REVIEW

CLINICAL FEATURES, DIAGNOSIS AND TREATMENT OF CEREBRAL SCHISTOSOMIASIS JAPONICA: LESSONS AND EXPERIENCES FROM CHINA

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Abstract. Schistosomiasis japonica, caused by infection with *Schistosoma japonicum* (Katsurada, 1904), remains a major public health concern in China. The central nervous system is an unusual site of ectopic infection of *S. japonicum* and cerebral schistosomiasis japonica, which is frequently misdiagnosed as intracranial tumor, may cause severe clinical complications and even death. This review summarizes the clinical data retrieved from 29 relatively complete reports pertaining to cerebral schistosomiasis japonica in China since 2000. A total of 1,007 cases with cerebral schistosomiasis japonica were reviewed, 98.0% classified as a chronic type. The review describes the clinical features of these patients, procedures required for positive diagnosis and treatment for alleviation of clinical symptoms and elimination of the parasite. Cerebral schistosomiasis japonica remains frequently misdiagnosed at the initial visit to a physician, and definitive clinical diagnosis requires a combination of case history interview, clinical manifestations, serological tests and imaging tools as chemotherapy given immediately following definitive diagnosis results in a satisfactory clinical outcome.

Keywords: cerebral schistosomiasis, *Schistosoma japonicum*; clinical features; diagnosis; treatment; China

INTRODUCTION

Schistosomiasis is a global neglected tropical disease that affects some 140 million people living in tropical and sub-tropical regions across the world, and this infectious disease ranks second only to malaria in terms of its public health and socioeconomic significance (Deol *et al*, 2019; LoVerde, 2019). In

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2017, schistosomiasis is responsible for 1,089,000 man-years lost globally due to morbidity, with annual 200,000 deaths across the world (King and Galvani, 2018).

There are three major species of family Schistosomatidae, genus *Schistosoma* that infect humans, namely, *S. haematobium*, *S. japonicum* and *S. mansoni*, with *S. japonicum* responsible the most serious disease (Colley *et al,* 2014). *S. japonicum* predominantly localizes in host portal and mesenteric veins and pathology involves liver, spleen and gastrointestinal tract (Tucker *et al,* 2013); however, ectopic infection of the parasite may occur in lung and central nervous system (Barsoum *et al,* 2013). Unlike *S. haematobium* or *S. mansoni*, the central nervous system damages caused by *S. japonicum* mainly occur in the brain and occasionally in the spinal cord (Carod Artal, 2012; Coyle, 2013).

Although the exact pathogenesis of cerebral schistosomiasis remains unclear, it is widely accepted deposition of parasite eggs in the brain causes the formation of egg granulomas and inflammatory lesions, resulting in clinical manifestations, such as epileptic seizure, headache, limb numbness and hemiplegia (Carod-Artal, 2010; Wang *et al*, 2010). Great advances have been achieved in imaging tools but definitive diagnosis of cerebral schistosomiasis remains a challenge, and this parasitic infection is frequently misdiagnosed as intracranial tumor (Wu *et al*, 2012; Huang *et al*, 2017; Suthiphosuwan *et al*, 2018; Wei *et al*, 2018). Early identification of cerebral schistosomiasis is vital as immediate administration of anti-parasitic drug praziquantel can achieve a satisfactory prognosis (Ross *et al*, 2012).

Here, a review of clinical features, diagnosis and treatment of patients with cerebral schistosomiasis japonica retrieved from 29 published clinical reports in China since 2000 is described to enable experiences and lessons learnt in management of cerebral schistosomiasis japonica in China to be available to a wider readership.

Data acquisition and general characteristics

In order to retrieve data pertaining to patients in China with cerebral schistosomiasis japonica, three Chinese electronic databases, namely, CNKI (www.cnki.net), Wanfangdata (www.wanfangdata.com.cn) and VIP (www.cqvip.com) were searched using term "cerebral schistosomiasis", from the year 2000 to the preparation of this manuscript (November, 2019). After exclusion of duplicate publications, all full-text files were carefully examined and literature with (almost) complete data were used for analysis.

In all, a total of 29 publications were included in the review, comprising 1,007 cases with cerebral schistosomiasis japonica, 251 females and 756 males, ranging from three months to 71 years of age, predominantly identified in young adults (mean age = 20.5-37.5 years) (from 19 studies) with shortest and longest duration from onset of illness to seeking healthcare service of three days and 13 years respectively (Table 1).

Clinical manifestations

In China, cerebral schistosomiasis japonica is classified as an acute and a chronic type (Li *et al*, 2011). Acute cases mainly present with fever, headache, spasm, paralysis, coma, signs of positive meningeal irritation, and mental symptoms; and chronic patients manifest epileptic seizure, headache, nausea, projectile vomiting (intracranial hypertension), hemiplegia, temporal

cognitive dysfunction and speech disorder (Hayashi, 2003; Shen *et al*, 2020). Among 1,007 case histories with cerebral schistosomiasis japonica, 987 (98.0%) and only 20 (2.0%) cases are classified as chronic and acute type respectively. Among the former patients, intracranial hypertension (58.8%), epileptic seizure (56.6%) and hemiplegia (27.7%) are the three most common manifestations (Table 1).

Diagnosis and misdiagnosis

There is no national guideline for diagnosis of cerebral schistosomiasis japonica in China, the widely accepted criteria based on clinical experience for diagnosis of this disorder are: (1) presence of such clinical manifestations as epileptic seizure, headache, hemiplegia, and temporal cognitive dysfunction, when other diseases with similar symptoms have been excluded, (2) head computerized X-ray tomography (CT)/magnetic resonance imaging (MRI) scan displays nodules or other abnormal changes in brain, (3) history of living in or travelling to schistosomiasis-endemic regions, (4) detection of specific antibody against *S. japonicum* in serum and/or cerebrospinal fluid, or identification of schistosome egg granulomas revealed by pathological examinations of biopsy specimens, and (5) praziquantel chemotherapy results in disappearance or improvement in

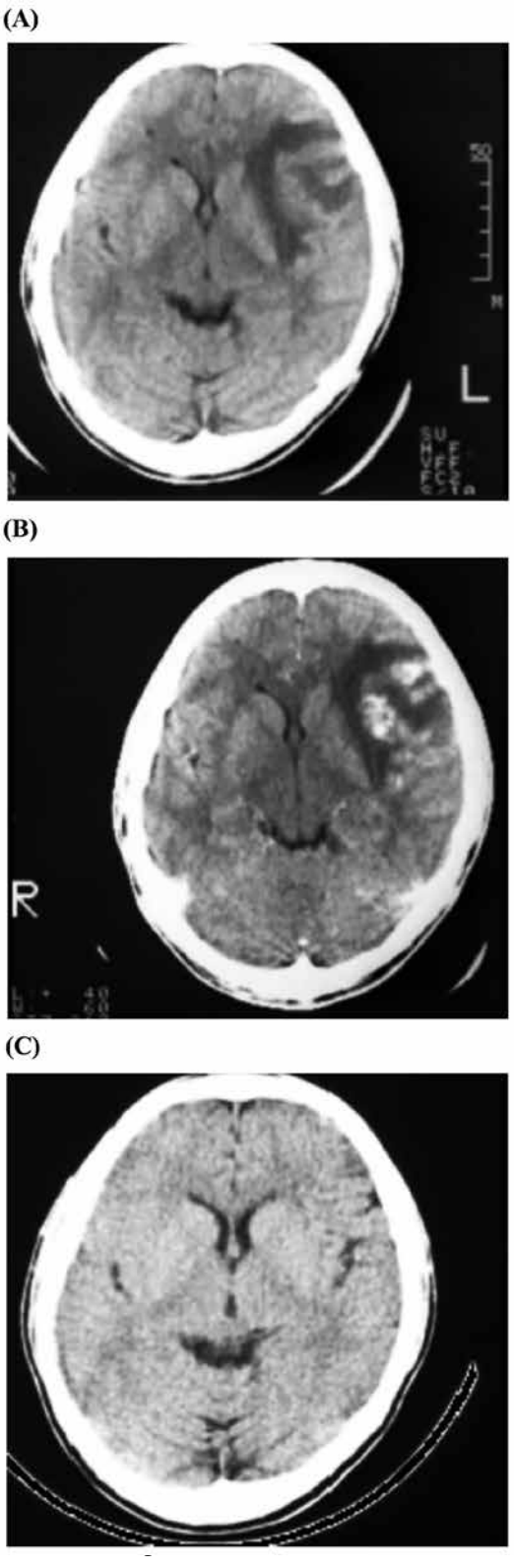

Fig 1-Brain X-ray computer tomography scan of patient with chronic cerebral schistosomiasis japonica.

(A) Appearance of multiple foci with unclear edges, surrounded by edema and mild space-occupying lesions; (B) Appearance of patchy enhanced foci prior to treatment with praziquantel; (C) Absence of foci and edema post-treatment with praziquantel (same patient as in B).

Table 1
Demographics and clinical manifestations of patients (n = 1,007) with cerebral schistosomiasis japonica in China obtained from the literatures (2000-2019).

Reference	Number of cases	Male / female	Age (years)	Course of disease	Clinical manifestation			
					Intracranial hypertension	Epilepsy	Hemiplegia	Others
Hu and Hu (2000)	33	26 / 7	16-61	NA	6	27	0	0
Zhang (2001)	39	27 / 12	15-49	NA	9	27	3	22
Wang *et al* (2002)	20	14 / 6	25-50	NA	6	10	4	0
Qian (2002)	12	10 / 2	30-50	NA	4	6	2	0
Zhang *et al* (2002)	87	56 / 31	16-62	NA	61	59	78	0
Huang *et al* (2004)	55	47 / 8	16-30	NA	28	25	5	3
Liu *et al* (2004)	9	7 / 2	NA	NA	7	6	4	1
Wu *et al* (2004)	42	28 / 14	15-64	NA	31	34	11	2
He *et al* (2005)	21	17 / 4	7-53	1 month - 10 years	21	13	0	0
Zhou and Zhou (2005)	11	8 / 3	10-53	NA	5	8	2	2
Hu *et al* (2006)	16	12 / 4	NA	NA	0	14	0	10
Wu *et al* (2007)	22	13 / 9	9-60	NA	18	14	6	1
Jing *et al* (2007)	67	58 / 9	9-71	NA	25	35	13	7
Zhou *et al* (2007)	15	12 / 3	17-50	3 months - 13 years	13	11	0	15
Ni and Wang (2007)	22	15 / 7	NA	3 months - 2 years	8	10	4	0
Huang *et al* (2008)	62	46 / 16	NA	NA	25	29	0	8
Huang *et al* (2008)	38	33 / 15	18-57	1 month - 1 year	26	27	14	3
Wu *et al* (2008)	48	36 / 12	16-62	NA	31	34	13	6
Gong (2010)	9	6 / 3	16-53	NA	4	6	1	5
Xie *et al* (2010)	11	8 / 3	16-53	3 days - 2 years	4	6	0	9
Wu *et al* (2011)	26	20 / 6	16-58	3 weeks - 5 months	11	16	3	0
Chen and Yang (2011)	21	16 / 5	16-62	NA	4	10	0	7
Su *et al* (2012)	19	16 / 3	8-55	1 month - 9 years	19	19	0	0
Zhou (2012)	15	11 / 4	15-60	2.5 - 16 months	15	8	0	0
Wang (2013)	46	29 / 17	14-60	NA	39	36	22	3
Wang *et al* (2013)	42	32 / 10	18-56	NA	31	8	13	39
Zhu *et al*, 2014	166	138 / 28	22-71	NA	115	45	76	96
Sun (2014)	19	14 / 5	18-65	NA	19	17	1	10
Yun *et al* (2017)	14	11 / 3	15-64	1 week - 3 years	7	9	4	5

Table 2
Diagnosis, treatment options, follow-up and outcomes of patients (n = 1,007) with cerebral schistosomiasis japonica in China obtained from the literatures (2000-2019).

Reference	Positive stool test/total testing	Positive serological test/total testing	Abnormal X-ray CT finding/ total scans	Abnormal MRI finding/ total scans	Chemo-therapy	Surgery and chemo-therapy	Followed-up	Clinical cured	Improved	Cured	Death from other diseases	Duration of follow-up
Hu and Hu (2000)	12/33	21/33	33/33	NA	33	0	33	32	1	0	0	NA
Zhang (2001)	30/39	35/39	NA	NA	39	0	39	34	5	0	0	3 years
Wang *et al* (2002)	NA	NA	20/20	NA	18	2	20	20	0	0	0	NA
Qian (2002)	10/12	10/12	7/12	NA	12	-	12	10	2/12	0	0	6 months
Zhang *et al* (2002)	NA	65/71	87/87	NA	47	40	59	56	3	0	0	2 years
Huang *et al* (2004)	25/35	36/46	22/25	4/4	51	4	55	53	2/55	0	0	NA
Liu *et al* (2004)	NA	9/9	9/9	7/7	1	8	9	8	1	0	0	4 years and 7 months
Wu *et al* (2004)	NA	38/42	42/42	42/42	29	13	34	33	1	0	0	2 years and 5 months
He *et al* (2005)	NA	18/21	21/21	NA	21	0	21	21	0	0	0	NA
Zhou and Zhou (2005)	N	9/11	NA	11/11	8	3	11	9	2	0	0	8 months to 3 years
Hu *et al* (2006)	3/16	8/16	16/16	NA	16	0	16	16	0	0	0	NA
Wu *et al* (2007)	NA	16/22	22/22	22/22	14	8	22	22	0	0	0	1 year
Jing *et al* (2007)	25/67	62/67	61/61	6/6	59	8	52	45	7	0	0	3 months to 5 years
Zhou *et al* (2007)	3/10	12/15	NA	15/15*	9	6	15	15	0	0	0	NA
Ni and Wang (2007)	NA	NA	22/22	NA	22	-	22	16	3	3	0	1 year
Huang *et al* (2008)	6/9	47/57	52/53	14/14	50	12	62	51	0	10	1	2 months to 2 years
Huang *et al* (2008)	NA	NA	NA	38/38	38	0	38	38	0	0	0	NA

Table 2 (Continued)

Reference	Positive stool test/total testing	Positive serological test/total testing	Abnormal X-ray CT finding/ total scans	Abnormal MRI finding/ total scans	Chemo-therapy	Surgery and chemo-therapy	Followed-up	Clinical cured	Improved	Cured	Death from other diseases	Duration of follow-up
Wu *et al* (2008)	NA	35/42	48/48	19/19	0	48	39	31	2	3	3	0.5 - 5 years
Gong (2010)	3/9	9/9	NA	9/9	9	0	9	8	1	0	0	2 months
Xie *et al* (2010)	3/11	11/11	NA	11/11**	11	0	11	9	1	1	0	2 months
Wu *et al* (2011)	0/26	12/26	26/26	26/26	12	14	26	23	3	0	0	3 months to 3 years
Chen and Yang (2011)	NA	18/21	21/21	21/21	0	21	21	20	1	0	0	0.5 - 2 years
Su *et al* (2012)	NA	14/19	19/19	NA	19	0	19	19	0	0	0	NA
Zhou (2012)	5/15	12/15	NA	15/15	14	1	15	14	1	0	0	8 months
Wang (2013)	NA	38/46	46/46	5/5	46	0	46	35	10	1	0	NA
Wang *et al* (2013)	NA	35/42	42/42	42/42	0	42	39	31	2	3	3	0.5 - 5 years
Zhu *et al*, 2014	13/96	142/166	166/166	78/78	102	64	81	66	7	5	3	3 months
Sun (2014)	NA	17/19	11/11	8/8	13	4	17	11	6	0	0	NA
Yun *et al* (2017)	7/14	14/14	10/10	14/14	13	1	14	12	2	0	0	0.5 - 5 years
Total	145/392	743/891	703/812	407/407	706	299***	857	758	63	26	10	2 months to 5 years

* One case with intracranial space-occupying lesions, two cases with inflammatory granulomas, two with metastatic tumors, three with astrocytoma, seven with gliomas; six patients were diagnosed as schistosome egg granulomas after craniotomy; all patients were cured by praziquantel therapy.

** Received MRI scans; three cases were diagnosed as glioma and one case as cerebral vasculitis.

***Two patients were not given medical treatment for cerebral schistosomiasis japonica because of treatment for other diseases.

CT: computer tomography; MRI: magnetic resonance imaging; NA: not available.

publications reported misdiagnosis of cerebral schistosomiasis japonica. Ni and Wang (2007) noted 54% misdiagnosis in 22 patients with cerebral schistosomiasis japonica at initial diagnosis; Gong (2010) recorded 2/9 (22%) patients with cerebral schistosomiasis misdiagnosed as cerebral glioma or cerebral vasculitis during initial diagnosis; and Wu *et al* (2011) reported initial misdiagnosis of 24 patients as encephalic space-occupying lesions and 2 as neurological disorders who initially are admitted to the neurology department and then transferred to the neurosurgery department of the hospital. However, all patients are ultimately diagnosed as definitive cerebral schistosomiasis japonica by pathological examinations and successfully cured with praziquantel chemotherapy and symptomatic treatment (Table 2).

Praziquantel chemotherapy and therapeutic efficacy

Of 1,007 patients with cerebral schistosomiasis japonica, 706 (70.1%) receive praziquantel chemotherapy together with symptomatic treatment including intracranial pressure-lowering and anti-epileptic therapy, and 299 (29.7%) undergone craniotomy and praziquantel chemotherapy, while 2 (0.2%) receive no praziquantel therapy because of urgent treatment of other concomitant diseases. In general, patients with cerebral schistosomiasis japonica are initially given dehydration therapy and anti-epileptic treatment, and after these symptoms are cleared, patients are treated with praziquantel (140 mg/kg body weight for adults or 120 mg/kg body weight for children) for a period of 4 to 6 days in a single course, depending on the severity of the symptoms, with the majority treated with one course of praziquantel, while a few with at least 2 courses at an interval of one week to one month. The majority of patients have no serious adverse reactions; however, some patients present with aggravation of temporal headache and vomiting, indicating an increase in intracranial pressure, which is relieved following dehydration therapy (Sun, 2014; Yun *et al*, 2017). A few patients still present serious contraindications: Wu *et al* (2011) reported a patient suffering from cerebral hernia during praziquantel administration, which is cured following surgical therapy. Taken together, since praziquantel may cross the blood-brain barrier (He *et al*, 2005), treatment with this agent results in remarkable relief and even disappearance of headache, epileptic seizure, hemiplegia or cognitive dysfunction in a majority of patients over a period of several days to several weeks.

Among 857 (85.1%) cases followed up for 2 months to 5 years, 758 (88.4%) achieve clinical cure, defined as absence of clinical signs and symptoms, of relapse during the whole follow-up period, and and/or shrinking of the original foci on CT and/or MRI scans; 63 (7.4%) show improvement, defined as alleviation of clinical signs and symptoms, and shrinking of original foci on CT and/or MRI scans (Fig 1); and 26 cases (3.0%) manifest no improvement (ineffectiveness), defined as failure in meeting abovementioned criteria. There are 10 (1.2%) mortalities stemming from other causes. During the follow-up period, there are no reports of recurrences of signs and symptoms of the disease in 88.4 % of the patients (Table 2).

CONCLUSION

Cerebral schistosomiasis japonica is frequently misdiagnosed as brain tumor and subsequently given

craniotomy, which increases disease and socioeconomic burdens. Definitive diagnosis of cerebral schistosomiasis japonica depends on determining case history of travel in regions endemic for schistosomiasis, clinical signs and symptoms, serological tests and imaging examinations, such as CT and MRI scans, the latter demonstrating great value in arriving at a definitive diagnosis of cerebral schistosomiasis japonica. Administration of praziquantel combined with intracranial pressure lowering is strongly recommended following diagnosis, achieving a satisfactory prognosis, but craniotomy should be considered if the combined treatments prove ineffective. Data from the review of the literature of the diagnosis and treatment of cerebral schistosomiasis japonica provided experiences from physicians treating the disease and should provide valuable insights into the management of cerebral schistosomiasis arising from infection of other *Schistosoma* spp across the world.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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