CLINICAL STUDIES ON CEREBRAL SCHISTOSOMIASIS JAPONICA IN THE PHILIPPINES

BY

Masataka Hayashi*1)

ABSTRACT

The author examined the cerebral schistosomiasis japonica (CSJ) in the Philippines which is one of the areas heavily infected with S. japonicum.

Seventy-five subjects were selected randomly from 307 patients with CSJ, who showed neurological symptoms such as convulsions, paroxysmal disturbance of consciousness and hemiparesis. The mean age of the subjects was 33. Of the 71 patients who had paroxysmal diseases, 54 had convulsions, in 33 of which it was of the Jacksonian type, and 24 had psychomotor seizures and 1 autonomic seizures. Thus, 58 patients or 82% of the paroxysmal disease group showed a sign of the localized lesion of the brain.

Fifty-one patients (72%) of this group had attacks more than once a month, and the onset of the paroxysmal disease was later than 20 years old in 49 (69%).

EEGs were judged as abnormal in 24 (32% of total subjects), borderline in 13 (17%) and normal in 38 (51%). The characteristic abnormal or borderline findings of EEG were random and paroxysmal slow waves with asymmetry.

Discussion was made in reference to the strong suspicion that the cerebral symptoms of the subjects, the paroxysmal diseases in particular, were a syndrome associated with Schistosoma japonicum and to the difference between CSJ in Japan and that in the Philippines.

INTRODUCTION

Schistosomiasis japonica (SJ) is caused by infection with Shistosoma japonicum, and the lesions are located mainly in the portal system and liver (Inuchi et al.1)). However, the so-called cerebral schistosomiasis japonica (CSJ) is sometimes seen complicated by neuropsychiatric symptoms due to the ectopic parasitism of the worm in the central nervous system (Ariizumi and Matsuo2)). The incidence of CSJ differs according to the condition of infection with S. japonicum; we have a few occasions at present here in the city area of Kofu to examine many cases of CSJ with a variety of symptoms as were reported by Ariizumi2) in 1945–1958.

Recently I was requested by the Japanese panel on parasitic diseases of the US-Japan Cooperation Council to conduct a survey on the actual conditions of CSJ in the Leyte Island of the Philippines, which is one of the areas heavily infected with S. japonicum. The present paper deals with the results of a preliminary survey with special reference to the clinical symptoms and electroencephalographic findings, which I have experienced so far, as compared with the same disease in the city area of Kofu in the Yamanashi Prefecture.

*1) Department of Neuropsychiatry (Director: Prof. Y. Shimazono), Faculty of Medicine, Tokyo Medical and Dental University (Tokyo Ikashika Daigaku).
Present Office: Department of Neurology, Kofu City Hospital (Director: T. Kakizaki).
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Subjects and Methods
Seventy-five subjects were selected randomly from 307 patients with suspected cerebral schistosomiasis japonica (CSJ) who showed symptoms of the central nervous system such as convulsions, paroxysmal disturbance of consciousness, dysphasia and hemiparesis, from the list of patients living in the Palo district of Leyte of the Philippines, which was prepared by the Schistosomiasis Control and Research Project (SCRP) of the Palo district. The ages of the subjects ranged from 14 to 63 years, with a mean of 33. The ratio of males to females was 48:27. On these 75 subjects, we conducted a detailed interview and physical, neurological, electroencephalographic and stool examinations and circunovval precipitation test (COP).

Results
I. Clinical Symptoms
1. Classification of Clinical Symptoms

The clinical picture of the subjects was classified as shown in Table 1. Except for the 4 patients, 71, corresponding to 95% of the total subjects, were of the paroxysmal disease group. Of the 71 patients, 54 had convulsions, and 16 of the remaining 17 had psychomotor seizures and 1 autonomic seizures.

Of the convulsive seizure group, Jacksonian convulsion was observed in 33 patients, 27 of whom showing progress from Jacksonian convulsion to generalized convulsion. Aside from these patients, there were 21 subjects having generalized convulsive seizures; 13 had this type of convulsion from the beginning and 8 developed it secondarily from psychomotor seizures.

Of these 71 patients in the paroxysmal disease group, disturbances localized in the brain were estimated from the type of seizure in 33 with Jacksonian convulsion, 24 with psychomotor seizure and 1 with autonomic seizure, a total of 58 which corresponded to 82% of the paroxysmal disease group, or 77% of the total subjects.

The 4 patients in the non-paroxysmal disease group consisted of one each with cerebellar ataxia, hepatosplenomegaly, dysthyroidism and Korsakoff’s syndrome. The patient with cerebellar ataxia was a 42-year-old male who had a lateral gaze horizontal nystagmus directed to the right and cerebellar symptoms predominant on the right side. Since he fell down from a tree several weeks before the onset of the cerebellar symptoms and developed a concussion of the brain, the relation with the trauma can not be denied.

The patient with hepatosplenomegaly was a 15-year-old boy whose liver was 4-finger-breadth palpable and whose splenomegaly was palpable 24 cm × 24 cm. Venous dilatation of the abdominal skin and ascites were observed, but there was no anamnesis of episodic disturbance of consciousness or extrapyramidal symptoms.

The patient with dysthyroidism was a 55-year-old female who complained of headache, finger tremor, insomnia and emotional instability. Examination revealed goiter, arrhythmia, hyperhidrosis and pal-
pitation. Hyperthyroidism was suspected and its relation to *S. japonicum* was uncertain.

The patient with Korsakoff’s syndrome was a 44-year-old male who had an anamnesis of delirium tremens at 33. Since he had been drinking about 4 liters of coconut wine a day and had a drinking history of over 20 years, the association with alcohol was suspected.

2. Properties of Seizures in the Paroxysmal Disease Group

The age when the initial seizure occurred was 19 or younger in 26 patients and 20 or older in 49. Patients with late onset seizure in which the initial seizure occurred after the age of 20 represent 69% of the seizure group (Table 2).

The frequency of the seizures was 1 to 3 times a day in 16 subjects, 1 to 3 times a week in 19, and 1 to 2 times a month in 16. There were 51 frequent-seizure subjects having seizures more than once a month and they represented 72% of the paroxysmal disease group (Table 3). No type of seizure showed a particular tendency in frequency.

The details of each type of seizure are described below. The typical Jacksonian type was the most frequently observed. Paresthesia runs from the left or right fingers to the upper limb, where, subsequently, twitching occurs, ascending to the left or right angle of the mouth. The neck turns to the side of the mouth angle with twitching, the so-called adverse seizure. Clonic convulsion is observed, also in the upper and lower limbs of the opposite side, progressing to generalized convulsion. Four of the cases showed only clonic hemi-convulsions with no adverisive seizure, and another 4 developed into generalized convulsive seizure. In 26 cases, however, clonic convulsion on one side of the mouth progressed to adverisive seizure and further to generalized convulsive seizure. This type was the most frequent.

Most of the patients with psychomotor seizures showed automatisms of the mouth and behavior. In some of them, who, after numbling, developed generalized convulsion, the differentiation from the seizure of

<table>
<thead>
<tr>
<th>Age</th>
<th>9</th>
<th>10-19</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60</th>
</tr>
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<tbody>
<tr>
<td>No. of cases</td>
<td>8</td>
<td>18</td>
<td>22</td>
<td>11</td>
<td>8</td>
<td>7</td>
<td>1</td>
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| Form and Frequency of Seizures |
| GM | J-GM | P-GM | P | J | Aut | Total |
| 1-3 times/day | 4 | 4 | 1 | 5 | 2 | 0 | 16 |
| 1-3 times/week | 0 | 11 | 4 | 2 | 2 | 0 | 19 |
| 1-3 times/month | 3 | 5 | 1 | 4 | 2 | 1 | 16 |
| 2-3 times/year | 4 | 6 | 2 | 2 | 0 | 0 | 14 |
| once/year | 2 | 1 | 0 | 3 | 0 | 0 | 6 |
| TOTAL | 13 | 27 | 8 | 16 | 6 | 1 | 71 patients |

(G: Grand mal J: Jacksonian seizure P: Psychomotor seizure Aut: Autonomic seizure)
the mouth angle of the Jacksonian type was difficult.

The case with autonomic seizure showed paroxysmal autonomic symptoms such as abdominal pain, palpitation, paleness of the face or epigastric sensation.

II Results of EEG Examination

EEG was normal in 24 (32%), borderline in 13 (17%), and abnormal in 38 (51%).

Table 4 classifies the abnormal EEGs. Twenty-eight cases showed mainly delta waves and sometimes a random mixture of delta waves and 27 showed an asymmetry in the burst-like slow waves or basic rhythm. In 16 cases with high voltage paroxysmal slow waves, the paroxysmal slow waves were diffused or localized and 7 of them showed asymmetry. In one of the 2 cases with fast waves, there was diffuse paroxysm of fast waves with moderate voltage and in the other there was an asymmetry with fast waves of around 25 c/s predominating in the left hemisphere. In the diffuse 8 c/s alpha pattern, the basic rhythm was monorhythmic, bipolar recording also resulting in a diffuse alpha pattern. The asymmetrical findings judged to be abnormal, including the asymmetry of random slow waves, were observed in 15 and asymmetry of background rhythm in 12; the side with bursts of slow waves coincided with the side with poor basic rhythm.

Of the borderline EEGs, cases showing asymmetrical findings sometimes showed an asymmetry in the amount and amplitude of the basic rhythm and in the amplitude of slow waves, but these findings were not constant. Cases of fast waves showed a remarkably small amount of alpha waves and basic rhythm of 20–25 c/s fast waves representing a low voltage irregular fast (L VF) pattern. Slow alpha waves of 8–9 c/s were the main frequency in the diffuse alpha pattern, showing no waxing and waning phenomenon of these amplitude. The case with high amplitude rhythm was a 19-year-old patient in whom the basic rhythm in the resting record was 10 c/s alpha waves of around 70 \( \mu V \), and the activation with hyperventilation resulted in extensive bursts of 8 c/s waves. The case with random slow waves was a 87-year-old patient in whom 7 c/s waves were mixed randomly in the alpha rhythm of the 8–10 c/s waves in the central to the parietal areas. In the 68-year-old patient with a slow alpha pattern, there were diffuse 8–9 c/s waves of moderate voltage, with waxing and waning of amplitude (Table 5).

It is noted in the above-mentioned abnormal and borderline EEGs that many asymmetrical findings are observed in bursts of slow waves and in basic rhythm and that in spite of the occurrence of frequent seizures clinically, none of the cases showed paroxysmal discharges other than slow wave bursts.

<table>
<thead>
<tr>
<th>Table 4. Contents of Abnormal EEG</th>
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<tbody>
<tr>
<td>Random slow waves</td>
</tr>
<tr>
<td>Asymmetry</td>
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<tr>
<td>Paroxysmal slow waves</td>
</tr>
<tr>
<td>Fast waves</td>
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<tr>
<td>Diffuse alpha waves (8 c/s)</td>
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<td>(°: Duplicated cases)</td>
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<tr>
<th>Table 5. Contents of Borderline EEG</th>
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<tr>
<td>Asymmetry</td>
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<tr>
<td>Fast waves</td>
</tr>
<tr>
<td>Diffuse alpha (3-9 c/s) waves</td>
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<tr>
<td>High amplitude rhythm</td>
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<tr>
<td>Slow waves (random)</td>
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<tr>
<td>Slow alpha waves</td>
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<td>(°: Duplicated cases)</td>
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III Representative Cases

Of the paroxysmal diseases, three repre-
sentative cases are described briefly below:

1. Case 1, 32-year-old male

Onset of seizure was at the age of 23. The seizure started with a violent twitching of the right angle of the mouth which progressed to an adverisive seizure on the right side, followed by loss of consciousness and generalized convulsion. Each seizure lasted for several minutes and this occurred once in 2 to 8 days and the patient had never been treated. There was no abnormal neuropsychiatric finding. Physically, the conjunctivae were slightly pale, but neither the liver nor the spleen was palpable. The stool was positive for S. japonicum ova and the COP test showed Type III reaction. The EEG showed abnormal findings, i.e., a mixture of random slow waves of 5-6 c/s and 7-8 c/s waves predominating in the right hemisphere, and in the left hemisphere there were remarkable random and sometimes paroxysmal high amplitude, irregular slow waves of 4-6 c/s which were predominant in the centro-parietal areas (Fig. 1).

2. Case 2, 47-year-old male

Initial seizure occurred at 35. After a delirious state, a generalized convulsive seizure developed. The frequency of the seizures was about once a day. The seizure was precipitated by insomnia, overwork and hunger. Neurologically, there was no pertinent finding, but mentally poor understanding, delay in reaction and improper discipline suggestive of decreased personality level were observed. Physically, although the liver was 4-finger-breadth palpable, no ascites or splenomegaly was noted. Laboratory findings showed ova of S. japonicum in the feces and Type III COP. The EEG showed abnormal findings with asymmetry in which regular alpha waves of 10 c/s appeared monorhythmically in the right hemisphere while the basic rhythm of

![EEG of case 1.](image)

In the left hemisphere, random, or sometimes paroxysmal 3-6 c/s, irregular slow waves predominate in the centro-parietal areas.

(R: right, L: left, aT: anterior temporal, mT: mid-temporal, pT: posterior temporal, C: central, P: parietal, O: occipital.)
the left hemisphere showed a low voltage pattern with a small amount of alpha waves in the left occipital area (Fig. 2).

3. Case 3, 16-year-old boy

His perinatal and postnatal growth was normal. The initial seizure occurred at the age of 9. After palpitation and anxious attack and sometimes déjà vu experience, oral automatism appeared with adverse seizure to the right, which developed to generalized convulsive seizures. The frequency of the seizures was about once daily to once monthly, sometimes several times a day. There was no physical abnormality, but his motions were slow, suggestive of mental retardation. Although his speech was intermittent, there was no cerebellar symptom. The EEG was abnormal, there being observed a small amount of slightly low amplitude, irregular alpha waves of 9–11 c/s predominantly in the right occipital area as well as low voltage irregular fast waves of 20–25 c/s. Fast waves appeared in all leads and irregular random slow waves of 4–5 c/s (sometimes 6–7 c/s) were occasionally seen scattered in small amounts (Fig. 3).

IV Therapeutic Effect on Seizures

We examined the effect of a trivalent antimony agent (Fuadin), which is an antischistosomal agent, on the seizures. There were 10 patients who had been treated only with Fuadin. Except for a 14-year-old boy, their ages ranged from 25 to 54 in 9 patients with a mean of 41. The seizures of these 10 patients were classified into the Jacksonian type in 7 (6 of them progressing to generalized convulsion), psychomotor seizure in 2 (one of them proceeding to grand mal) and grand mal in 1. The frequency of the seizures before the treatment of Fuadin was more than once a day in 4 patients, more than once a week in 3 and once in 3 months in 3.

In 4 effectively treated cases the seizures disappeared completely, in 3 cases the fre-
A small amount of low amplitude, irregular alpha waves of 9-11 c/s is observed predominantly in the right occipital area, and low amplitude fast waves of 20-25 c/s appear in all leads sometimes accompanied by the mixture of a small amount of irregular random slow waves of 4-7 c/s.

Because there was no subject who took diphenylhydantoin, an anticonvulsant, regularly, we were unable to judge its effect on the seizures. However, since the seizures disappeared or decreased remarkably by the continuous administration of Fuadin for about 1 week in the 4 subjects examined, the drug was thought to have been effective.

**Discussion**

The lesions caused by *S. japonicum* are located mainly in the liver but sometimes the central nervous system is affected. Schistosomiasis japonica that is complicated by the central nervous symptoms is called cerebral schistosomiasis japonica and is caused by the direct or indirect effect of infection with *S. japonicum*. The direct effect is divided into that of laying of eggs in the brain (Kane and Most); Shimizu and Tsunoda; Hunt et al.). In the case of laying of eggs in the brain, it is presumed that *S. japonicum* is able to enter the cerebral vein through some route, and the brain reacts to the eggs laid, resulting in neurological manifestations. Granuloma occurs in the chronic stage, and clinically there are symptoms of brain tumor. The tissue of the granuloma consists of 3 layers; the center is a necrotic layer containing ova and the middle layer contains epitheloid cells, giant cells, ova and small lymphocytes. Small
lymphocytes aggregate densely in the outermost layer where the plasma cells, eosinophils, fibroblasts and giant cells are also seen (Kanc and Most\(^5\); Shimizu\(^8\)).

On the other hand, in the case of egg embolism, the above-mentioned granulomata do not aggregate densely in a localized region but develop diffusely or sporadically in large numbers in the cortex or the subcortex over a considerably wide range of the cerebral hemisphere. The brain tissue of the regions shows glial proliferation, perivascular infiltration and degeneration of nerve cells. Egg embolism is also observed in the smallest blood vessels (Hunt et al.\(^7\)). In addition to the above histopathological tissue damage, the toxin and foreign protein of the ova of \textit{S. japonicum} exert biochemical or immunological effect on the central nervous system to provoke cerebrospinal meningitis-like symptoms or allergic symptoms of the brain.

As to the indirect effect, hepatic disorder and portal hypertension due to infection with \textit{S. japonicum} cause primarily an intrahepatic shunt and a shunt between the portal hepaticus and inferior vena cava. Intermediate metabolic substances of the liver, such as ammonium (Teukiya\(^8\)), lower fatty acid (Takahashi\(^9\)) and unknown substance of liver failure (Kitani\(^10\)), affect the central nervous system secondarily, resulting clinically in the episodic disturbance of consciousness and flapping tremor which are observed in the special type (Inose type) (Inose\(^11\)) of hepatocerebral disease.

The diagnosis of SJ is made by skin test (Ishizaki\(^12\)), COP (Yokogawa et al.\(^13\)) or other immunological examinations such as ouchterlony and complement fixation test, and the demonstration of ova by stool examination. Even if all of these tests are positive, it is difficult to prove the direct relationship of the disease to \textit{S. japonicum} or its ova. Hence, it is difficult to diagnose the 71 patients showing seizures clinically and symptomatically as due to CSJ. However, since the subjects are living in the endemic area of SJ where they are always exposed to infected water and since a high infection rate of 64% was obtained by a single fecal examination for ova and that the COP test was positive in 87%, the possibility of infection was very high in comparison with the conditions of infection in the city area of Kofu.

The fact that 71 of the 75 subjects from the Palo area had paroxysmal diseases may indicate the high prevalence of this condition in this district. The population of the Palo district where the subjects live is about 26,000, and about 300 of the patients on the SCRP list have complications of central nervous symptoms. Accordingly, since about 95 per cent of the subjects in the present preliminary survey had paroxysmal diseases, there are probably 285 patients with paroxysmal diseases, which correspond to about 1.1% of the inhabitants. In general, the incidence of the epileptic disease is about 0.3 to 0.5%, not differing greatly according to district or race (Wada\(^14\)). The reason for the presence of patients with paroxysmal diseases at a rate 2 to 3 times higher in this particular district of the Philippines may be due to some exogenous factors and we take the relation to \textit{S. japonicum} into consideration.

It is said that the late onset seizure occurs in the cases of symptomatic or cerebral organic diseases, and in this survey it was observed in 66% of the subjects. Paroxysmal diseases such as Jacksonian and psychomotor seizures suggestive of localized cerebral foci were observed in as many as 77% of the subjects. Asymmetrical findings were frequently observed in those with abnormal
and border line EEGs. These findings strongly suggest the direct effect of the ova or the worm on the brain. The anti-schistosomal medicine for the seizures of CSJ was studied and it was found to be effective in 9 of 10 patients with the paroxysmal diseases. This seems to prove the theory of Ariizumi and Matsuno that the symptoms of CSJ can be cured by taking trivalent antimony preparations and therefore, the drugs could be used for therapy and for differential diagnosis in the endemic district of SJ.

According to Kane and Most, 1,200 American soldiers, who landed on the island of Leyte of the Philippines in 1944, became infected with S. japonicum. By 1948, 27 (2.3%) of them had complications of motor paralysis, meningitis and central nervous symptoms, similar to those of brain tumor. The report shows the infection with S. japonicum in special environments among the officers and men who moved from a non-infected area to an infected area and is the only literature showing the incidence of CSJ with clear figures.

Because there has been no survey made on CSJ among the native Filipinos, it was believed that there were only a few cases of the cerebral type among the natives in the area infected with S. japonicum (Mitsuno, T.). However, by our survey CSJ was discovered in many of the inhabitants. Thus, it is thought that CSJ is highly prevalent in the Philippines where schistosomiasis japonica is heavily endemic and where there are repeated heavy infections, the number of cases of S. japonicum and ova in the host being large, so that the direct effect on the brain is correspondingly increased leading to the multiple occurrence of CSJ.

There are certain differences between CSJ in the Philippines and that in the city area of Kofu. With regard to CSJ in the Philippines, first, the clinical symptoms did not include the special type of hepatocerebral disease. Second, there was no case showing seizure discharges in the EEG findings other than the paroxysmal slow waves. Third, the rate of abnormal EEG was low, compared with the high frequency of clinical seizures.

All of our 8 cases of CSJ with paroxysmal diseases in the city area of Kofu had seizure discharges which corresponded to the clinical symptoms (Hayashi and Waka). However, the seizure discharges were observed during waking record in 2 of 8 cases, and during sleep recording in the remaining 6. Since the present survey was a preliminary one, only waking record was made for all of the subjects. The absence of seizure discharges may be related to such a methodological problem. The same reason should be considered for the difference between the rate of abnormal EEG in the Japanese cases of CSJ and that in the Philippine cases. During our survey 3 subjects developed clinical seizures immediately after EEG recording, but their EEGs which were recorded before clinical manifestations showed no seizure discharges. It is considered that the examination should be repeated and the induced sleep patterns should be recorded.

The infrequency of the special type of hepatocerebral disease in the Philippines may be due to the fact that this type develops after a considerably long period after infection with S. japonicum. The mean age of the 49 cases which we observed in the city area of Kofu was 53 (Hayashi et al.), suggesting that the length of the average span of life may also be related. In addition, the eating and drinking habits of the host and the differences in the pathological factors of the
strains of *S. japonicum* in the two countries may have to be taken into consideration. In this connection, we are presently examining the effect of *S. japonicum* on the cerebral and hepatic functions using cats with chronic infection with the Philippine and Japanese strains of *S. japonicum*. We expect to perform a regular survey later on, based on the results of the present preliminary survey, which will be able to shed light on the above mentioned problems.

**CONCLUSION**

Neurological and EEG examinations were performed on 75 of 307 cases with suspected cerebral schistosomiasis japonica among the inhabitants of the Palo district of Leyte in the Philippines.

The results obtained are as follows:

1. Of the 75 subjects, 71 (95%) had paroxysmal diseases, consisting of the Jacksonian type in 33, psychomotor seizures in 24, grand mal in 13 and autonomic seizures in 1. Each of the remaining 4 had cerebellar ataxia, hepatosplenomegaly, dysthyroidism and Korsakoff’s syndrome respectively.

2. Of the 71 with paroxysmal diseases, there were 49 with late onset seizures (onset after the age of 20) and 51 with frequent seizures (more than once monthly).

3. EEG was judged to be normal in 24 (32% per cent), borderline in 13 (17%) and abnormal in 38 (51%). The abnormal and borderline EEGs were characterized by the asymmetrical findings in the slow waves and by the mode of appearance of the main rhythm. There was no case with seizure discharges other than the paroxysmal slow waves.

4. Discussion was made in reference to the strong suspicion that the cerebral symptoms of the subjects, the paroxysmal diseases in particular, were a syndrome associated with *Schistosoma japonicum*. The difference between CSJ in Japan and that in the Philippines was also discussed.

**ACKNOWLEDGEMENTS**

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