT = computed tomography, MRI = magnetic resonance imaging.

Keywords: aspergillosis, *aspergillus* infection, central nervous system, next-generation sequencing, voriconazole

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This study was approved by the Institutional Ethics Committee of the Chinese People's Liberation Army General Hospital.

Informed written consent was obtained from the patients or their guardians.

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Highlights

1. Central nervous system aspergillosis is usually complicated with cerebrovascular diseases especially in patients with meningeal aspergillosis.
2. Annular enhancement on MRI may suggest a favorable prognosis.
3. Cerebrospinal fluid culture and next-generation sequencing can facilitate early diagnosis.
4. Voriconazole is effective for the treatment of central nervous system aspergillosis.

1. Introduction

Soil and rotten leaves contain a large amount of *Aspergillus*, which can be fungal pathogens of encephalomycosis in humans.[1] *Aspergillus* infection in the central nervous system (CNS) generally occurs in immunocompromised patients. In recent years, with the increasing trend of organ transplantation, there is

a rising incidence of immunodeficiency diseases, and more patients have been clinically diagnosed with aspergillosis.[1] The mortality rate of *Aspergillus* infection in the immunocompetent population is approximately 10% to 20%, while that in immunocompromised patients can be as high as 85% to 100%.[2–4] The clinical manifestations and prognosis of CNS aspergillosis are distinctly different in immunocompetent and immunocompromised patients.[5] In immunocompromised patients, a clear history of immune abnormalities is usually noted and the *Aspergillus* often invades multiple sites. CNS aspergillosis in immunocompetent patients usually manifests as isolated brain lesions that present a great diagnostic challenge.[5]*Aspergillus* infection in the CNS is relatively rare and is frequently misdiagnosed and undertreated in the immunocompetent population. The clinicoradiological features of CNS aspergillosis have not been well elucidated, and the clinical treatment remains challenging in immunocompetent patients. The aim of this study was to investigate the clinical characteristics of CNS aspergillosis in immunocompetent patients.

2. Methods

This study enrolled six immunocompetent patients with CNS aspergillosis from our institute. Aspergillosis was diagnosed based on pathological biopsy, cerebrospinal fluid (CSF) culture, or second-generation sequencing of the CSF. Immunodeficiency refers to human immunodeficiency virus infection or autoimmune diseases requiring long-term administration of corticosteroids or immunosuppressants. The exclusion criteria included:

(1) previously immunodeficient cases without a clinically confirmed etiology;
(2) incomplete follow-up data;
(3) age < 18 years or > 75 years; or
(4) the presence of a complex multipathogen infection.

The age, gender, etiology of *Aspergillus* infection, clinical manifestations, signaling features on magnetic resonance imaging (MRI), CSF characteristics, location of the lesion, treatment, and prognosis were analyzed. The follow-up period lasted for at least six months for all six patients.

A literature search was performed in the PubMed database using the keywords ("aspergillosis" OR "Aspergillus") AND "immunocompetent" AND ("central nervous system" OR "CNS"). A total of 28 immunocompetent cases with CNS *Aspergillus* infection were retrieved. The clinical and radiological profiles were collected, and the data were analyzed together with our case series.

3. Case descriptions

3.1. Case 1

A 20-year-old man presented to us with numbness in the right arm and right face for four months. Neurological examination showed a muscle strength of Grade 3/5 in the right upper limb and right-sided central facial palsy. The CSF routine test was normal. Brain MRI demonstrated hypointensity on T1-weighted imaging and hyperintensity on T2-weighted imaging; after the administration of contrast medium, petal-like enhancement was observed (Fig. 1A-E). A diagnosis of vasculitis was suspected, and methylprednisolone (500 mg) was administrated. The symptoms were alleviated, and the lesion shrank (Fig. 1F). However, after two months of corticosteroid treatment, the lesion was enlarged (Fig. 1G). After the biopsy, pathological examination confirmed a diagnosis of *Aspergillus* infection (Fig. 1H). Following the administration of voriconazole (6 mg/kg every 12 hours on the first day and 4 mg/kg every 12 hours thereafter), the patient's condition gradually improved.

3.2. Case 2

A 46-year-old man presented with progressive walking instability for eight months and slurred speech with choking for 4 months. The CSF routine test was normal. Brain MRI showed a lesion involving the right cerebellum and brachium pontis, with hyperintensity on T2-weighted imaging and beehive-like enhancement (Fig. 2A-B). After the biopsy, the pathological examination revealed *Aspergillus* infection (Fig. 2E). Fluconazole was administrated (400 mg daily) but failed to provide significant benefits. Two months later, contrast-enhanced MRI showed that the lesion was slightly enlarged (Fig. 2C). The patient was treated with voriconazole (dosage as described above). After a 2-week treatment, the symptoms were markedly improved, and the enhancement was reduced on repeated MRI (Fig. 2D).

3.3. Case 3

A 59-year-old woman presented to us with progressive headaches for six months. Physical examination showed bilateral exophthalmos, and binocular vision was reduced. The CSF routine test was normal. Contrast-enhanced MRI showed abnormal signals involving the bilateral cavernous sinuses and retrobulbar regions, and the mucosa of the paranasal sinuses and optic nerves were thickened (Fig. 3A-C). Computed tomography revealed a space-occupying lesion in the left sinus, and the bilateral orbital bone was damaged (the bone destruction was more severe on the left side; Fig. 3D). Biopsy of the nasal mucosa was performed, and pathological examination confirmed a diagnosis of *Aspergillus* infection (Fig. 3E). The patient was treated with voriconazole (6 mg/kg every 12 hours on the first day and 4 mg/kg every 12 hours thereafter), and her symptoms were alleviated.

3.4. Case 4

A 23-year-old woman presented to us with a six-month history of pain in the right orbitofrontal region, ptosis in the right eyelid, and fixation of the right eyeball with decreased vision. Brain MRI revealed abnormal signals in the right cavernous sinus. CSF examination revealed pressure of 100 mmH_2O, a glucose level of 4.24 mmol/l, a leukocyte count of 60×10^6/L, and a monocyte percentage of 60%. A diagnosis of local inflammation in the cavernous sinus was suspected. Dexamethasone (20 mg/d for 2 days, 40 mg/d for 4 days, and 15 mg/d for 4 days) was administrated, followed by an improvement in the symptoms. One week before admission, the symptoms reappeared. Physical examination showed the right eyelid was drooping, and the movement of the right eyeball was limited; the light reflex of the pupils disappeared, and visual acuity was reduced bilaterally. The patient was treated with methylprednisolone (1 g/d for 2 days). Repeated brain MRI showed hyperintensity on T2- and diffusion-weighted imaging in the right cavernous sinus, and annular enhancement was noted (Fig. 4A-D). The serum IgM antibody against *Aspergillus*-specific antigen was positive. A diagnosis of

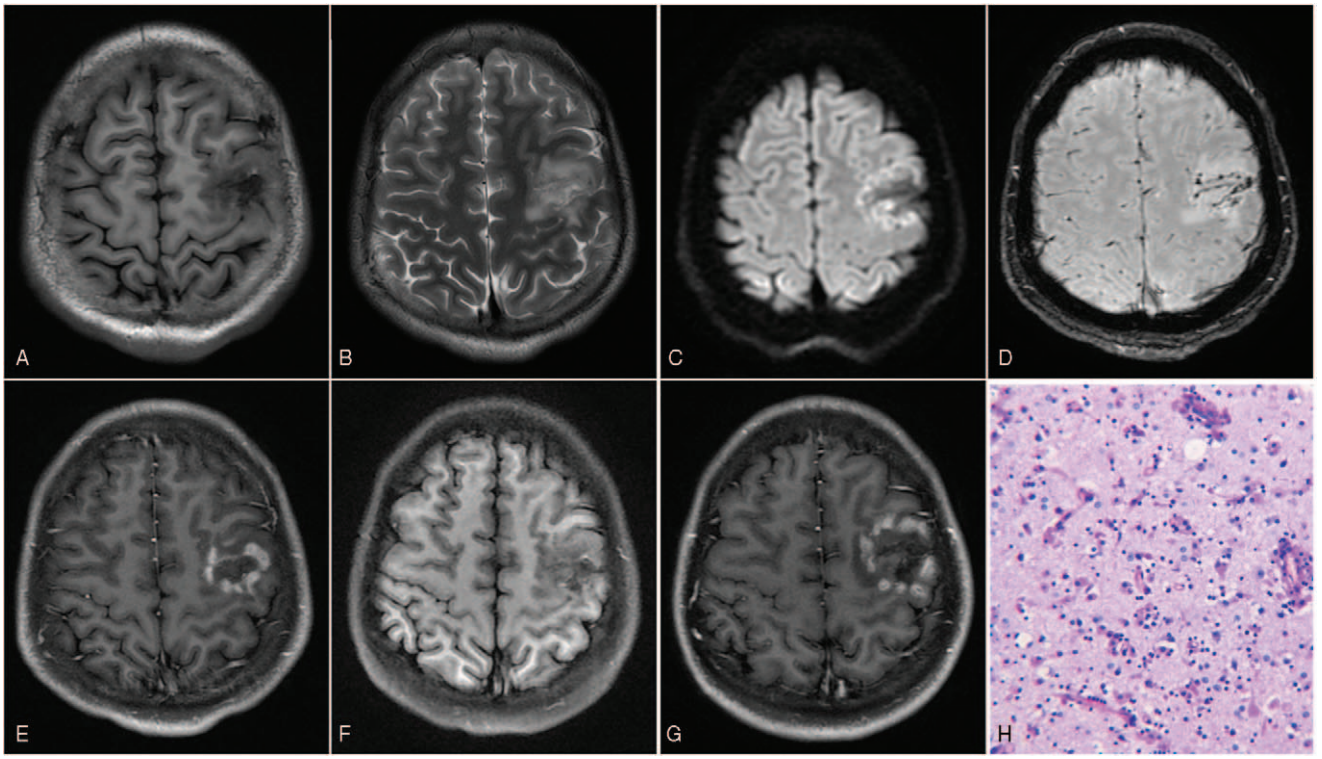

Figure 1. Brain magnetic resonance imaging and pathological examination of Case 1. Brain magnetic resonance imaging showed a lesion in the left frontal lobe with hypointensity on T1-weighted imaging (A) and hyperintensity on T2-weighted imaging (B). (C) Diffusion-weighted imaging showed a focal lesion with mildly restricted diffusion. (D) Susceptibility-weighted imaging showed intralesional hemorrhagic foci; (E) Contrast-enhanced imaging demonstrated petal-like enhancement. (F) After methylprednisolone administration, contrast-enhanced imaging showed the lesion shrank. (G) Two months later, the lesion was enlarged on contrast-enhanced imaging. (H) Pathological examination confirmed a diagnosis of *Aspergillus* infection (200 × magnification).

Aspergillus infection was made, and the patient was treated with voriconazole. Eight days later, the patient developed left hemiplegia and unconsciousness. Computed tomography showed subarachnoid hemorrhage and infarctions in the right frontal, temporal, and parietal lobes (Fig. 4E). The patient died 44 days later. Autopsy pathology confirmed *Aspergillus* in the CNS.

3.5. Case 5

A 56-year-old man patient presented with headache, fever, nausea, and vomiting one day after nasal polypectomy. His temperature was 39.2°C. Cephalosporin antibiotics were prescribed, and the fever was alleviated. Four days earlier, the patient had developed lalopathy, weakness in the right limbs, and repeated generalized convulsions. Physical examination showed bradylalia and decreased muscle strength of 2/5 in the right upper and lower extremities. The CSF test results were as follows: the count of leukocytes was 380×10^6/L, the percentage of polykaryocytes was 0.72, the protein level was 1556.9 mg/L, the glucose level was 3.7 mmol/L, and the chloride level was 110.4 mmol/L. Brain MRI showed abnormal signals in the bilateral frontoparietal fissures, and the adjacent meninges was

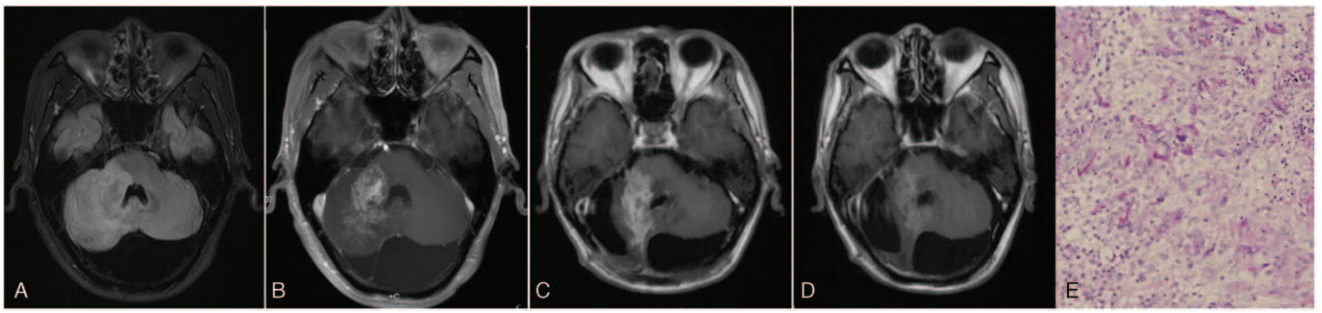

Figure 2. Brain magnetic resonance imaging and pathological examination of Case 2. (A) Brain magnetic resonance imaging showed a lesion involving the right cerebellum and brachium pontis with hyperintensity on T2-weighted imaging. (B) Contrast-enhanced imaging demonstrated beehive-like enhancement. (C) Two months later, contrast-enhanced MRI showed that the lesion was slightly enlarged. (D) After a two-week treatment with voriconazole, the enhancement was reduced. (E) Pathological examination revealed *Aspergillus* infection (200 × magnification).

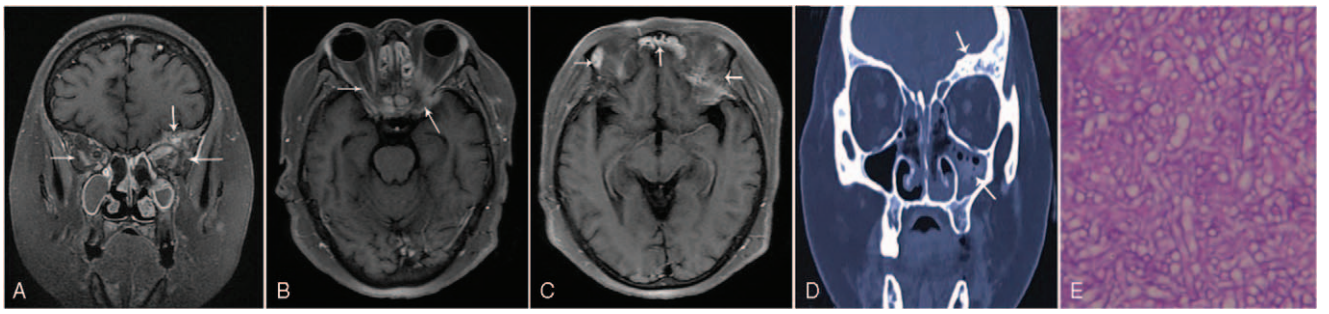

Figure 3. Radiological and pathological images of Case 3. (A) Contrast-enhanced magnetic resonance imaging showed abnormal signals involving the bilateral cavernous sinuses and retrobulbar regions. (B) Contrast-enhanced magnetic resonance imaging showed abnormal enhancement of bilateral orbital apex, and the bilateral optic nerves and nasal mucosa were thickened. (C) There were multiple ring enhancements between the orbital bone and the frontal lobe, which was more prominent on the left side. (D) Computed tomography revealed a space-occupying lesion in the left sinus, and the bilateral orbital bone was damaged (the bone destruction was more severe on the left side). (E) Hematoxylin and eosin staining revealed *Aspergillus* infection (200 × magnification).

enhanced (Fig. 5A). The patient was injected with levofloxacin (0.3 g once daily), metronidazole (0.5 g once daily), and valproate (800 mg/d). Additionally, oral sulfamethoxazole (0.96 g twice daily) was administrated. After a 1-week treatment, MRI showed abnormal signals in the bilateral frontoparietal fissures and annular enhancement in the frontal lobes (Fig. 5B-D). Next-generation sequencing of CSF showed 36 copies/ml of *Aspergillus*. A diagnosis of *Aspergillus* infection was made, and the patient was treated with voriconazole (dosage as described above). After 2-week treatment, the symptoms were significantly improved. Brain MRI showed the enhancement was significantly alleviated (Fig. 5E).

3.6. Case 6

A 23-year-old woman presented to us with a 3-week history of numbness on the right forehead, face, and upper extremity, vertigo, walking deflection, and diplopia. Brain MRI showed a lesion

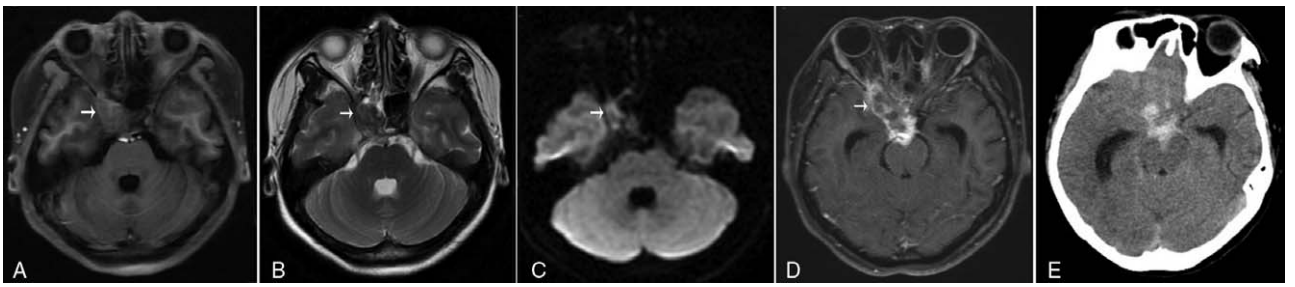

Figure 4. Brain magnetic resonance imaging and computed tomography of Case 4. Brain magnetic resonance imaging showed a lesion in the right retroorbital region and cavernous sinus (arrows), which appeared isointense on T1-weighted imaging (A), and hyperintense on T2- (B) and diffusion-weighted (C) imaging. After the administration of contrast medium, the lesion showed heterogeneous enhancement (D). Computed tomography showed subarachnoid hemorrhage and infarctions in the right frontal, temporal, and parietal lobes.

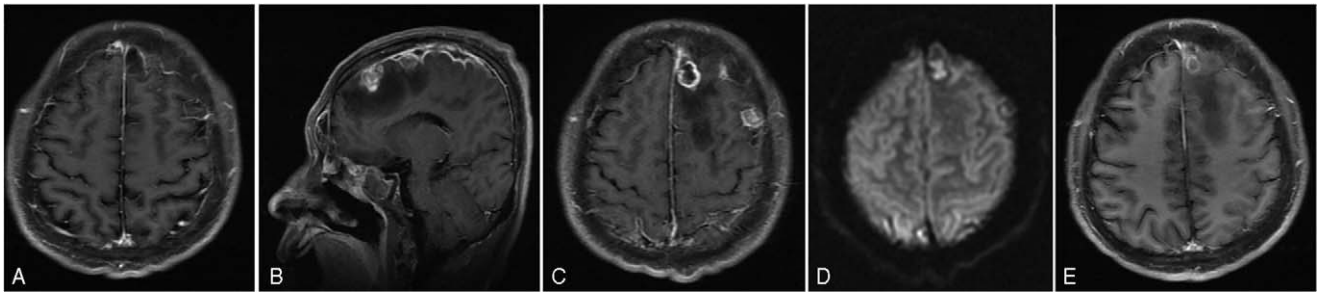

Figure 5. Brain magnetic resonance imaging of Case 5. (A) Brain magnetic resonance imaging showed lesions in the bilateral frontal sinuses, superior sagittal sinus, and left meninges with remarkable enhancement. (B-C) The meninges of the left frontal lobe were significantly enhanced, and multiple annular enhancements were noted. (D) Diffusion-weighted imaging demonstrated a lesion with limited diffusion in the left frontal lobe meninges. (E) Two weeks after voriconazole treatment, the meningeal enhancement in the left frontal lobe was significantly alleviated.

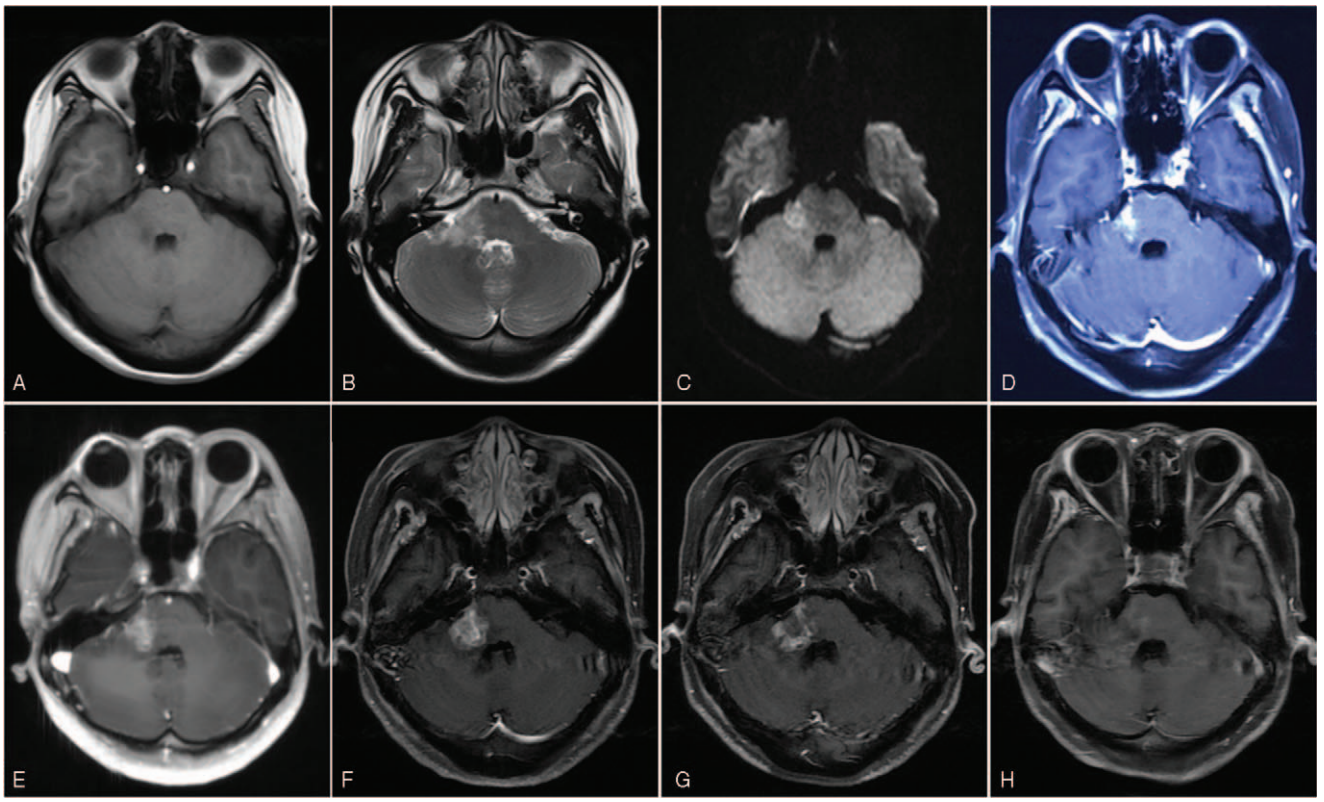

Figure 6. Brain magnetic resonance imaging of Case 6. Brain magnetic resonance imaging showed a lesion involving the right pons, brachium pontis, and medulla oblongata, with hypointensity on T1-weighted imaging (A) and hyperintensity on T2- (B) and diffusion-weighted imaging (C). (D-F) After the methylprednisolone treatment, repeated MRI (22, 36, and 46 days after the treatment, respectively) demonstrated an enhanced lesion in the right brachium pontis. (G-H) Follow-up MRI (16 and 30 days after the voriconazole treatment, respectively) showed the enhancement was significantly relieved.

involving the right pons, brachium pontis, and medulla oblongata, with hypointensity on T1-weighted imaging and hyperintensity on T2- and diffusion-weighted imaging (Fig. 6A-C). A diagnosis of demyelination was suspected, and the patient was treated with methylprednisolone (500 mg/d). One week later, vertigo and nausea were improved, but the patient gradually developed extremity weakness, dysphagia, and choking. Physical examination showed decreased muscle strength (Grade 3/5) in the right limbs, dysarthria, right-sided drooping eyelid, rotational nystagmus, and right facial paralysis. Repeated MRI demonstrated an enhanced lesion in the right brachium pontis (Fig. 6D-F). The CSF test results were as follows: the count of leukocytes was 0×10^6/L, the protein level was 585.5 mg/l, the glucose level was 3.6 mmol/L, and the chloride level was 117.1 mmol/L. Next-generation sequencing of the CSF showed four copies/ml of *Aspergillus*. A diagnosis of *Aspergillus* infection was made, and the patient was treated with voriconazole (dosage as described above). The symptoms gradually improved, and follow-up MRI confirmed a radiological remission (Fig. 6G-H).

4. Literature review

There were 19 men (average age, 54.6 ± 14.3 years) and 15 women (average age, 47.0 ± 19.4 years). The main clinical manifestations were headache (55.9%; n = 19), visual impairment (32.4%; n = 11), diplopia (32.4%; n = 11), hemiplegia (20.6%; n = 7), fever (17.6%; n = 6), and epilepsy (8.8%; n = 3). The clinical characteristics of these cases and our case series are summarized in Table 1. The etiology of CNS *Aspergillus* infection in immunocompetent patients is shown in Table 2.

According to the radiological features, CNS aspergillosis lesions were divided into two subtypes: parenchymal lesions in the cerebral lobes (n = 11), and meningeal lesions in the meninges (n = 23). The clinical manifestations and prognosis of these two groups are summarized in Table 3.

The clinical diagnosis of *Aspergillus* infection was mainly based on brain biopsy (n = 14), autopsy (n = 8), pathological examination of adjacent brain tissues (n = 7), CSF or tissue culture (n = 3), and next-generation sequencing analysis of the CSF (n = 3). Overall, clinical improvement was achieved in 23 cases, and 11 patients succumbed to the disease. Voriconazole treatment was effective in 24 (70.6%) cases.

5. Discussion

CNS aspergillosis is generally considered an opportunistic infection. The etiology of *Aspergillus* infection in immunocompetent patients remains unclear. *Aspergillus* cerebral infection usually occurs secondary to *Aspergillus* infection in tissues adjacent to the brain or through blood transmission. The most common cause of CNS aspergillosis is *Aspergillus* infection in the nasal sinuses, followed by dental and ear infections, contamination during cerebral or cardiac surgery, and lumbar puncture.[6–9] Diabetic patients are more susceptible to *Aspergillus* infection.[10] Among 34 cases of CNS aspergillosis analyzed in the current study, 23.5% were caused by sinusitis, and 16.6% had

Table 1

Clinical profiles of 34 cases with central nervous system aspergillosis.

No.	Author	Year	Sex	Age	Etiology	Clinical manifestation	MRI	CT and angiography	Diagnostic method	Localization	Treatment	Outcome
1	R Wang	2016	M	64	Trigeminal neuralgia surgery	Headache, visual impairment and ocular motility disorders	Left cerebellar lesion	N.A.	Biopsy pathology and CSF culture	Parenchyma	Voriconazole and itraconazole	Death
2	R Wang	2016	F	46	Uncertain	Headache and diplopia	Abnormal signal of cavernous sinus	N.A.	Biopsy pathology	Meninges	Voriconazole and fluconazole	Improved
3	R Wang	2016	M	46	Nasosinusitis	Fever, headache and hear impairment	Round lesion in the temporal lobe with annular enhancement	N.A.	Biopsy pathology	Parenchyma	Voriconazole	Improved
4	Herlon	2007	F	56	Uncertain	Hemiplegia	Extensive meningeal enhancement and parietal sulcus nodule enhancement	N.A.	CSF culture	Meninges	Amphotericin B	Death
5	Marinovic	2007	M	65	Severe brain trauma	Headache	N.A.	Round lesion of left frontal lobe with circular enhancement and peripheral edema	Biopsy pathology	Parenchyma	Amphotericin B and itraconazole	Improved
6	Lihao	2008	F	65	Uncertain	Headache and vision impairment	Space-occupying lesion in the sellar region	Bone destruction in the sellar region	Biopsy pathology	Meninges	Amphotericin B and surgery	Improved
7	April C	2009	M	50	Lumbar puncture	Headache, backache and unconsciousness	Multiple small infarcts within cortical and deep structures	Subarachnoid hemorrhage; multiple angiostenosis and aneurysms	Autopsy pathology and CSF culture	Meninges	Amphotericin B and itraconazole	Death
8	Köse S	2011	F	23	Nasosinusitis	Headache, vision impairment and diplopia	Bilateral frontal meningeal lesions with annular enhancement	Local bone destruction of the frontal sinus	Biopsy Pathology	Meninges	Voriconazole	Improved
9	Miki Y	2012	M	65	Uncertain	Headache, visual impairment and abducent nerve paralysis	Thickening of the skull-base dura mater and sphenoid sinus mucosa.	Subarachnoid hemorrhage	Autopsy pathology	Meninges	No antifungal treatment	Death
10	Lee G	2013	M	48	Diabetes	Visual field defect	Lesion in the right temporal and occipital lobe with annular enhancement	N.A.	Biopsy pathology	Parenchyma	Amphotericin B and voriconazole	Improved
11	Segundo	2014	M	55	Sinusitis and diabetes	Headache, epilepsy, fever and hemiplegia	Right cerebral infarction and abnormal signals in the cavernous sinus	Cerebral infarction	Biopsy pathology	Meninges	Amphotericin B	Improved
12	Bao Z	2014	M	42	Surgical treatment of meningioma	Headache and hemiplegia	Right parietal abscess with annular enhancement	Low-density lesions with meningeal enhancement	Biopsy pathology	Parenchyma	Fluconazole and amphotericin B	Improved
13	Ganesh P	2015	F	40	Gingivitis	Inflammation of right cheek	Lesions in the right retroorbital region with annular enhancement	N.A.	Biopsy pathology	Meninges	Amphotericin B and voriconazole	Improved
14	Morgand M	2015	F	71	Uncertain	Visual impairment	Lesions in the right retroorbital region with meningeal enhancement	N.A.	Biopsy pathology	Meninges	Voriconazole	Improved
15	Morgand M	2015	F	68	Otitis media and mastoiditis	Hearing impairment	Left dural hypertrophy and abnormal enhancement of the left mastoid process	N.A.	Biopsy pathology and tissue culture	Meninges	Voriconazole	Improved
16	Sun Y	2015	M	60	Uncertain	Intermittent headache and partial paralysis in the right lower limb	Lesion in the left temporal lobe with annular enhancement	Postoperative bleeding	Biopsy pathology	Parenchyma	Voriconazole	Death
17	Shinya Y	2015	M	77	Sinusitis surgery and diabetes	Visual impairment and ocular motility disorders	Dural hypertrophy and enhancement in the frontal sinus mucosa	Subarachnoid hemorrhage and irregular aneurysm	Autopsy pathology	Meninges.	Voriconazole	Death
18	Marjorie M	2015	M	65	Diabetes and sinusitis	Diplopia	Meningeal hypertrophy with annular enhancement and abscess in the left frontal lobe	N.A.	Biopsy pathology	Meninges.	Voriconazole and shaboconazole	Improved
19	Muraoka S	2016	M	56	Paranasal sinusitis	Headache, fever and abducent nerve paralysis	Abnormal enhancement in the ventral brainstem and infarctions in the right thalamus and cerebella	Subarachnoid hemorrhage and aneurysm	Biopsy pathology	Meninges	Voriconazole	Improved
20	Winterholler M	2017	M	64	Diabetes	Headache, dizziness, walking instability and diplopia	Left thalamic infarction	Subarachnoid hemorrhage and aneurysm	Autopsy pathology	Meninges	No antifungal treatment	Death

(*continued*)

Table 1
(continued).

No.	Author	Year	Sex	Age	Etiology	Clinical manifestation	MRI	CT and angiography	Diagnostic method	Localization	Treatment	Outcome
21	Menaka DS	2009	F	22	Spinal analgesia via lumbar puncture	Fever, headache and neck pain	N.A.	Bilateral thalamic infarctions	Autopsy pathology	Meninges	Amphotericin B	Death
22	Jayson A	2016	M	69	Uncertain	Headache and visual impairment	Abnormal enhancement involving the right cavernous sinus, orbit and temporal lobe	Bone destruction and multiple vascular stenosis	Biopsy pathology	Meninges	Voriconazole	Improved
23	Kowacs PA	2004	M	26	Drowning	Headache	Meningeal enhancement and multiple granulomatous lesions in the brain	Normal	CSF culture	Meninges	Amphotericin B and itraconazole	Death
24	Kavi T	2017	F	59	Cardiac surgery	Multiple organ failure	N.A.	N.A.	Autopsy pathology	Parenchyma	No antifungal treatment	Death
25	Panda PK	2017	F	25	Uncertain	Headache, exophthalmos, ophthalmoplegia and epilepsy	Lesions in the left parietal-occipital junction with annular enhancement and edema	Low-density lesions in the left parietal-occipital junction	Biopsy pathology	Parenchyma	Surgery, voriconazole and amphotericin B	Improved
26	Carrie M	2016	F	55	Uncertain	Headache, vision impairment, vertigo and paralysis	Abnormal signal in the left cavernous sinus and posterior orbit and brainstem infarction	Multiple vascular stenosis	Autopsy pathology	Meninges	No antifungal treatment	Death
27	Zamora J	2018	F	71	Surgical treatment of acoustic neuroma	Headache and fever	Meningeal enhancement	Normal	Biopsy pathology	Meninges	Voriconazole	Improved
28	Okada M	2015	M	63	Otitis media and mastoiditis	Abducent nerve palsy	Local thickening and enhancement of the dura mater in the left petrosal sinus	Destruction of the mastoid bone	Next-generation sequencing analysis	Meninges	Voriconazole	Improved
29	Case 1	Present study	M	20	Uncertain	Hemianesthesia	Round lesion in the left frontal lobe with annular enhancement	Low-density lesion in the left frontal lobe	Biopsy pathology	Parenchyma	Voriconazole	Improved
30	Case 2	Present study	M	46	Uncertain	Ataxia, choking and aphasia	Lesions in the right cerebellum and left temporal lobe with annular enhancement	Low-density lesions	Biopsy pathology	Parenchyma	Voriconazole	Improved
31	Case 3	Present study	F	59	Sinusitis and diabetes	Visual impairment and eye movement disorder	Abnormal enhancement of meninges in the cavernous sinus, retroorbital and frontal lobe and annular enhancement of meninges in the frontal lobe	Bilateral orbital bone destruction	Biopsy pathology	Meninges	Voriconazole	Improved
32	Case 4	Present study	F	23	Uncertain	Visual impairment and eye movement disorder	Lesion involving the right cavernous sinus and pia mater with annular enhancement,	Right cerebral infarction and subarachnoid hemorrhage	Autopsy pathology	Meninges	Voriconazole	Death
33	Case 5	Present study	M	56	Surgical treatment of nasosinusitis	Epilepsy, hemiplegia and fever	Abnormal enhancement of the left frontal meninges with annular enhancement	Low-density lesion in the frontal lobe	Next-generation sequencing analysis	Meninges	Voriconazole	Improved
34	Case 6	Present study	F	22	Dental implant	Trigeminal neuralgia, hemiplegia, ataxia and choking	Annular enhancement of the right pontine and medulla oblongata	Normal	Next-generation sequencing analysis	Parenchyma	Voriconazole	Improved

CSF = cerebrospinal fluid, F = female, M = male, N.A. = not available.

Table 2

Etiology of 34 cases with central nervous system aspergillosis.

Etiological analysis	Case number (%)
Unknown	11 (32.4%)
Nasosinusitis	8 (23.5%)
Diabetes	6 (17.6%)
Craniotomy	4 (11.8%)
Mastoiditis, mastoiditis and otitis media	2 (5.9%)
Dental diseases (gingivitis or dental implants)	2 (5.9%)
Lumbar puncture	2 (5.9%)
Heart surgery	1 (2.9%)
Drowning	1 (2.9%)
Brain trauma	1 (2.9%)

concomitant diabetes; other causes included gingivitis, mastoiditis, and meningioma surgery.

Radiologically, CNS aspergillosis can be classified into parenchymal lesions in the cerebral lobes and meningeal lesions in the meninges. The location of primary infection of aspergillosis, such as the paranasal sinuses, otitis media, and mastoid process, can be identified based on the local bone destruction. Meningeal lesions usually occur in the cavernous sinus, the retroorbital region, and the frontotemporal areas. Clinical manifestations of meningeal lesions include headache, vision loss, and oculomotor neuropathy.[6,11,12] In the current study, among patients with meningeal lesions, 26.1% had nasosinusitis, 39.1% had decreased visual acuity, and 35.8% had oculomotor disturbance, whereas among patients with parenchymal lesions, these percentages were 9.1%, 18.2%, and 18.2%, respectively. Hematogenous infections mainly involve cerebral lobes, with lesions commonly located at the corticomedullary junction and clinically manifesting as localization-related symptoms.[13] In our study, 11 (32.4%) patients had parenchymal lesions, and the causes included cardiac surgery, dental implant, and surgical treatment of trigeminal neuralgia. The clinical manifestations of parenchymal lesions were nonspecific and localization-related. Additionally, we found that patients with meningeal lesions were more likely to present with cerebral infection-related aneurysms or vascular stenosis, cerebral infarction, and subarachnoid hemorrhage. One possible explanation is that *Aspergillus* in meningeal lesions invaded the large blood vessels, especially the vessels at the skull base. The pathological changes of *Aspergillus* vascular invasion included aneurysm formation, hemorrhage, and thrombosis.[14,15]

Table 3

Clinical analysis of central nervous system aspergillosis in the parenchyma or meninges.

Characteristics	Parenchyma	Meninges
Case number	11 (32.4%)	23 (67.6%)
Clinical manifestation		
Sinusitis	1 (9.1%)	6 (26.1%)
Headache	6 (54.5%)	13 (56.5%)
Vision loss	2 (18.2%)	9 (39.1%)
Ocular motility disorders	2 (18.2%)	8 (35.8%)
Hemiplegia	3 (27.3%)	3 (13.0%)
Cerebrovascular disease		
Aneurysm or stenosis	0	6 (26.1%)
Subarachnoid hemorrhage	0	5 (21.7%)
Cerebral infarction	0	6 (26.1%)
Annular enhancement on MRI	8 (72.8%)	6 (26.1%)
Outcome		
Improved	8 (72.7%)	14 (60.9%)
Death	3 (27.3%)	9 (39.1%)

The major pathological manifestations of *Aspergillus* infection are brain abscess and granulomatous changes. The pathogenesis is closely related to the location of *Aspergillus* infection and the immune functions of the entire body. When the infection occurs in immunocompetent patients, parenchymal lesions in the cerebral lobes often manifest as brain abscesses with an intact cyst wall. However, there can be ruptured abscess walls or even nodular granulomatous changes in immunocompromised patients.[16–18] Typical pathological characteristics can be indicated on brain MRI and are generally identified as annular enhancements. We found that 72.8% of parenchymal lesions showed annular enhancement, while this radiological feature could only be found in 26.1% of meningeal lesions. This phenomenon suggests that parenchymal lesions are usually limited, while meningeal lesions are prone to diffuse proliferation. Moreover, a few patients showed decreased glucose and chloride levels in the CSF.[15] CSF examination can facilitate the diagnosis of *Aspergillus* infection. Positive fungal culture of the CSF can lead to a definitive diagnosis.[9,19] Although the diagnosis of *Aspergillus* infection primarily relies on pathological examination and CSF culture, some advanced experimental modalities can also be valuable, such as next-generation sequencing analysis. In the present study, 14 cases were diagnosed by brain biopsy, eight cases by autopsy, seven cases by pathological examination of adjacent tissues, three cases by CSF culture, and three cases by next-generation sequencing of the CSF. Early infection in adjacent tissues should be taken seriously in cases with *Aspergillus* infection, and the differential diagnosis should be highlighted, especially in patients with infection in paranasal sinuses or cavernous sinus. Early treatment of *Aspergillus* sinusitis may prevent cerebral aspergillosis.[12] Antigen-specific positive IgM binding in the CSF has always been considered one of the most definitive means for the diagnosis of CNS aspergillosis. Aspergillosis can currently be detected using next-generation sequencing, which provides a more convenient approach for the early diagnosis of CNS aspergillosis.[17,20–22]

The prognosis of CNS *Aspergillus* infection in immunocompetent patients is more favorable than that in immunocompromised patients. Voriconazole is widely accepted as an effective first-line treatment for *Aspergillus* infection. Among the cases evaluated in the present study, the symptoms improved in 21 patients (61.2%) after the administration of voriconazole; nevertheless, 11 (32.4%) patients succumbed to the disease. Timely diagnosis and appropriate treatment at the early stage are extremely critical to improve the clinical outcomes.

Patients with impaired immunity, including AIDS infection, long-term use of immunosuppressive drugs and cancer, may be at increased risk of aspergillus infection.[23] After the aspergillus infection, due to the absence of granulocytes, the lesions cannot be easily located and often spread to multiple organs.[24–27]*Aspergillus* spreads through the blood and may form multiple lesions in the brain. Patients with impaired immunity may need high-dose drug treatment than patients with normal immunity. For those who have long-term use of immunosuppressants, they need to reduce the dose of immunosuppressants appropriately. Immunocompromised patients often need to take a variety of drugs, drug interactions may reduce the efficacy of antifungal drugs, and sometimes patients can not tolerate the effects of multiple drugs. In our study, patients

with normal immunity had aspergillosis, which had a special etiology in most cases. Meningeal lesions were generally related to nasosinusitis, mastoiditis, and trauma, and brain parenchymal lesions were generally related to blood-borne spread following cardiac surgeries and various puncture contaminations. Aspergillus encephalopathy in patients with normal immunity is often isolated and has a long medical history.[5,28] Aspergillus infection is difficult to diagnose in patients with normal immunity compared with those with low immunity. Once Aspergillus infection is confirmed in patients with normal immunity, voriconazole should be administered in time and the prognosis is favorable.

6. Limitations

There are some limitations to the present study. First, the sample size of our case series is limited. As the clinical manifestations and radiological characteristics are variable, statistical analysis could not yield a valid power, and we could not use a uniform objective scale to evaluate the individual functions. Additionally, the therapeutic regimen for the patients had heterogeneity, and the optimal treatment for CNS aspergillosis cannot be concluded.

7. Conclusions

Our findings indicate that immunocompetent subjects are also at risk for *Aspergillus* infections. Based on radiological features, CNS aspergillosis can be classified into parenchymal lesions in the cerebral lobes and meningeal lesions. Concomitant cerebrovascular diseases are common in patients with CNS aspergillosis, especially in patients with meningeal aspergillosis. Parenchymal aspergillosis lesions are usually localized and manifest as brain abscesses with annular enhancement on MRI. Biopsy, CSF culture, and next-generation sequencing are mainstream diagnostic modalities. Furthermore, voriconazole is an effective treatment for *Aspergillus* infection. Early diagnosis and treatment should be highlighted.

Author contributions

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