[Jap. J. Parasit., Vol. 20, No. 2, 95-102, 1971]

Evaluation of Disease Activity in Cerebral Paragonimasis*

SHIN JOONG OH

Division of Neurology, University of Alabama School of Medicine
Veterans Administration Hospital, Birmingham, Alabama, U.S.A.
and
Department of Neurology, National Medical Centre;
Institute of Endemic Diseases,
Seoul National University
Seoul, Korea

(Received for publication; February 8, 1971)

Cerebral paragonimiasis is a major neurological problem in the Far East, especially in Korea. There are three distinct stages in the pathology of this disease; stage I: the meningoencephalitic form; stage II: the granulomatous form; stage III: the organization-calcification form (Oh, 1969a). The clinical features also vary according to the different pathological stages; meningitis in stage I; subacute encephalitis and tumorous symptoms in stage II; non-progressive neurological symptoms such as dementia, epilepsy, and hemiplegia in stage III (Oh, 1969a).

Because of this varying pathological and clinical feature, there has been confusion in the clinical management of patients. In my experience, the concept of "activity" has minimized this confusion and has been the convenient guideline in management of the cases. This concept of activity has not been advocated by the previous authors.

The purpose of this article is to elaborate the concept of activity, to test its validity by laboratory data, and to discuss its therapeutic implications.

Materials and Methods

Over a six year period (1958-1964), 62 patients with cerebral paragonimiasis were seen in the Department of Neurology, National Medical Centre, Seoul, Korea. Various aspects of this disease were reported by the present author in previous communications (Oh, 1967 a, b, 1968 a, b, c, 1969a, b).

In each case, a diagnosis of paragonimiasis was made on the basis of a positive complement fixation test, detection of *Paragonimus westermani* (P.W.) ova in the sputum, stool, and/or gastric juice, and detection of P.W. ova or worm in biopsy or autopsy materials.

Cerebral paragonimiasis was diagnosed by one or a combination of: (1) A positive complement fixation test in spinal fluid, (2) characteristic lesions on microscopic examination of biopsy or autopsy materials, (3) the characteristic radiological calcificationin the skull x-ray (type 4 calcification) (Oh, 1968c) and (4) the detection of eosinophils, abnormal colloidal gold reaction, abnormal routine spinal fluid findings in cases with concomitant neurological symptoms and pulmonary paragonimiasis. In these cases, other diseases were ruled out by various tests including pneumoencephalography, angiography, brain scan and electroencephalography.

The complement fixation tests were done at the Catholic Institute of Parasitology, Seoul, Korea, employing the essentially same method as the standard Kolmer's complement fixation test for syphilis (Gradwohl, 1956). The essential difference was the antigen used. Antigen used here was a

*Reprint Address: University of Alabama School of Medicine, Division of Neurology, 1919 Seventh Avenue South Birmingham, Alabama 35233 U.S.A.

1 : 4,000 veronal buffer saline extract of the adult worms of *Paragonimus westermani* worm (Chu and Lee, 1961). The dilution of serum and spinal fluid in the first tube was 1 : 10. The subsequent tubes were diluted by two fold dilution technique.

The test was positive in the serum when the reaction was more than 1 (+) at 1 : 10 dilution. However in the spinal fluid the reaction more than weakly positive (±) at 1 : 10 dilution was considered positive.

Paper electrophoresis for protein was done using the modified apparatus of the Sinu Durrum Cell, Whatmann No. 1 filter paper, barbital buffer with a pH of 8.6 and ionic strength of 0.06, and employing the method described by Henry *et al.* (1957). For concentration of spinal fluid protein, cellophane tube in 0.9% carbowax 6,000 saline solution was used as described by Ito (1961).

In retrospective analysis, our cases were labeled either "active" or "inactive" according to the following arbitrary criteria of activity :

(1) when there were definite signs of clinical progression by history and on examination : meningitic, tumorous, and subacute encephalitic form were included here (the majority of these patients showed abnormal spinal fluid findings) ;

(2) when there are definite abnormalities in the routine spinal fluid examination : protein, over 60 mg% ; lymphocyte, over 11 per mm^3 or polymorphs, over 1 ; sugar, below 40% of blood sugar ; chloride, below 119 meq./liter.

Using these arbitrary criteria, 25 cases were classified as "active" and 36 cases as "inactive". Average duration of disease in the "active" group was 29.9 months. Average duration in the "inactive" group was 7.6 years. This difference was statistically significant ($P<0.01$).

Various labortatory data were compared between two groups to test the validity of the arbitrary criteria of activity. In each test, the number of patients varied mainly because all of the tests were not performed uniformly in every case.

Results

Hematological findings : As noted in Table 1, abnormal hematological findings were noted in less than 50% of the cases of this disease investigated. Leukocytosis and elevated sedimentation rate were noted more commonly in the "active" group ; this difference is statistically significant ($P<0.01$).

Electrophoretic findings of serum protein : In this disease, the significant decrease of albumin, alpha one and beta globulin and increase of gamma globulin were noted as seen in Table 2 ($P<0.01$). Between "active" and "inactive" groups there was no difference.

Colloidal gold reaction in the spinal fluid : The Lange colloidal gold test was abnomal in 71.4% of 28 cases (Table 3). The most common abnormal curve was a mid-zone (tabetic) curve. Definite abnormal colloidal gold curve was mostly noted in the "active" group although three "inactive" cases had abnormal curves. A normal curve was never observed in the "active" group. The rate of abnormal colloidal gold curve in the "active" group is statistically significant ($P<0.01$).

Complement fixation test : Positive reaction was noted in 18 of 21 cases where serum was examined (Table 4).

Table 1 Hematological findings

	Active group	Inactive group	χ^2*	Total cases
Eosinophilia (above 7%)	62.7% (10/16)**	31.5% (11/32)	3.40	43.7% (21/48)
Anemia (Hgb. below 12 gm%	21.1 (4/19)	7.2 (3/39)	2.11	12.1 (7/58)
Leucocytosis (above 10,000)	52.9 (9/17)	16.7 (5/30)	6.67	30.0 (14/47)
Elevated sedimentation rate (above 20 mm/hr)	78.9 (15/19)	20.5 (8/39)	18.41	36.5 (23/58)

* Statistical test between active group and inactive group : $\chi^2=3.84$, $P<0.05$ and $\chi^2=6.63$, $P<0.01$.

** Number of cases with abnormality/number of cases examined.

Table 2 Electrophoretic findings in serum protein

	N	Total protein	Albumin	Alpha 1 globulin	Alpha 2 globulin	Beta globulin	Gamma globulin
Normal	20						
Mean			56.66%*	5.00%	7.48%	11.85%	19.12%
S. D.			4.35	1.56	1.6ε	2.25	2.65
Total cases	41						
Mean		7.52	52.15	3.80	7.38	9.59	26.50
S. D.		0.69	7.57	0.91	2.22	1.74	6.25
t**			2.49	3.81	0.18	4.38	4.15
Active group	12						
Mean		7.59	50.85	3.17	7.75	9.79	27.86
S. D.		0.68	8.13	0.47	2.10	1.51	6.96
Inactive group	29						
Mean		7.49	52.69	4.07	7.22	9.47	25.94
S. D.		0.72	7.48	1.03	2.30	1.88	6.22
t***		0.40	0.65	1.14	0.67	0.52	0.86

* % ; percentage of total protein
** Statistical test between normal and total cases of cerebral paragonimiasis. $t>2.39$, $P<0.01$.
*** Statistical test between active and inactive groups. $t>2.44$, $P<0.01$.

Table 3 Colloidal gold reaction findings in the Spinal fluid

	Active group (N15)	Inactive group (N13)	Total cases (N28)
Normal curve	0	8	8
Slightly abnormal curve	3	2	5
Abnormal curves	12	3	15
First zone curve	4	1	5
Mid-zone curve	6	2	8
Final zone curve	2	0	2

χ^2 value of abnormal curve between active and inactive groups is 9.23.

Negative reaction was seen in two cases without any active pulmonary or cerebral paragonimiasis and in one case with active pulmonary but inactive cerebral paragonimiasis. The difference between the rates of positive reaction between "active" and "inactive" groups was barely significant (χ^2-3.98).

Table 4 Findings of the complement fixation test in serum and spinal fluid

	Active group	Inactive group	Total cases
In serum : *	(N11)	(N10)	(N21)
Positive	11	7	18
Negative		3	3
In spinal fluid : **	(N12)	(N14)	(N26)
Positive	9	2	11
Negative	3	12	15

*χ^2 value of positive rates between active and inactive groups is 4.00.
**χ^2 value of positive rates between active and inactive groups is 9.63.

The reaction in the spinal fluid was positive only in 11 of 26 cases ; 9 "active" and 2 "inactive" cases. Being a specific test (Chung *et al.*, 1956a), it is not surprising that the very high correlation of positive

Table 5 Electrophoretic finding in the spinal fluid protein

	N	Albumin	Alpha 1 globulin	Alpha 2 globulin	Beta globulin	Gamma globulin
Normal	10	58.51%*	5.32%	7.73%	11.40%	17.41%
Total cases	12	56.85	4.00	4.65	14.67	17.67
Active group	3	44.86	3.73	4.63	9.66	37.00
Inactive group	9	60.96	4.09	4.67	16.33	13.45

*% is percentage of total protein.

rate was noted in the "active" group ($P<0.01$).

Electrophoretic findings of spinal fluid protein: This study was performed only in 12 cases (Table 5). There seems to be an increase of gamma globulin in the "active" cases and a slight increase of beta globulin in the "inactive" cases. Because of the small number of cases, a definite conclusion cannot be made.

Discussion

Hematological abnormalities are not commonly observed in pulmonary paragonimiasis. Bercovitz (1937) was impressed with the essentially normal blood picture in the pulmonary form of paragonimiasis. Leukocytosis was observed in cases with systemic or complicated paragonimiasis (Tillman and Phillips, 1948). Elevated sedimentation rate was also observed commonly in the complicated cases such as those with empyema or pleural effusion due to pulmonary paragonimiasis (Sadun and Buck, 1960).

Eosinophilia has been reported in cerebral paragonimiasis in the rates ranging from 50% (Lee *et al.*, 1958) to 80% (Sim 1964 a), of the cases. Yoon 1960). Nagano *et al.* (1959) reported cases of "leukemoid reaction of eosinophilia" in systemic paragonimiasis. Chang *et al.* (1958) reported leukocytosis in 26% and an elevated sedimentation rate in 70% of cases with cerebral paragonimiasis. These reports, including the present one, suggest that hematological abnormalities are much more common in cerebral paragonimiasis than in pulmonary paragonimiasis.

Our study further showed that leukocytosis and elevated sedimentation rate were predominately seen in "active" cases. However, these abnormalities could not be good indices to determine the activity of cerebral paragonimiasis since they are also observed commonly in complicated pulmonary and systemic paragonimiasis.

Electrophoretic study of serum protein in cerebral paragonimiasis has not been reported previously. In pulmonary paragonimiasis, Sadun and Buck (1960) reported a significant increase of gamma globulin with a consequent reduction in the albumin and in the other globulin fractions in their 49 cases. Our study showed similar changes in cerebral paragonimiasis. These changes therefore, reflect rather manifestation of paragonimiasis per se. In our experience, however, the marked increase of serum gamma globulin is helpful in supporting diagnosis of cerebral paragonimiasis against brain tumor.

Colloidal gold test run on the spinal fluid to aid in the diagnosis of cerebral paragonimiasis was highly valued by Mitzuno (1956) who found abnormal curves in 7 of 9 cases examined. The first zone (paretic) curve was most commonly seen in his series.

Our study also showed that there was definitely a high rate of abnormality in this disease. This was especially true in the "active" group. This indicates that this is one of the best non-specific tests in determination of activity. In cerebral schistosomiasis, 7 out of 10 cases had an abnormal curve (Kane and Most, 1948). A similar high rate of abnormality was also reported in cerebral

cysticercosis (Arseni, 1957). It would appear that an abnormal colloidal gold curve is a very common finding in cerebral helminth diseases.

The complement fixation test was first introduced by Ando (1921). Its value in the diagnosis of paragonimiasis and as a guideline in the treatment of this disease was well established by various authors (Chung *et al.*, 1956 b; Chu and Lee, 1961; Yokogawa *et al.*, 1962; Sadun *et al.*, 1959). One draw back to its use is that there is some degree of cross reaction with other trematode diseases such as clonorchiasis, schistosomiasis, or fascioliasis (Chung *et al*, 1956 a). Fortunately this difficulty is not a great problem in Korea since fascioliasis and schistosomiasis are reportedly non-existent and clonorchiasis can be easily ruled out by the concomitant intradermal test or by stool examination.

According to Chung *et al.* (1956 a, 1956 b), no cross reaction or false reaction was noted in the complement fixation reaction in the spinal fluid. 83% of his examined cases showed positive reaction, suggesting that this is a very specific test in the diagnosis of cerebral paragonimiasis. In our study, it was positive only in 43.3% of examined cases as a whole but in 81.1% of the active group. The difference in the results of the two studies may be explained in two ways: (1) it may be due to the different techniques used; Chung *et al.* (1956 a, 1956 b) used the dilution of 1:1 in the first tube and, (2) their cases may be mostly active according to our criteria of activity. Our study concludes that there is a high correlation between activity of the disease and positive complement fixation reaction in the spinal fluid. This test, therefore, can be used as a specific test in the determination of activity.

Electrophoretic study of the spinal fluid protein has not previously been reported. An increase of gamma globulin in the active group was suggested in our study but further study with more cases is needed to reach a conclusion.

Thus, our study concluded that our arbitrary criteria of activity is reasonably valid and that complement fixation test and colloidal gold test in the spinal fluid are helpful in determining the activity of cerebral paragonimiasis.

With this background, the following criteria of activity are formulated. Any case of cerebral paragonimiasis is active when one or more of the following criteria is met: (1) When there are definite signs of clinical progression noted by the history and seen on examination; (2) When there are definite signs of abnormalities in the routine spinal fluid; (3) When the complement fixation test in the spinal fluid is positive and (4) When the colloidal gold test in the spinal fluid is abnormal.

The concept of activity is in agreement with the pathological stage of this disease (Oh, 1969 a; Mitzuno *et al.*, 1952). In the author's opinion, the early meningoencephalitic stage and the intermediate granulomatous stage most often correspond to active cerebral paragonimiasis and the organization calcification stage to inactive cerebral paragonimiasis.

This pattern of early active and late inactive cerebral paragonimiasis is well expressed in the natural history of this disease, in which an early fulminating course is usually followed by a benign stationary one and the fatality occurs usually in the first few years of the disease.

It is also important to point out that acute exacerbation of symptoms is seen occasionally in benign stationary cases which are not treated early in the course of illness. Whether this is due to the reinfection from the primary active pulmonary paragonimiasis or due to the reactivation of already existing lesions in the brain is not clear. Probably the former would be more responsible. In such cases, treatment of pulmonary paragonimiasis would be vitally important. Whether acute exacerbation of the symptoms will occur in bithionol treated cases remains to be seen.

The guideline for treatment becomes clearer once activity is determined. Bithionol was reported to be effective in active cases,

especially in meningitic cases (Oh, 1967a; Sim *et al.*, 1964 b). Bithionol, therefore, is indicated in two categories of cerebral paragonimiasis: (1) Active cerebral paragonimiasis; and (2) inactive cerebral paragonimiasis with active pulmonary paragonimiasis.

In the former cases, prolonged and repeated therapy may be needed to get the maximum benefit but in the latter, one course of bithionol treatment is usually satisfactory (Oh, 1967 a).

In contrast, bithionol was not effective in inactive cases (Sim *et al.*, 1964b). Therefore, only conservative and supportive therapy is indicated.

One may argue that every untreated case has to be treated with bithionol in a fear of acute exacerbation in untreated inactive cases. The author does not recommend this empirical and blind approach since we are able to distinguish between two types by our criteria.

Craniotomy has been practiced without much review in the past. Our experience with craniotomy in 18 cases suggested that it is definitely indicated in "tumorous" cases but not in active cases. It could be detrimental as noted in our two fatal cases who had subacute encephalitic form and died post-operatively.

Since we have not performed the colloidal gold test and complement fixation test in every case, the present study has some limitations. In this respect, further evaluation of concept of activity is needed.

Summary

The concept of activity of cerebral paragonimiasis is a practical and convenient guide-line in the clinical management of patients. Four criteria are set for determination of activity: (1) The definite clinical and (2) spinal fluid signs of active cerebral lesions; (3) the positive complement fixation test in the spinal fluid; and (4) the abnormal colloidal gold curve in the spinal fluid.

Bithional is indicated in two conditions: (1) Active cerebral paragonimiasis; and (2) inactive cerebral cases with active pulmonary paragonimiasis. Conservative therapy is indicated in all inactive cases. Surgical therapy is only indicated in the "tumorous" cases.

The concept of activity is also discussed in relation to the histopathological stages and to the natural couse of the disease.

Acknowledgement

The author would like to express his gratitude to Prof. Shim Suck Hahn, Seoul National University College of Medicine for his steady encouragement in this study.

References

1) Ando, R. (1921): On the complement fixation reaction in the human paragonimiasis cases and in the experimental animals. Jap. J. Microb., 15, 391-404.
2) Arseni, C. (1957): Cysticercosis of the brain. B.M.J., 2, 494-47.
3) Bercovitz, Z. (1937): Clinical studies on human lung fluke disease (endemic hemoptysis) caused by *Paragonimus westermani* infestation. Am. J. Trop. Med., 17, 101-122.
4) Chang, H., Wang, C., Yu, C., and Fang, J. (1958): Paragonimiasis. A clinical study of 200 adult cases. Chin. M.J., 77, 3-9.
5) Chu, I., and Lee, O. H. (1961): The complement fixation test of paragonimiasis. Bull. of N.I.H. Republic of Korea, 4-16.
6) Chung, H., Hou, T., and Weng, C. (1956a): Further study on paragonimiasis complement fixation test and cross complement fixation reaction of sera of patients with paragonimiasis, clonorchiasis, and schistosomiasis to different trematode antigens. Chin. M. J,. 74, 207-222.
7) Chung, H., Hou, T., Li, T. Schen, M., and Yang, C. (1956b): Recent advances in diagnosis of paragonimiasis. Chin. M. J., 74, 1-16.
8) Gradwohl, R. B .H. (1956): Clinical laboratory methods and diagnosis. 5 th Edition. The C.V. Mosby Co. St. Lousi. 1956.
9) Henry, R. J., Gould O. J., and Soble, C. (1957): Some of the variables involved in the fractionation of serum protein by paper electrophoresis. Clin. Chem., 3, 46-63.
10) Ito, S. (1961): The practice of filter electrophoresis method of fraction of the protein in the spinal fluid. Rinsho Kensa, 5, 485-491.
11) Kane, C. A. and Most, H. (1948): Schisto-

somiasis of the central nervous system. Arch. of Neurol. and Psych., 59, 141-183.
12) Lee, C. K., Mok, D. S., and Kim, S. W. (1958) : Cerebral paragonsmiasis. Kor. Med. J., 3, 115-132.
13) Mitzuno, T., Siko, T., Inanaga, K. and Zimmerman, L. S. (1952) : Cerebral paragonimiasis, a neurosurgical problem in the Far East. J. of Nerv. and Ment. Dis., 116, 68-5714.
14) Mitzuno, T. (1956) : Colloidal gold reaction in the surgical brain diseases. Sinryo to Keiken, 43, 77-82.
15) Nagano, A., Takeuchi, M. Seki, J., Takeshita, Y., and Kurakata, T. (1959) : Ueber Eine Fall von eosinophilen Leukemoid Bei Paragonimiasis Cerebri. Yokohama Medical Bulletin., 10, 61-67.
16) Oh, S. J. (1967a) : Bithionol treatment in cerebral paragonimiasis. Amer. J. Trop. Med. Hyg., 16, 585-590.
17) Oh, S. J. and Jordan, E. J. (1967b) : Findings of intelligence quotient in cerebral paragonimiasis. Jap. J. Parasit., 16, 436-440.
18) Oh, S. J. (1968a) : Ophthalmological signs in cerebral paragonimasis. J. Trop. Geograph. Med., 20, 13-20.
19) Oh, S. J. (1968b) : Paragonimus meningitis. J. Neurol. Sci., 6, 419-433.
20) Oh, S. J. (1968c) : Roentgen findings in cerebral paragonimiasis. Radiology., 90, 292-299.
21) Oh, S. J. (1969a) : Cerebral and spinal paragonimiasis. A histopathological study. J. Neurol. Sci., 9, 205-236.
22) Oh, S. J. (1969b) : Cerebral paragonimiasis. J. Neurol. Sci., 8, 27-48.
23) Sadun, E. H., Buck, A. H., and Walton, B. C. (1959) : The diagnosis of paragonimiasis westermani using purified antigens in intradermal and complement fixation tests. Military Medicine., 124, 187-195.
24) Sadun, E. H., and Buck, A. H. (1960) : Paragonimiasis in Korea, immunodiagnostic, epidemiologic, clinical, roetgenologic and therapeutic studies. Am. J. Trop. Med. Hyg., 9, 562-599.
25) Sim, B. S. (1964a) : Cerebral paragonimiasis. J. Kor. Acad. Ped., 7, 3-9.
26) Sim, B. S., Chu, J. W., Chu, D. S., Yoon, K. C., Choi, K. S., and Suh, J. K. (1964b) : Clinical observation on the chemotherapy of cerebral paragonimiasis with bithionol. Kor. Central J. Med., 7, 757-764.
27) Tillman, A., and Phillips, H. (1948) : Pulmonary paragonimiasis. Am. J. Med., 15, 167-187.
28) Yokogawa, M., Tsuji, M. and Okura, T. (1962) : Studies on the complement fixation test for paragonimiasis as the method of criterion of cure. Jap. J. Parasit., 11, 117-122.
29) Yoon, D. (1960) : Paragonimiasis in children in Korea, related to the custom of ingesting raw crayfish for the treatment of measles. J. Ped., 56, 736-715.

脳肺吸虫症における病勢判断について

Shin Joong OH

Division of Neurology, University of Alabama School of Medicine
Veterans Administration Hospital, Birmingham, Alabama, U.S.A.
and
Department of Neurology, National Medical Centre;
Institute of Enkemic Diseases,
Seoul National University
Seoul, Korea

過去6カ年間にわたる62例の脳肺吸虫症患者についての諸種研究の結果，その病勢を判断する上における実際的かつ有用な指標として以下の4つの規準を設定することができた．すなわち（1）活動的な脳障害を思わせるような明確な臨床症状（2）髄液所見（3）髄液についての補体結合反応が陽性を示すこと（4）髄液についての異常な金ゾル反応等である．

ビチオノールは活動性の脳および肺の肺吸虫症に使用の適応がある．外科的治療が必要となるのは慢性の脳腫瘍を起こした場合に限られる．

尚上記の病勢についての考え方を病理組織学的な面および病気の進行と関連して考察した．