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

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 encephalomyelitis in humans. 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%.\(^3\) The clinical manifestations and prognosis of CNS aspergillosis are distinctly different in immunocompetent and immunocompromised patients.\(^3\) 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.\(^3\) 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, proptosis 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\(_2\)O, a glucose level of 4.24 mmol/l, a leukocyte count of 60 × 10\(^6\)/L, and a monocye 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
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 x 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

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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 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).

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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 (500mg/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 \times 10^6/L, the protein level was 585.5mg/l, the glucose level was 3.6mmol/L, and the chloride level was 117.1mmol/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
| 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 and ocular motility disorders | 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 | Abnormal signal of cavernous sinus | N.A. | CSF culture | Meninges | Itraconazole | Improved |
| 3   | R Wang | 2016 | M   | 46  | Nasosinusitis | Fever, headache and hearing 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 partial subdural enhancement | N.A. | CSF culture | Meninges | Amphotericin B | Improved |
| 5   | Marinovic | 2007 | M   | 65  | Severe brain trauma | Headache | 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 itraconazole | Improved |
| 7   | Kisse S | 2011 | M   | 23  | Nasosinusitis | Headache, vision impairment and diplopia Multiple small intracts within cortical and deep structures | Subarachnoid haemorrhage, multiple arteriothrombosis and aneurysms | Autopsy pathology and CSF culture | Meninges | Amphotericin B and itraconazole | Death |
| 8   | Miki Y | 2012 | M   | 65  | Uncertain | Headache, visual impairment and abducens nerve paralysis Bilateral fronto-parietal lesions with annular enhancement | Local bone destruction of the frontal sinus | Biopsy Pathology | Meninges | Voriconazole | Improved |
| 9   | Bao Z  | 2014 | M   | 42  | Surgical treatment of meningioma | Headache and hemiplegia | Thinning of the skull-base dura mater and sphenoid sinus mucosa. | Autopsy pathology | Meninges | None | Improved |
| 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  | Margand M | 2015 | F   | 71  | Uncertain | Visual impairment Lesions in the right retroorbital region with meningeal enhancement | N.A. | Biopsy pathology | Meninges | Voriconazole | Improved |
| 15  | Margand M | 2015 | F   | 68  | Otitis media and mastoiditis | Hearing impairment Left dorsal hypotrophy and abnormal enhancement of the left medullary 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 hypotrophy and enhancement in the frontal sinus mucosa Meningitic hypotrophy with annular enhancement and abscesses in the left frontal lobe | Subarachnoid haemorrhage and irregular aneurysm | Autopsy pathology | Meninges | Voriconazole | Death |
| 18  | Matjorle M | 2015 | M   | 65  | Diabetes and sinusitis | Diplopia Abnormal enhancement in the vertebral brainstem and infarctions in the right thalamus and cerebellum | N.A. | Biopsy pathology | Meninges | Voriconazole and shakoonazole | Improved |
| 19  | Murakka S | 2016 | M   | 56  | Nasosinusitis | Headache, fever and abducens nerve paralysis Abnormal enhancement in the ventral brainstem and infarctions in the right thalamus and cerebellum | Subarachnoid haemorrhage and aneurysm | Biopsy pathology | Meninges | Voriconazole | Improved |
| 20  | Winterholler M | 2017 | M   | 64  | Diabetes | Headache, dizziness, walking instability and diplopia Left thalamic infarction | Subarachnoid haemorrhage and aneurysm | Autopsy pathology | Meninges | None | Improved |

*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       |
|-----|--------------|------|-----|-----|----------------------------------------|-------------------------------------------------------------|------------------|----------------------------------------------------------------------------------|-----------------------------|--------------|-----------------------------------------|---------------|
| 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 caudate, orbit, and temporal lobe | Bone destruction and multiple vascular stenosis | Biopsy pathology  | Meninges    | Voriconazole                           | Improved      |
| 23  | Kovacs PA    | 2004 | M   | 26  | Drowning                               | Headache                                                   | Meningiitis enhancement and multiple granulomatous lesions in the brain | Normal            | CSF culture                         | Meninges | Amphotericin B and Voriconazole | Death         |
| 24  | Kowacs PA    | 2017 | F   | 59  | Cardiac surgery                        | Multiple organ failure                                      | N.A.             | Lesions in the left parieto-occipital junction with annular enhancement and edema | Autopsy pathology           | Parenchyma  | No antifungal treatment               | Death         |
| 25  | Kavi T       | 2017 | F   | 71  | Uncertain                              | Headache, vision impairment, vertigo and paralysis           | Abnormal signal in the left caudate, orbit and brainstem infarction | Multiple vascular stenosis                  | Biopsy pathology  | Meninges    | No antifungal treatment               | Death         |
| 26  | Carrie M     | 2016 | F   | 55  | Surgical treatment of acoustic neuroma | Headache and fever                                          | Meningiitis enhancement                                   | Normal                | Biopsy pathology  | Meninges    | Voriconazole                           | Improved      |
| 27  | Zamora J     | 2018 | F   | 71  | Surgical treatment of acoustic neuroma | Absent nerve palsy                                          | Degenerative thickening and enhancement of the dura mater in the left petroclival sinus | Destruction of the mastoid bone | Biopsy pathology  | Meninges    | Voriconazole                           | Improved      |
| 28  | Olads M      | 2015 | M   | 63  | Otitis media and mastoiditis           | Headache                                                   | Normal            | Biopsy pathology  | Meninges    | Voriconazole                           | Improved      |
| 29  | Case 1       | 2018 | M   | 20  | Uncertain                              | Hemicraniaesthesia                                          | Lesions in the left frontal lobe with annular enhancement     | Low-density lesion in the left frontal lobe | Biopsy pathology  | Parenchyma  | Voriconazole                           | Improved      |
| 30  | Case 2       | 2017 | 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       | 2018 | F   | 59  | Sinusitis and diabetes                 | Visual impairment and eye movement disorder                 | Abnormal enhancement of meninges in the caudate, orbito-basal and frontal lobe and annular enhancement | Bilateral orbital bone destruction | Autopsy pathology  | Meninges    | Voriconazole                           | Improved      |
| 32  | Case 4       | 2018 | F   | 23  | Uncertain                              | Visual impairment and eye movement disorder                 | Lesion involving the right caudate sinus and pia mater with annular enhancement | Right cerebral infarction and subarachnoid hemorrhage | Autopsy pathology  | Meninges    | Voriconazole                           | Death         |
| 33  | Case 5       | 2018 | M   | 56  | Surgical treatment of maxoantralitis   | 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       | 2018 | 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.
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. 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. 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 meningeval 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.

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. 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. CSF examination can facilitate the diagnosis of Aspergillus infection. Positive fungal culture of the CSF can lead to a definitive diagnosis. 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. 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.

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 aspergillosis infection. After the aspergillus infection, due to the absence of granulocytes, the lesions cannot be easily located and often spread to multiple organs. 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. Immunosuppressed 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

### 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%) |
| Craniodural | 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%) |

### Table 3

| 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%) |
with normal immunity had aspergillosis, which had a special etiology in most cases. Meningeval 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. 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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