Brief Reports

Hemorrhagic Stroke and Cerebral Paragonimiasis

Yong Xia, MD; Yan Ju, MD; Jing Chen, MD; Chao You, MD

Background and Purpose—We retrospectively analyzed the clinical and imaging characteristics, diagnosis, and treatment outcomes of 10 patients with hemorrhagic cerebral paragonimiasis (CP), and we evaluated the influence of Paragonimus infection on cerebrovascular damage.

Methods—Ten patients (7 male and 3 female; median age 15.7 years, range 4–46 years) with hemorrhagic CP were diagnosed between April 2009 and January 2013. All patients underwent the head computed tomography scans and 9 patients underwent MRI examinations. Four patients underwent computed tomographic angiography, magnetic resonance angiography, and digital subtraction angiography. Liquid-based cytological examination of cerebrospinal fluid was performed in 7 patients. Follow-up examinations were performed for 9 cases for a period of 12 to 62 months.

Results—Hemorrhagic CP accounted for 37% of CP cases (10/27). No patients were initially diagnosed with CP. The major symptoms of hemorrhagic CP included acute headache, vomiting, hemiparalysis, epilepsy, blurred vision, sensory impairment, and tinnitus. Four cases were surgically treated. Most symptoms markedly improved, but fine motor dysfunction and mental dysfunction remained in 3 surgical patients.

Conclusions—Hemorrhagic stroke typically occurred during the acute stage and in the early stages of further Paragonimus migration. Delay of treatment increased the risk of initial and recurrent stroke. (Stroke. 2014;45:3420-3422.)

Key Words: intracranial hemorrhages ■ paragonimiasis ■ surgery

Because of increased prevalence in previously endemic areas and increased international travel, Paragonimus infection has reemerged over the past 20 years. The brain is the most common extrapulmonary organ involved in ectopic Paragonimus migration, and cerebral paragonimiasis (CP) is always associated with a high bleeding rate, particularly in children or adolescents. Hemorrhagic cerebral paragonimiasis (HCP) typically manifests as various hemorrhagic strokes, and it resembles various cerebrovascular diseases. Paragonimus infection is rarely fatal, and the infection can be cured by chemotherapy on early diagnosis. However, delayed treatment can result in severe sequelae and even death. The mortality rate is as high as 5%. Contemporary neurosurgeons and neurologists are typically unfamiliar with this disease. We sought to investigate and compare the clinical and imaging characteristics of various HCP cases with those of common cerebrovascular diseases and to supply a reference for the differential diagnosis of HCP clinically.

Methods

Case Information

All 10 patients diagnosed at the West China Hospital, Sichuan University, from April 2009 to January 2013 were included in the study. All research procedures conformed to the guiding principles of the Declaration of Helsinki and were approved by the Ethics Committee of West China Hospital. The male to female ratio was 7:3 (median age 15.7 years, range 4–46 years). The diagnosis of CP was based on a positive ELISA reaction for a Paragonimus-specific antibody in the serum combined with clinical manifestations and laboratory testing. The details of positive ELISA reactions have been described elsewhere. The consumption of undercooked crustaceans within the last 2 years was confirmed in 7 cases (Table).

Laboratory Examination

ELISA serological testing for Paragonimus-specific immunoglobulin antibody and blood eosinophil quantification was conducted on blood samples from all patients. Sputum and fecal samples were examined for the presence of eggs. Sputum was also stained by the Ziehl–Neelsen method and cultured for acid-fast bacilli to exclude the possibility of pulmonary tuberculosis. Lumbar puncture was performed in 7 patients with nuchal rigidity to eliminate other diseases.

Imaging Examination

All patients underwent a head computed tomography (CT) examination. Nine patients underwent MRI examinations. Four patients underwent computed tomographic angiography, magnetic resonance angiography, and digital subtraction angiography examinations. Nine patients underwent chest CT/computed radiography examinations.

Treatment

Neurosurgery was performed in 4 cases. All patients were treated with praziquantel (25 mg/kg, thrice daily) for 3 consecutive days.
Results

All of the patients had positive serological test results for *Paragonimus*-specific antibody. HCP accounted for 37% of the CP cases (10/27), and no patients were initially diagnosed with CP. Vascular malformation (Figure 1), tumoral apoplexy (Figure I in the online-only Data Supplement), subarachnoid hemorrhage and spontaneous intracerebral hemorrhage (Figure II in the online-only Data Supplement), intraventricular hemorrhage (Figure III in the online-only Data Supplement), subdural hematoma (Figure IV in the online-only Data Supplement), and cavernous hemangioma (Figure V in the online-only Data Supplement) were initially suspected in these patients. The average time from the onset of central nervous system clinical symptoms to vessel rupture was 29 days. The cardinal symptoms of HCP included acute headache, vomiting, hemiparesis, epilepsy, blurred vision, sensory impairment, and tinnitus. High peripheral blood eosinophil counts were observed in 8 cases. Liquid-based cytology examination of cerebrospinal fluid revealed eosinophil infiltrates in 5 patients. Nine patients underwent chest computed radiography/CT scans, and pulmonary disorders were detected in 7 cases. Case nos. 2, 4, and 6 underwent craniotomy, and case no. 10 underwent laminotomy (Table), and the pathological examinations were consistent with CP. Follow-up examinations revealed that most clinical symptoms often disappeared completely. However, fine motor dysfunction of the distal limbs and mental disorders separately remained in 3 surgical patients. To exclude the possibility of other cerebrovascular diseases, computed tomographic angiography, magnetic resonance angiography, and digital subtraction angiography were performed in 4 cases, and no cerebrovascular disorders were identified.

Discussion

In our study, HCPs vividly simulated vascular malformation, tumor apoplexy, subarachnoid hemorrhage and spontaneous intracerebral hemorrhage, intraventricular hemorrhage, subdural hematoma, and cavernous hemangioma. The aforementioned diseases revealed avascular masses on digital subtraction angiography, computed tomographic angiography and magnetic resonance angiography. The clinicians could

<table>
<thead>
<tr>
<th>Case No./Age (y)/Sex</th>
<th>History</th>
<th>Lung Lesion</th>
<th>Onset of Symptoms</th>
<th>Invaded Site</th>
<th>Peripheral Eosinophilia, 10^9/L</th>
<th>Eosinophils in CSF</th>
<th>Tx</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>1/6/M</td>
<td>Yes</td>
<td>Yes</td>
<td>Seizure</td>
<td>Frontotemporal insula</td>
<td>0.04</td>
<td>/</td>
<td>Praziquantel</td>
<td>Cured</td>
</tr>
<tr>
<td>2/9/M</td>
<td>Yes</td>
<td>No</td>
<td>HA, blurred vision</td>
<td>Trigonum, thalamus</td>
<td>0.42</td>
<td>/</td>
<td>Op and praziquantel</td>
<td>Cured</td>
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<tr>
<td>3/5/M</td>
<td>No</td>
<td>Yes</td>
<td>Seizure</td>
<td>Frontal</td>
<td>0.67</td>
<td>/</td>
<td>Praziquantel</td>
<td>Cured</td>
</tr>
<tr>
<td>4/8/M</td>
<td>No</td>
<td>Yes</td>
<td>HA, vomiting</td>
<td>Parietal</td>
<td>0.68</td>
<td>–</td>
<td>Op and praziquantel</td>
<td>Fine motor dysfunction</td>
</tr>
<tr>
<td>5/46/M</td>
<td>No</td>
<td>Yes</td>
<td>HA, vomiting, paralysis</td>
<td>Parietal, occipital</td>
<td>0.08</td>
<td>+ (46%)</td>
<td>Praziquantel</td>
<td>Cured</td>
</tr>
<tr>
<td>6/19/M</td>
<td>Yes</td>
<td>Yes</td>
<td>Seizure</td>
<td>Trigonum, frontals</td>
<td>2.47</td>
<td>–</td>
<td>Op and praziquantel</td>
<td>Mental disorder</td>
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<tr>
<td>7/23/F</td>
<td>Yes</td>
<td>Yes</td>
<td>HA, blurred vision, tinnitus</td>
<td>Hippocampus, brain stem, subdural</td>
<td>1.81</td>
<td>+ (50%)</td>
<td>Praziquantel</td>
<td>Cured</td>
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<tr>
<td>8/29/M</td>
<td>Yes</td>
<td>Yes</td>
<td>Cough, fever, HA</td>
<td>Fourth ventricle</td>
<td>1.79</td>
<td>+ (50%)</td>
<td>Praziquantel</td>
<td>Cured</td>
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<tr>
<td>9/4/F</td>
<td>Yes</td>
<td>/</td>
<td>HA</td>
<td>Frontal, temporal, parietal</td>
<td>3.2</td>
<td>+ (51%)</td>
<td>Praziquantel</td>
<td>/</td>
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<tr>
<td>10/8/F</td>
<td>Yes</td>
<td>Yes</td>
<td>Cough, paralysis</td>
<td>Parietals, periventricle, extradural</td>
<td>4.14</td>
<td>+ (60%)</td>
<td>Op and praziquantel</td>
<td>Fine motor dysfunction</td>
</tr>
</tbody>
</table>

+ indicates positive; −, negative; /, no data; HA, headache; and History, clear history of raw food consumption.

Figure 1. Hemorrhage in the cerebral cortex. The head computed tomography and MRI showed acute intracerebral hemorrhage with light perihematomal enhancement (A–D). An occult vascular malformation or small arteriovenous malformation compressed by the hematoma was initially suspected. The lesion progressed for ~2 months until delayed surgery was performed.
not explain the cause and considered the possibility of occult vascular malformation or small vascular malformations compressed by a hematoma. The patients were advised to undergo repeat examinations after 1 to 3 months. However, the symptoms progressively worsened during the time between examinations, and 3 patients experienced bleeding episodes because of further migration of the Paragonimus.

The clinical symptoms depended on the site of invasion, amount of bleeding, and specific stage of this disease. The symptoms, including headache, epilepsy, blurred vision, motor and sensory dysfunction of limbs, or other neurological deficits, were nonspecific. However, in comparison, the patients typically exhibited prodromal symptoms, such as epileptic seizure, headache, dizziness, cough, fever, nausea, and vomiting. The headache symptoms were relatively mild, and patients exhibited no combined disturbance of consciousness, except at the time of epileptic seizures. Motor dysfunction of the limbs was generally limited to mild muscle weakness. In most situations, an elevated eosinophil count was observed in peripheral blood and cerebrospinal fluid, and the patients typically had histories of migratory subcutaneous nodules after eating raw freshwater crabs. In addition, concomitant pulmonary involvement was another important feature of most Paragonimus infections. These appearances are highly suggestive of Paragonimus infection and play a key role in making a differential diagnosis.

On CT scan, HCP typically exhibited irregular hemorrhages of various degrees, ranging from small hemorrhagic spots to irregular hemorhages. The shapes of hemorrhages appeared as dot-, strip-, sheet-, or cord-like hematoma on CT and MRI examinations. The small hemorrhagic spots in cerebral white matter were often surrounded by disproportionately larger edema; these spots were apparently not because of spontaneously ruptured blood vessels (Figure 1A in the online-only Data Supplement). When the bleeding was heavy, the hemorrhages themselves were detected as low or isointense with surrounding hyperintensity on T2WI and FLAIR images (Figure 1C). The adjacent meninges and the hematoma rim exhibited light enhancement on contrast-ENhanced CT and MR images (Figure 1B and 1D). For intraventricular hemorrhages, imaging typically revealed a high-signal bleeding spot on CT scans and was first suspected as an aneurysmal hemorrhage (Figure 1C in the online-only Data Supplement). MRI is superior for visualizing the typical imaging characteristics that are concealed by hemorrhages, including a conglomerate of ring-shaped lesions, tunnel signs, and worm-eaten signs (Figure 1C and VB in the online-only Data Supplement).

Figure 2. Pathological process of hemorrhagic cerebral paragonimiasis. The migrating worm and Paragonimus eggs (A, arrow) caused prominent eosinophilic infiltration and granuloma formation (A, arrowhead and D, arrow), concentric thickening of the small-vessel wall (B, arrow) and congestion (B, arrowhead), lumen stenosis or occlusion (C, arrowhead), and capillary rupture (D, arrowhead).

Infection is a conventional vascular risk factor. Chen et al confirmed the existence of focal cerebral vasculitis by digital subtraction angiography, but pathological evidence was lacking. The pathological analysis revealed prominent eosinophilic infiltration and granuloma formation. The small vessel walls exhibited concentric thickening, lumen stenosis, and occlusion. Eroded vessels eventually ruptured, causing various degrees of bleeding (Figure 2A–2D). A few specimens exhibited Paragonimus eggs surrounded and distorted by inflammatory granulation (Figure 2A). Given the high eosinophil counts in the cerebrospinal fluid and the results of surgical specimens, we speculated that increased eosinophils extensively eroded the cerebrovascular system and induced the rupture of small blood vessels.

The bleeding peak of CP is a critical factor in selecting the timing of therapy and intervention. Our study indicated that the highest risk of stroke occurred within 1 month after the onset of central nervous system clinical symptoms or early in further migration processes in patients without timely treatment. Early diagnosis and therapy can reduce the risk of stroke and recurrent stroke.

Conclusions

The rate of misdiagnosis of HCP was ≈100%. Simulated hemorrhagic strokes were not limited to a single common type of cerebrovascular disease but were common to almost all cerebrovascular events. Clinicians should exercise caution when diagnosing occult cerebral vascular malformations and unexplained bleeding in children and adolescents.

Disclosures

None.

References

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Supplemental Material

Hemorrhagic stroke and cerebral paragonimiasis

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Supplemental Figure I: Errhysis in the acute stage. The patient was initially suspected to have tumoral apoplexy (A). But MRI showed the typical imaging characteristics, including conglomerated lesions and tunnel signs, of cerebral paragonimiasis on T2WI and FLAIR (B, C, D).

Supplemental Figure II: Secondary stroke in a patient without timely treatment. This patient had pulmonary symptoms (A) and experienced weakness and numbness of the right upper limb. A head CT revealed a low-density lesion in the left parietooccipital lobe (B). Multiple hemorrhages, combined with a subarachnoid hemorrhage, developed in the cerebellum and cerebellum-pontine angle between examinations (C).
Supplemental Figure III: Fourth intraventricular hemorrhage. The patient, with persistent cough, fever and headache, was treated with a diagnostic anti-tuberculosis treatment, but the symptoms worsened. Chest CT showed multiple nodule formation (A). A head CT showed a punctuate hemorrhage in the fourth ventricle (B), which manifested as a strip-shape lesion with short T1 and short T2 and without enhancement on MRI (C, D).

Supplemental Figure IV: Subdural hematoma. Pulmonary lesions (A) and wide subdural hemorrhage in right hemisphere, combined with multiple lesions in the left hippocampus and brainstem (B, C).

Supplemental Figure V: Small hemorrhagic spots. The isolated high-density hemorrhagic spot in the white matter was initially suspected to be a cavernous
hemangioma (A). However, the “tunnel sign” was observed on T2WI and FLARI (B, C), with no enhancement (D).