Cerebral paragonimiasis: a retrospective analysis of 27 cases

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OBJECT The authors retrospectively analyzed the clinical characteristics, existing problems, and treatment experiences in recently diagnosed cerebral paragonimiasis (CP) cases and sought to raise awareness of CP and to supply reference data for early diagnosis and treatment.

METHODS Twenty-seven patients (22 male and 5 female; median age 20.3 years, range 4–47 years) with CP were diagnosed between September 2008 and September 2013. These diagnoses were confirmed by IgG enzyme-linked immunosorbent assays. Follow-up was performed in 24 cases for a period of 6–56 months.

RESULTS Cerebral paragonimiasis accounted for 21.6% of paragonimiasis cases (27 of 125). The average duration from onset to praziquantel treatment was 69 days. All patients resided in rural areas. Twenty patients had positive lung results, which included visible lung lesions in 14 cases. The lesions were surgically removed in 8 of these cases. Twenty-four patients had high eosinophil counts ($\geq 0.08 \times 10^9/L$), and eosinophilic meningitis was noted in 17 cases. The rate of misdiagnosis and missed diagnosis was 30.4%. Most symptoms were markedly improved after treatment, but mild movement disorders combined with impaired memory and personality changes remained in a small number of patients.

CONCLUSIONS Clinicians should be alert to the possibility of CP in young patients (4–16 years) with the primary symptoms of epilepsy and hemorrhage. Early diagnosis and timely treatment can reduce the need for surgery and further impairments to brain function. Liquid-based cytological examination of CSF and peripheral blood eosinophil counts can aid in differentiating CP from similar lesions.

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KEY WORDS cerebral paragonimiasis; *Paragonimus westermani*; *Paragonimus skrjabini*; praziquantel; surgery; infection

MOUNTING evidence indicates that *Paragonimus* infections have reemerged globally after decades of neglect. Currently, 293.8 million people are at risk for infection with *Paragonimus* species, and in China alone, 195 million people are infected.^{3,6} *Paragonimus* species are highly capable of ectopic migration. Cerebral paragonimiasis (CP), which accounts for 2%–27% of all paragonimiasis cases, is the most common and severe complication of *Paragonimus* infection.⁸ Its principal harms include focal neurological deficits caused by damaged brain tissue and intracranial hypertension caused by extensive inflammation. In contrast to infections in other organs, the delayed treatment or misdiagnosis of CP often results in severe sequelae and even death.³

Catabolism of the brain tissue, mechanical damage, toxicity, and defense reactions constitute the pathological basis of CP.² Patients with early diagnosis can be successfully treated by chemotherapy with praziquantel. However, most contemporary clinicians, clinical pathologists, and neuroradiologists are unfamiliar with CP in clinical practice. Effective management presents extensive challenges for neurosurgeons worldwide, especially for sporadic cases in nonendemic areas. Southwest China is known to be an endemic area of *P. westermani* and *P. skrjabini*. An analysis of current sources of infection is very useful in evaluating the current worldwide trends of *Paragonimus* infection and in diagnosing and treating sporadic cases in nonendemic areas.

ABBREVIATIONS CP = cerebral paragonimiasis; ELISA = enzyme-linked immunosorbent assay.

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We retrospectively analyzed the CP diagnosis process based on clinical characteristics, with the goals of reminding physicians that CP is not an archaic disease and alerting them to the possibility of CP in differential diagnoses of CNS diseases. Early diagnosis and timely treatment of this disease are vital for a positive prognosis.

Methods

Patient Population

All 27 patients with CP diagnosed at the West China Hospital and the number 2 hospital of Western China, Sichuan University, from 2008 to 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. All patients came from rural areas of southwest China, including the Sichuan and Yunnan Provinces. There were 17 young patients (≤ 16 years old), and the male/female ratio was 22:5 (median age 20.3 years, range 4–47 years). A majority of the patients had been taken to cities by their parents as rural migrant workers.

The diagnosis of CP was based on a positive enzyme-linked immunosorbent assay (ELISA) reaction for *Paragonimus*-specific antibody in serum, simultaneously combined with clinical manifestations and results of laboratory testing, including a history of eating raw food, typical characteristics on imaging studies of the head and chest, and the identification of eggs in surgical specimens and sputum. Details of the positive ELISA reactions have been described elsewhere.⁷ A full clinical evaluation was performed in all patients before and repeatedly after treatment. A systematic review of the chest radiographs and CT scans obtained in 25 patients was undertaken. No patient had evidence of malignancy. The consumption of undercooked crustaceans within the preceding 2 years was confirmed in 20 cases (Table 1).

Laboratory Examination

Serum IgG ELISAs and blood eosinophil quantification were conducted on blood samples from all patients; an above-normal range ($\geq 0.08 \times 10^9/L$) for 24 patients and normal eosinophil counts for 3 patients were observed. Sputum and fecal samples were examined for the presence of eggs. Sputa were also stained using the Ziehl-Neelsen method and cultured for acid-fast bacilli to exclude the possibility of pulmonary tuberculosis. Lumbar puncture was performed in patients with positive neck resistance and was used to rule out other diseases (20 of 27 cases). Pleural effusions and bronchial samples were stained for cytology investigation in only 8 cases.

Imaging Examination

All patients underwent head CT scans and 22 patients underwent MRI examinations. Twenty-five patients also had chest CT and/or radiographic examinations, and 4 underwent digital subtraction angiography examinations.

Treatment

Neurosurgery was performed in 8 cases. All patients

were treated with praziquantel (25 mg/kg, 3 times daily) for 3 consecutive days. One patient coinfecting with *Trichostrongylus orientalis* received albendazole treatment (0.2 g/day for 6 days).

Results

Cerebral paragonimiasis accounted for 21.6% of the observed paragonimiasis cases (27 of 125). These cases were distributed among the neurosurgery, neurology, pediatrics, and infectious disease departments. The cardinal symptoms of CP mainly include headache, vomiting, paralysis, visual abnormalities, speech disturbances, sensory impairment, vertigo, and ataxia. The sites of brain migration varied, encompassing almost all brain regions. Twenty-five patients underwent chest CT or radiographic examinations. Visible lung lesions were detected in 14 cases (51.9%) on chest CT scans. High peripheral blood eosinophil counts were observed in 24 cases. Twenty-three patients underwent CSF examination, including liquid-based cytology for 20 cases. These results revealed eosinophil infiltrates in 17 patients, accompanied by increased CSF protein levels in 12 patients and hypoglycemia in 6 patients. The average time from the onset of symptoms to obtaining effective drug treatment was 69 days; the time exceeded 3 months for 9 cases. Patients with an onset of cerebral hemorrhage usually received the correct treatment in a relatively short amount of time (31 days).

Follow-ups revealed that most clinical symptoms, including headache, cough, and so on, often disappeared completely. A small number of patients, however, had slight functional impairments, including dizziness, memory loss, and personality changes. Six patients with hemiparesis clearly improved but experienced fine motor dysfunction of the distal limbs. One of 5 patients with epileptic seizures suffered relapsed epilepsy due to *Paragonimus* reinfection. The patients in Cases 2, 4, 7, 9, 11, and 12 underwent conventional surgery (craniotomy), whereas Cases 1 and 17 underwent laminotomy for extradural paragonimiasis and MRI-guided stereotactic biopsy, respectively (Table 1).

Discussion

Southwest China is the principal endemic region for *P. westermani* and *P. skrjabini*. These diseases have been controlled or eradicated in the past 50 years due to improvements in public health and changes in dietary habits. However, in 2004, a national sampling survey of the current status of major human parasitic diseases in China suggested that the prevalence of paragonimiasis had increased significantly, impacting national food safety and public health over the past 20 years.¹¹ Unfortunately, awareness of CP as a public health problem has not been raised. Currently, CP remains an unfamiliar disease to contemporary neurosurgeons. The control of infection sources will contribute to a reduction in the prevalence of *Paragonimus* infections worldwide. An analysis of the current status of infection sources has high educational value and may contribute to the early diagnosis and treatment of other sporadic cases globally.

The cardinal symptoms of CP vary depending on dif-

TABLE 1: General information in 27 patients with CP*

Case No.†	Age (yrs), Sex	History	Lung Lesion	Onset of Symptoms	Eosinophil Counts‡	Invaded Site	Eosinophils in CSF	Duration (days)§	Outcome
1	8, F	Yes	Yes	Cough, paralysis	4.14	Parietal, periventricle, extradural	+	120	Mild motor dysfunction
2	38, M	Yes	Yes	HA, paralysis	7.08	Parietal	-	5	Motor and sense impairment
3	6, M	Yes	Yes	Seizure	0.04	Frontotemporal	ND	95	Cured
4	9, M	Yes	No	HA, blurred vision	0.42	Trigonom, thalamus	ND	17	Cured
5	16, F	Yes	No	HA, paralysis	1.6	Temporal	ND	30	Motor dysfunction
6	8, M	No	Yes	Seizure	1.15	Parietal	ND	120	Cured
7	15, M	Yes	Yes	HA, vomiting	3.74	Temporal, occipital	ND	150	Cured
8	5, M	No	Yes	Seizure	0.67	Frontal	ND	18	Cured
9	8, M	No	Yes	HA, vomiting	0.68	Parietal	-	40	Fine motor dysfunction
10	46, M	No	Yes	HA, vomiting, paralysis	0.08	Parietal, occipital	+	25	Cured
11	9, M	No	No	HA, vomiting, paralysis	0.66	Frontal, parietal	+	50	Motor dysfunction
12	19, M	Yes	Yes	Seizure	2.47	Trigonom	-	110	Mental disorder
13	15, F	Yes	Yes	HA, speech disorder	1.2	Temporal, occipital	+	45	Impaired memory
14	39, M	No	No	HA	0.91	Frontal, insular	+	30	Dizziness
15	23, F	Yes	Yes	HA, blurred vision, tinnitus	1.81	Hippocampus	+	30	Cured
16	47, M	Yes	Yes	Paralysis, numbness	1.84	Parietal	+	330	Fine motor dysfunction
17	16, M	Yes	Yes	HA, vomiting, paralysis	1.98	Parietal	+	40	Cured
18	35, M	Yes	Yes	Cough	0	Hippocampus, temporal	+	250	Death
19	46, M	Yes	Yes	Numbness, fever	0.14	—	+	720	Death
20	29, M	Yes	Yes	Cough, fever	1.79	Fourth ventricle	ND	620	Cured
21	50, M	Yes	Yes	HA	0	Frontal	+	35	Lost to FU
22	5, M	Yes	Yes	HA, fever, vomiting	6.19	Parietal	+	46	Cured
23	4, F	Yes	ND	HA	3.2	Frontal, temporal, parietal	+	50	Lost to FU
24	8, M	Yes	ND	Seizure	7.2	—	+	80	Personality change
25	12, M	Yes	Yes	Fatigue	0.91	—	+	14	Cured
26	8, M	No	No	HA, fever	0.27	Temporal, parietal	+	45	Lost to FU
27	12, M	Yes	Yes	HA	3.78	Hippocampus, cingulate gyrus	+	33	Cured

FU = follow-up; HA = headache; History = clear history of raw food consumption; ND = no data; + = positive; - = negative.

* The ELISA results were positive in all cases.

† Case numbers in bold type indicate surgical treatment.

‡ Mean eosinophil counts; high counts defined as $\geq 0.08 \times 10^9/L$.

§ Duration denotes the average time between onset of symptoms and achieving effective drug treatment.

ferent infection sites and the parasite's developmental stages. Generally, they are primarily due to the elevated intracranial pressure caused by extensive inflammation and persistent neurological deficits caused by local brain tissue damage. The former category includes headache, vomiting, fever, seizure, vertigo, and ataxia, whereas the latter frequently includes visual abnormalities, mental disorders, motor weakness, speech disturbances, and sensory impairment. Cerebral cortex inflammation is an important cause of seizures, especially in children and adolescents. Generalized and focal seizures are often observed in patients with multiple and single intracranial lesions, respectively, which may be related to immature brain development. Most clinical symptoms caused by inflammation often completely disappear during follow-up. However, those symptoms induced by local brain tissue damage, including dizziness, memory loss, personality changes, and loss of fine motor function, often do not completely resolve. Although 6 patients with hemiparesis clearly improved, slight fine motor dysfunction of the distal limbs persisted (Table 1); this outcome could have been avoided through early diagnosis and timely treatment.

The most characteristic imaging findings for CP were thought to include conglomerations of multiple ring-enhancing lesions with surrounding edema¹ and a “tunnel sign” that demonstrated the migratory track of the adult worm. However, it is difficult to accurately diagnose patients with atypical imaging findings because they often have clinical symptoms that are very similar to gliomatosis cerebri, vascular malformation, and other inflammatory disorders. Furthermore, all of these clinical symptoms can be relieved by hormones and by dehydration with mannitol or diuretics, which make the clinical presentations difficult to distinguish from one another, especially for patients positive for *Paragonimus*-specific IgG combined with gliomatosis cerebri. These patients are usually discharged early because their clinical symptoms improve after receiving hormones, dehydration, and praziquantel treatments, which are often delayed (Fig. 1). In our experience, liquid-based cytological examinations of CSF have a high positive rate (17 of the 20 who underwent testing) for CP and are an effective diagnostic tool for patients with this disease. High CSF eosinophil and lymphocyte counts were observed in almost all patients with CP. The presence of eosinophils is crucial for differential diagnosis and often indicates the possibility of CP. Alternately, if patients have suspicious brain and chest imaging findings but are negative for CSF eosinophils on liquid-based cytological examinations, clinicians should consider the possibility of an intracranial tumor or a nonparasitic disease.

For most patients with *Paragonimus* infection, pulmonary paragonimiasis is thought to be the most common clinical manifestation. Furthermore, pulmonary symptoms usually precede CNS symptoms. However, it is noteworthy that patients with negative results on chest examinations are more easily misdiagnosed as having a tumor or occult vascular malformation, which is then treated by surgery. In this study, 5 patients had a negative chest examination, 3 of them were treated with surgery, and the pathological diagnosis was confirmed. Some authors believe that southwest China is an endemic region for *P.*

FIG. 1. Imaging studies obtained in a 30-year-old man who presented with a sudden loss of consciousness; the initial diagnosis was an inflammatory disease. Brain MRI studies showed multiple intracranial lesions with extensive inflammatory reaction in the left hemisphere, which was most consistent with an inflammatory disease (**B and C**). In addition to a positive serological result for *Paragonimus* and a lung disorder (CT scan; **A**), secondary epilepsy caused by CP was initially suspected. The patient was discharged early after praziquantel treatment. He was readmitted 37 days after his initial discharge for intractable epilepsy. As shown in preoperative MRI studies, these lesions significantly progressed for more than 1 month until a delayed surgery was performed (**D and E**). Results of the pathological examination were consistent with glioblastoma multiforme. The patient died due to unmanageable high intracranial pressure (CT scan; **F**) 2 months later. This case alerts practicing clinicians that CP has extremely similar clinical symptoms and imaging characteristics to those of gliomatosis cerebri, which often delays the correct diagnosis and leads to severe sequelae, even death.

westermani and *P. skrjabini*, which cannot develop into adults in the lung and thus directly migrate into the brain. The present study demonstrated that these patients often have severe brain tissue damage.

The leading view is that the increasing prevalence of food-borne parasitic infections is due to the rapid development of aquaculture and the expansion of the global food trade.⁵ However, all of the infections in this study took place in suburbs and their adjacent rural areas where no aquatic products are farmed. They were mainly observed in people who were in the habit of eating raw food and who had family members who were urban migrant workers. The frequent population flows between different re-

gions are erasing the differences between endemic and nonendemic areas and increasing the prevalence of parasitic infections. This is a new feature of the current situation with parasitic infection in China.

One of the striking hallmarks of *Paragonimus* infection is a peripheral blood eosinophil count that is commonly as high as 25%.¹⁰ Twenty-four of 27 patients in our study had high peripheral blood eosinophil counts. Although the role of eosinophils in parasitic infections depends on different hosts and parasite stages,¹⁰ we contend that the eosinophil count remains an important diagnostic tool for determining the presence of parasitic infections in patients living in developing countries. Notably, 3 patients had normal eosinophil counts, which may be related to the acute stage of this disease and/or early large doses of hormone and antiinflammation therapy.

Additionally, eosinophilic meningitis is secondary to parenchymal lesions⁹ and can mainly be observed in patients with *Angiostrongylus cantonensis*.⁴ However, when our patients were examined using CSF liquid-based cytology, they registered highly positive results. Eosinophilic meningitis caused by *Paragonimus* was significantly underestimated on routine CSF examination. Therefore, liquid-based cytological examinations of CSF should be used in patients with suspicious brain imaging findings.

The exact correlation between epilepsy and CP is unclear. In an earlier study, only 37.08% of the patients had epilepsy, and most of them reacted well to antiepileptic treatment.² In fact, surgical specimens are typically obtained under an indefinite preoperative diagnosis. The preferred treatment for an indefinite diagnosis is MRI-guided stereotactic biopsy. If an intraoperative frozen section indicates inflammatory lesions and excludes the possibility of a tumor, the goal should be to protect brain function rather than to perform total removal of the lesion or the *Paragonimus*. Conventional surgery should be considered only when the patient presents with cerebral hernia or significant spinal cord compression. The early diagnosis and timely treatment of patients with CP may reduce the need for surgery and surgery-related complications. Delayed treatment often carries a higher risk of focal brain tissue damage and postoperative neurocognitive deficits. The migration of the parasites and the subsequent inflammation often destroy brain tissue, which then results in neurological deficits (Fig. 2).

Due to the difficulty of obtaining an actual fluke for the final diagnosis, the morphological identification of *Paragonimus* eggs plays an important role for those patients with atypical clinical symptoms and imaging results. The eggs of trematode species usually have characteristic opercular ridges or “shoulders” at one pole. The *Paragonimus* ova is large (approximately 80 × 50 μm), and the ovum is encapsulated by a double shell. The shell becomes thicker at the end opposite to the operculum (Fig. 3A). Most surgical specimens usually do not contain typical *Paragonimus* eggs and only show the formation of eosinophil granulomas with central necrosis, combined with the proliferation of small blood vessels (Fig. 3C) and the formation of Charcot-Leyden crystals (Fig. 2D). Only a few specimens showed *Paragonimus* eggs surrounded and distorted by inflammatory granulation (Fig. 3B). Most patients with

FIG. 2. Imaging studies obtained in a 9-year-old boy who presented with acute headache, nausea, and clumsiness of the left hand; the initial diagnosis was an inflammatory disease. Brain CT scanning showed a lesion with edema in the right frontal lobe (A). The postoperative axial CT scan (B) and photomicrograph of a specimen obtained for pathological examination (D; H & E, original magnification ×40) also indicated the possibility of an inflammatory or proliferative disease. The patient was discharged early without praziquantel treatment but required rehospitalization for unsteady walking 15 days after his initial discharge. The head MRI study (C) showed that the lesion had progressively extended, with obvious surrounding edema and multiple small, irregular, ring-like masses that had conglomerated and aggregated, which are typical characteristics of CP. After chemotherapy with praziquantel, the patient's symptoms improved, but the motor dysfunction of the left upper limb persisted. This case shows that, currently, pathologists often miss and misdiagnose this disease due to their lack of knowledge about *Paragonimus* infection, and that the role of surgery is very limited. Figure is available in color online only.

CP often have positive results if treated with praziquantel. However, this therapy is not effective for nematode and fascioliasis infections. Clinicians should be particularly alert to the potential for a poor prognosis in these patients. In some cases, when new lesions evolve or epilepsy occurs repeatedly during follow-up, clinicians should be alert to the possibility of *Paragonimus* reinfection or coinfection by other parasites.

Conclusions

The diagnosis and management of CP are very difficult, even for physicians and neurologists who specialize in infectious disease, but strong clinical suspicion and supportive laboratory data will help. Enhancing public education regarding food-borne parasites and necessary lifestyle changes are the scientific basis for the prevention and control of parasitic diseases. Neurosurgeons and neurologists should be particularly alert to clues such as increased eosinophils in blood and/or CSF and a history of

FIG. 3. Photomicrographs of brain tissue specimens showing morphological features of CP. H & E, original magnification $\times 40$ (A and C), $\times 20$ (B). Figure is available in color online only.

consumption of raw freshwater crabs. Surgery itself does not guarantee complete parasite removal. Timely diagnosis may reduce the rate of surgery and the risk of surgery-related complications.

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Conception and design: Xia. Acquisition of data: Xia, Chen. Analysis and interpretation of data: Xia, Ju. Drafting the article: Xia. Critically revising the article: You. Reviewed submitted version of manuscript: You, Ju. Approved the final version of the manuscript on behalf of all authors: You. Administrative/technical/material support: Chen.

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