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ORIGINAL RESEARCH

Clinical Features and Outcomes of Pediatric Intraspinal Paragonimiasis

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Background: Central nervous system infection is the most common and severe clinical subtype of ectopic paragonimiasis. Intraspinal paragonimiasis is rarely reported. This study aimed to provide experience for diagnosis and treatment strategies of pediatric intraspinal paragonimiasis.

Methods: We performed a retrospective clinical analysis of patients hospitalized for intraspinal paragonimiasis between January 1, 2015, and December 31, 2021.

Results: Nine patients were included. The median age was 9 years. Clinical symptoms mainly included weakness (9/9), sensory disturbances (6/9), urinary retention (2/9), fever (4/9), chest pain (3/9), cough (2/9), dyspnea (2/9) and subcutaneous nodules (1/9). Spinal magnetic resonance imaging revealed intraspinal extradural enhancing lesions in the thoracic spine in 8 patients and isolated cervical spinal cord lesions in 1 patient. Seven extradural lesions were connected with the pleural lesion and subcutaneous nodes. All patients received praziquantel without undergoing spinal surgery. After a median follow-up of 36 months, two patients had sequelae of mild weakness and urinary urgency, and seven patients recovered completely after a median time of 13 weeks of initial praziquantel treatment.

Conclusion: Pediatric intraspinal paragonimiasis mainly involves the thoracic segment of the spine. Weakness is the most common manifestation, and some patients may develop sensory disturbances and sphincter dysfunction. Most patients can recover completely with praziquantel treatment. Lesion resection is no longer a necessary treatment strategy.

Keywords: lung fluke infection, intraspinal lesion, pediatric, praziquantel

Introduction

Paragonimiasis is a worldwide food-borne parasitic infestation caused by the lung flukes of the genus Paragonimus.[1] It was estimated that more than 20 million people were infected worldwide, with the vast majority occurring in East Asia.[2] The infection is mainly caused by improperly cooked crab and crayfish consumption in humans. In addition, the consumption of raw meat from wild boar or deer infected with Paragonimus metacercariae has also been reported.[3] The major Paragonimus species infectious to humans in southwest China include *P. westermani* and *P. skrjabini*.[4]

Human paragonimiasis mainly causes pleural and pulmonary lesions. The larvae migrating to other organs or sites can lead to ectopic infections. Central nervous system infection is a common and severe clinical subtype of ectopic paragonimiasis, accounting for approximately 50% of extrathoracic diseases.[5,6] Cerebral involvement has been reported to occur in approximately 0.8–1% of paragonimiasis and up to 16–31% in areas where *P. skrjabini* is endemic in China.[2,7,8] The incidence of spinal involvement in central nervous system paragonimiasis is approximately 2%-10%.[9] According to a previous literature

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review, due to technical limitations, when patients with pulmonary or cerebral paragonimiasis presented with spinal symptoms, the available tests at that time mainly included cerebrospinal fluid examination and myelography.[10] Spinal surgery was the most commonly performed therapy. However, only 16% of patients were diagnosed with spinal paragonimiasis before surgery. Patients may experience moderate or marked improvement after resection surgery for intraspinal cysts or granulomas. Individuals died due to disease or post-surgical complications.[10] Despite developing diagnostic techniques, intraspinal paragonimiasis has rarely been reported since the 1960s. Information on the efficacy of drugs remains limited compared with surgery. Therefore, this study summarized and retrospectively analyzed the clinical characteristics, treatment and prognosis of nine children with intraspinal infection.

Materials and Methods

Patients and Data Collection

We screened patients admitted to the Children's Hospital of Chongqing Medical University, the largest tertiary medical center for children in southwest China, from January 1, 2015, to December 31, 2021. Medical records of patients with intraspinal paragonimiasis were retrospectively collected and analyzed. Inclusion criteria included (1) radiologically confirmed pulmonary, pleural, and intraspinal lesions; (2) positive immunologic, parasitological, or molecular diagnostic tests; and (3) stable neurologic functional status for more than one year.[2] We obtained epidemiological, demographic, clinical, laboratory, imaging, and therapeutic data from the patient's medical records. Participants underwent chest computed tomography (CT), spinal magnetic resonance imaging (MRI), and infectious agent testing. Brain CT or MRI and cerebrospinal fluid examination were used to assess the extent of neurological involvement and differential diagnosis. Specimens of serum and other body fluids (cerebrospinal fluid or pleural effusion) were preserved in transport media and tested for Paragonimus-specific immunoglobulin G using an enzyme-linked immunosorbent assay. Pathogen detection of samples using next-generation sequencing technology at a third-party clinical testing center is required when the infectious agent is determined.

Statistical Analysis

Statistical analyses were performed using SPSS statistical software, version 23.0 (IBM Corporation, Armonk, NY, USA). For a normal distribution, quantitative variables were shown as mean and standard deviation (SD), and for a non-normal distribution, median (interquartile range (IQR)). Frequency and percentages were used to present qualitative characteristics.

Results

Epidemiological and Clinical Characteristics

One hundred thirty patients with central nervous system paragonimiasis were hospitalized between January 1, 2015, and December 31, 2021. Nine patients with intraspinal paragonimiasis were included in this study. All cases were from rural areas of southwestern China where paragonimiasis is endemic, including Chongqing (n=5), Sichuan (n=2), and Guizhou (n=2) provinces. Males accounted for the absolute proportion (100%,9/9), with a median age of 9 years (IQR 5.5–11 years). The season of onset was predominantly autumn and winter (67%,6/9). Six patients presented a history of consuming raw or undercooked freshwater crabs or drinking unboiled stream water.

The initial clinical manifestations can be divided into neurological symptoms and extra-neurological symptoms (supplementary Tables 1–2). Six patients initially presented with neurological symptoms, including headache (1/9), weakness (1/9), sensory disturbances (1/9), and radicular pain (back pain, 3/9). Three patients presented with respiratory and gastrointestinal symptoms, including cough, chest pain, and abdominal distension. All patients developed paresis during the disease, 7 with bilateral lower limb weakness, 1 with left lower limb weakness and 1 with bilateral upper and lower limb weakness. There were 6 cases of sensory disturbances, 2 cases of bilateral horizontal sensation, 2 cases of unilateral horizontal sensation, and 2 cases of lower limb numbness. Urinary retention occurred in 2 patients. The main extra-neuropathic symptoms were fever, chest pain, cough, dyspnea, and subcutaneous nodules (Figure 1).

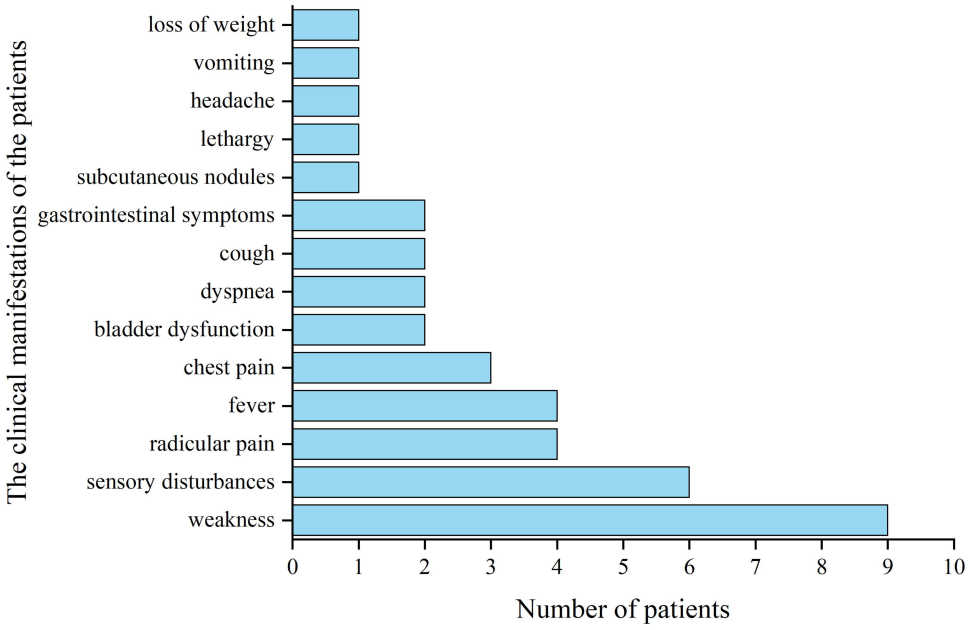

Figure 1 Clinical manifestations of patients in the acute phase.

Laboratory Findings

Laboratory findings are summarized in Table 1. The peripheral blood eosinophil counts was elevated in all patients, with a median of 4660 cells/μL (IQR 1905–6580 cells/μL.) on admission. By enzyme-linked immunosorbent assay, nine serum samples and one cerebrospinal fluid sample were detected positive for Paragonimus-specific immunoglobulin G. One patient presented with unexplained pleural effusion early in the disease, and the diagnosis of lung fluke infection was confirmed by next-generation sequencing of pleural effusion pathogenesis. The cerebrospinal fluid examination was performed on six patients, 5 with elevated protein levels and 2 with decreased glucose levels. Five patients showed elevated white blood cell counts with a predominance of polymorphonuclear cells. Elevated levels of eosinophils in the cerebrospinal fluid were detected in 60% (3/5). The detection rate of eggs in fecal samples was 0%. Among patients tested for inflammatory markers, procalcitonin levels were elevated in 50% (2/4), c-reactive protein levels were elevated in 25% (2/8), and erythrocyte sedimentation rate was prolonged in 80% (4/5).

Radiological Profile

Spinal MRI scans in the acute phase showed both extradural and intramedullary lesions in 7 patients, extradural lesions only in 1 patient, and cervical spinal cord lesions only in 1 patient (Table 1 and Figures 2–4). All extradural lesions involved the thoracic spinal canal and showed enhanced signals on the contrast-enhanced sequence. The sagittal view was long fusiform-shaped with a median longitudinal length of 8.5 vertebral bodies (IQR 7.25–9). Seven lesions were connected with the pleural lesion and subcutaneous nodes through the intervertebral foramen. The other patient showed only intervertebral foraminal strengthening. In 6 of the eight patients with extradural lesions, the corresponding spinal cord segment exhibited various degrees of compression and edema. One patient showed enhanced lesions in the cervical spinal cord distant from the extradural lesion. The distribution of intramedullary lesions in the cervical spinal cord was in 2 cases, cervicothoracic spinal cord in 2 cases, and thoracic spinal cord in 4 cases. The median length of lesions was 7.5 vertebral bodies (IQR 4–13.25). The contrast-enhanced sequence showed circumferential or heterogeneous enhancement in four spinal cord lesions. Five extradural lesions and one isolated cervical spinal cord lesion presented with irregular hemorrhagic foci with hyperintensity on T1WI (Figures 3a and 4a, white arrowheads). 83%(5/6) brain MRI and 80%(4/5) brain CT were normal, and one patient showed softening foci in the right basal ganglia. Abnormal chest and abdominal CT scan findings mainly included pleural effusion (78%, 7/9), pulmonary exudation (67%, 6/9), pulmonary nodules (22%, 2/9), atelectasis (22%, 2/9), lymph node enlargement (33%, 3/9), pericardial effusion (11%, 1/9) (supplementary Tables 1–2).

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Table 1 Laboratory and Imaging Findings of Nine Patients with Intraspinal Paragonimiasis

Patient	**1#**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Age	9Y	11Y	11Y	5Y	9Y	2Y	6Y	11Y	13Y
Blood eosinophils	2280	4660	6680	1450	12,970	6480	5440	1530	3840
CSF									
WBC	3	43410	NA	35	NA	NA	12	475	246
Prot	66	1712	NA	40	NA	NA	2433	327	275
Glu	3.78	2.51	NA	3.14	NA	NA	2.67	1.86	1.11
eosinophils	0	13200	NA	10	NA	NA	0	NA	220
Antibody detection	Serum +	Serum +	Serum +	Serum +, CSF +	Serum +	Serum +	Serum +	Serum +	Serum +
Brain MRI	Softening foci	Normal	NA	Normal	Normal	NA	Normal	Normal	NA
Brain CT	Softening foci	Normal	Normal	NA	NA	NA	Normal	NA	Normal
Spinal MRI (acute phase)									
Extradural lesion‡	T9-T12	T5-T12	T1-T8	Normal	T1-T9	T1-T12	T2-T10	T2-T10	T2-T8
Spinal cord lesion‡	T10-T11	C2-C5	T1-T8	C2-C5	T1-T7	Normal	T3-T10	C1-T12	C4-T11
Spinal MRI (follow-up††)	No resolution (4W)	NA	NA	Normal (2W)	NA	NA	Partial resolution (28W)	NA	Normal (6W)

Notes: #Lung fluke was detected by next-generation sequencing of the patient's pleural effusion pathogen. ††Time interval from initial praziquantel treatment to repeat MRI scan. ‡Lesions at the level of the spinal vertebrae corresponding to MR sagittal imaging.

Abbreviations: Y, years; eosinophils, cells/μL; CSF, cerebrospinal fluid; WBC, white blood cells/μL; Prot, CSF total protein, mg/dl; Glu, CSF glucose level, mmol/L; NA, not applicable; MRI, magnetic resonance imaging; W, weeks.

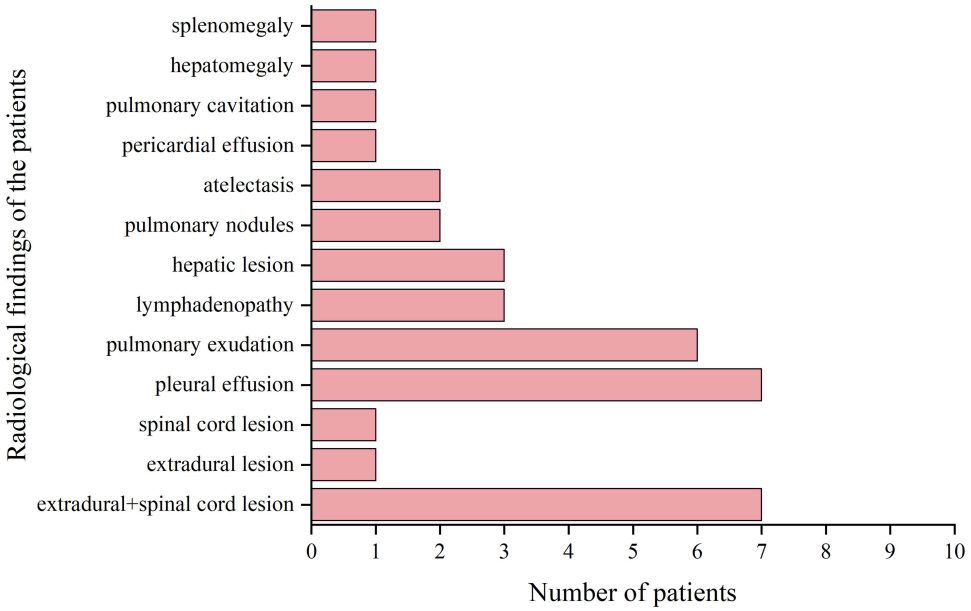

Figure 2 Radiological findings of patients in the acute phase.

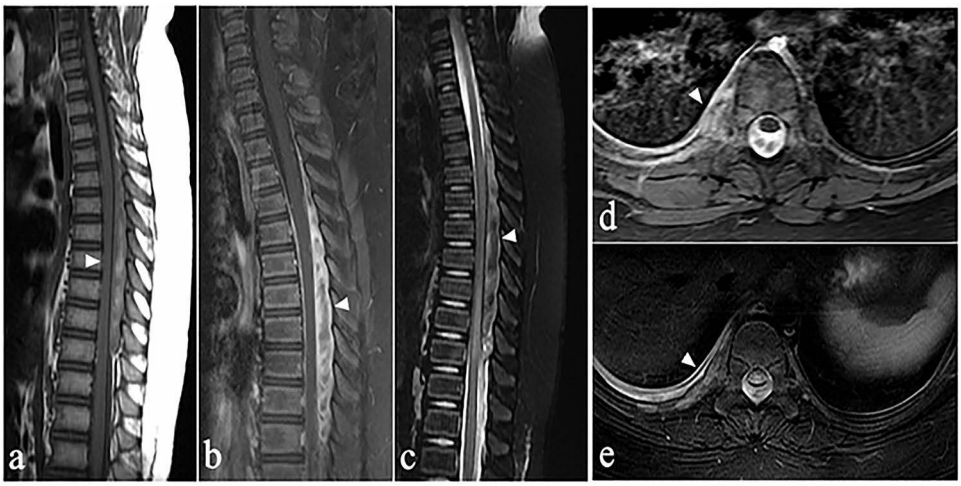

Figure 3 MRI imaging of intraspinal paragonimiasis in a 6-year-old patient (patient 7). As indicated by the white arrowheads, sagittal T1WI (**a**), contrast-enhanced T1WI (**b**), and T2WI (**c**) show that the lesion mainly with isointense on T1WI and hyperintensity on T2WI extends from T2 to T10 and is circumferential, mainly with posterior involvement. Multiple irregular hemorrhagic areas within the lesion, with slight hyperintensity, are shown on T1WI. Contrast-enhanced T1WI shows that lesions and adjacent spinal meninges are enhanced. The spinal cord adjacent to the lesion at the T3-T10 vertebral level is compressed. As indicated by the white arrowheads, axial contrast-enhanced T1WI (**d**) and T2WI (**e**) show that the intraspinal lesion is connected to the right pleural lesion through the right intervertebral foramen.

Treatment and Outcome

The standard praziquantel course in this group of patients was administered at 25 mg/kg three times daily for three days. The median interval between disease onset and initial praziquantel therapy was 17 days (IOR 10.5–23.5 days). Response to treatment was assessed based on peripheral blood eosinophil counts, clinical symptom improvement, and pleural or pericardial effusion absorption. The course of praziquantel was increased when treatment was ineffective. The adverse events of praziquantel were monitored, and no adverse drug reactions occurred. Three patients were treated with low-dose prednisone for three weeks. The symptoms of spinal cord injury in six patients had gradually improved before diagnosis, and the guardians of the other three patients refused surgical intervention. Consequently, none of the patients underwent spinal surgical treatment. One patient received closed thoracic drainage due to a large pleural effusion.

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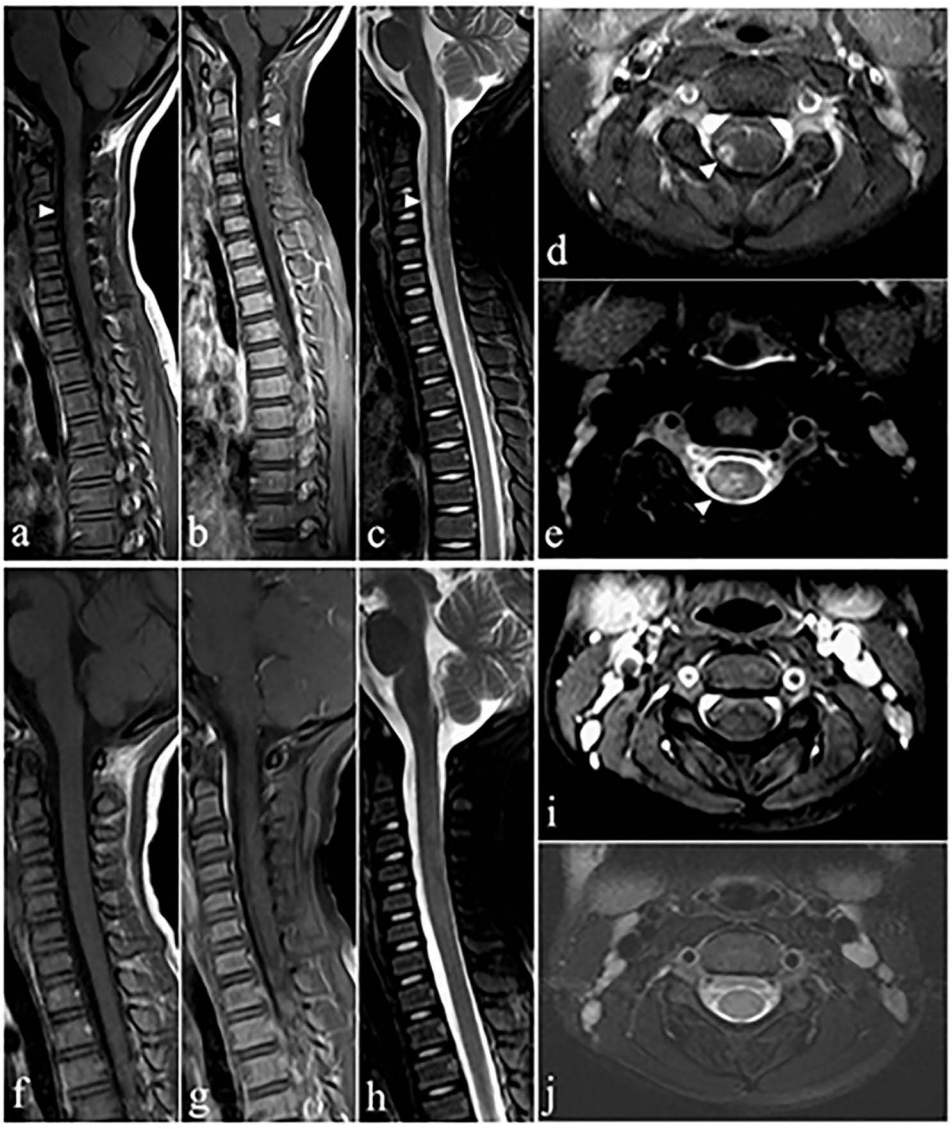

Figure 4 MRI imaging of a 5-year-old patient shows a lesion in the cervical spinal cord (patient 4). As indicated by the white arrowheads, sagittal T1WI (**a**), contrast-enhanced T1WI (**b** and **d**), sagittal T2WI (**c**), and axial T2W1 (**e**) show a lesion located in the spinal cord extends from C2 to C5. Multiple irregular hemorrhagic areas are present within the lesion, with hyperintensity on T1WI and T2WI. Contrast-enhanced T1WI shows circumferential enhancement within the lesion (**b** and **d**). The cervical spinal cord lesion disappeared after two weeks of praziquantel treatment (**f–j**).

The follow-up was conducted through outpatient visits or telephone interviews. All patients were followed up longitudinally (median 36 months, IQR 36–36 months) after discharge and achieved a stable clinical status with no recurrence (supplementary Tables 1–2). Seven patients recovered completely after a median time of 13 weeks (IQR 4–24 weeks) of initial praziquantel treatment. Two patients had sequelae, one of whom presented with a mild right lower limb limping gait and the other with mild right hemiparesis and urinary urgency. The median time to achieve stable neurological status in all patients was 13 weeks (IQR 3.5–24 weeks) after initiation of praziquantel treatment. Four patients underwent an MRI of the spine during follow-up. The lesions disappeared in 2 patients after 2 and 6 weeks of initial praziquantel treatment (Figure 4). The lesions in the other two patients showed partial or no resolution.

Discussion

In this retrospective study, we summarized the clinical features and outcomes of 9 children with intraspinal paragonimiasis. Our results suggested that significant neurological dysfunction may occur in the acute phase, and praziquantel treatment is effective.

Diagnostic evidence of central nervous system paragonimiasis includes epidemiologic history, abnormal neurologic manifestations, elevated blood eosinophils, and imaging abnormalities including pulmonary pleural, brain or intraspinal lesions. Confirmation of the diagnosis is based on positive pathogenetic test results including eggs, specific antibodies, or Paragonimus DNA. The diagnosis of paragonimiasis is easily established when eggs are detected in the sputum or stool of the patient. However, the egg detection rates are very low (approximately 7.3–65.1%), especially in pediatric patients (approximately 0.8–4.1%).[1,11–15] The reasons for the differences in detection rates are unclear and may be related to the time of detection, specimen handling, and species of lung flukes. The interval between initial infection and the development into ovipositing adult worms is approximately five weeks to three months.[6,16,17] Most *P. skrjabini* parasites are in the juvenile stage in the human lungs.[6] Komiya and Yokogawa's study significantly improved the detection rate by the AMS III concentration technique.[15] The fecal worm egg detection rate in this group of patients was 0%. The median duration of illness at admission was two weeks, and the patients were native to a region where *P. skrjabini* is endemic, which may explain the low egg detection rate. Enzyme-linked immunosorbent assay is a reliable diagnostic tool widely used in clinical practice with superior sensitivity and specificity.[18] In fact, the diagnosis of paragonimiasis is mainly based on clinical manifestations, imaging studies, and the detection of specific antibodies.[1]

Typical symptoms of transverse myelopathy include paresis, a sensory level, and autonomic impairment below the lesion level.[19] Intraspinal paragonimiasis may not exhibit all of these symptoms, which is consistent with the anatomic localization of the lesion primarily involving the extradural space of the spinal cord. In a comprehensive review of the literature, 96% of patients presented with a proportion of weakness or difficulty walking (71% with paraplegia, 13% with hemiplegia, and 8% with unilateral lower limb weakness), 72% with sensory disturbances (72% with sensory levels and 28% with limb pain, numbness, or hypoesthesia), 44% with sphincter dysfunction, and 8% with seizures.[10] The prevalence of sensory levels (56% vs 44%) and sphincter dysfunction (50% vs 33%) was higher in adults compared with children. Compared with the pediatric patients in the literature review, rates of weakness and sensory disturbances were similar in this study, but sphincter dysfunction and seizure rates were lower. In addition, some patients presented asymmetrical sensory levels, which have never been described.

The pathogenesis of intraspinal paragonimiasis remains uncertain. Early studies proposed the theory of direct larval migration, with larvae reaching the intervertebral foramen from the lung and pleura through the intercostal nerves or perivascular tissues.[10] This pathogenesis has been supported by autopsy and spinal MRI evidence. In addition, three patients with cerebral paragonimiasis developed spinal paragonimiasis several weeks to months after craniotomy. Based on such cases, the alternative hypothesis was proposed that the larvae may spread directly into the dura mater through the cerebrospinal fluid.[10,20] Seven patients in this group showed a direct anatomic link in imaging between the epidural lesion and the pleural and subcutaneous nodes. One of them showed cervical spinal cord lesions isolated from the epidural lesion. The hypothesis of direct migration or cerebrospinal fluid transmission seems to explain the imaging phenomenon. Interestingly, one patient's cranial and spinal cord MRI scans showed lesions in the cervical spinal cord with foci of hemorrhage and no extraspinal lesions. Cerebrospinal fluid examination suggested an increased eosinophil count and positive anti-Paragonimus antibody. Although chest imaging showed significant pleural and pulmonary lesions in this patient, no signs of direct larval migration were found. Immature larvae may migrate through the loose connective tissue surrounding the jugular vein or carotid artery, penetrate the meninges and invade the central nervous system.[21] Therefore, a possible mechanism for developing imaging abnormalities in this patient is the invasion of larvae into the cerebrospinal fluid along this migratory pathway and their spread to the spinal cord. However, we cannot exclude the possibility that traces of migration along the intervertebral foramen have disappeared or that no migrating lesions were detected due to the limitations of imaging techniques.

The WHO currently recommends praziquantel and triclabendazole as primary treatments for human paragonimiasis. A single course of praziquantel (25 mg/kg thrice daily for 2 to 3 days) has been reported to increase the cure rate to

90–100%.[22] More than one course of praziquantel treatment may be required for patients with prolonged respiratory symptoms, high antibody titers, multiple pulmonary lesions, pleural effusion, pericardial effusion, or a few cerebral paragonimiasis.[23–28] Experience with praziquantel for treating intraspinal paragonimiasis remains lacking due to the scarcity of incidence. Previous case reports showed progressive improvement with a single course of praziquantel after lesion excision surgery, but a long-term prognosis was not provided.[29,30] In a comprehensive review of the literature, 23 pediatric and adult patients with spinal paragonimiasis were reported.[10] In the lesion resection group, 18 improved, one did not improve, and one died of postoperative complications. While in the nonsurgical group, one died, and two improved with medication. A study focusing on imaging features showed no residual motor or sensory deficits after multiple courses of praziquantel or lesion excision combined with multiple courses of praziquantel.[20] Our group of patients received praziquantel therapy without lesion excision, with 7 cases recovering completely and two cases with mild neurological sequelae. One patient presented mainly with a large pleural effusion in the early stage of the disease, and neurological symptoms progressed despite closed thoracic drainage and two courses of praziquantel treatment. Therefore, a single course of praziquantel treatment for intraspinal paragonimiasis may be inadequate. In this study, praziquantel treatment significantly improved disease prognosis and reduced mortality compared with earlier medications and surgical treatment. Due to the small sample size, further research is needed to determine whether praziquantel therapy always leads to a good prognosis. All patients in this group lived in rural areas where regular follow-up and review of spinal MRI were not possible due to transportation and economic reasons, so radiological outcomes could not be known.

Limitations of this study include the retrospective collection of clinical data, the very low prevalence of intraspinal paragonimiasis, the small final sample size of the single-center study, no sequencing to identify species, and the absence of continuous MRI evaluation at follow-up, all of which prevented us from further analyzing the factors affecting the prognosis of the disease. More studies are needed to summarize the clinical characteristics, therapeutic strategy and prognosis of the disease.

Conclusion

Our study highlights the clinical features and outcomes of pediatric intraspinal paragonimiasis in southwest China. Due to the low positive egg detection rate, diagnosis of intraspinal paragonimiasis based on epidemiological, clinical, imaging, and specific antibodies is appropriate. Patients often present with weakness in the acute phase, which may be accompanied by sensory disturbances or sphincter dysfunction. Most patients can have a favorable outcome in treatment with praziquantel without spinal surgery. Dietary health education for populations in epidemic areas may be relevant for disease prevention and control. Further studies are still needed regarding the pathogenesis, prognostic factors, and optimal treatment strategy for intraspinal paragonimiasis.

Data Statement

All data generated or analyzed during this study are included in this published article, if further inquiries for any scientific use can be directed to the corresponding author.

Ethics Approval and Consent to Participate

All procedures will be carried out in compliance with the Helsinki Declaration. This study was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University (Approval Letter No: 456/2022). The requirement for informed consent by individual patients was waived by Ethics Committee of the Children's Hospital of Chongqing Medical University given the retrospective nature of the study. All information about the participants will be kept strictly confidential.

Acknowledgments

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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