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REVIEW

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Ocular Gnathostomiasis: A Comprehensive Review

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Abstract

Gnathostomiasis is a food-borne zoonotic nematodiasis caused by the larval stage of *Gnathostoma* spp. The larvae preferentially migrate to the skin resulting in mobile cutaneous lesions, such as migratory panniculitis or serpiginous eruptions. The larvae occasionally migrate into the viscera, eyes and central nervous system causing serious complications. Ocular gnathostomiasis is rare with most cases being reported in local journals only. We conducted a comprehensive literature review of ocular gnathostomiasis. Most ocular gnathostomiasis cases are predominant in Japan, Thailand and Mexico, gnathostomiasis endemic areas. A significant number of cases have been reported from India, Sri Lanka and Bangladesh, where cutaneous gnathostomiasis is only rarely reported.

Keywords: *Gnathostoma*, gnathostomiasis, ocular

Introduction

Gnathostomiasis is a food-borne zoonotic nematodiasis caused by the larval stage of *Gnathostoma* spp. Infection in humans occurs by ingesting raw or undercooked fish, amphibians, reptiles, birds or mammals, all of which carry advanced third stage larvae (AL3) of *Gnathostoma* species and serve as second-intermediate hosts and/or paratenic hosts [1]. *Gnathostoma spinigerum* is the most common *Gnathostoma* species in Asia, but *G. hispidum*, *G. doloresi* and *G. nipponicum* have also been proven as causes of human gnathostomaisis in Asia [2]. In the Americas, *G. binucleatum* is the only proven *Gnathostoma* species causing human disease [4], although 7 *Gnathostoma* species have been described [3]. The disease is endemic mainly in the countries where people have a custom of consuming raw fish dishes. Therefore, Thailand, Japan and Mexico are known as the three major endemic countries [4]. Once ingested by humans, the *Gnathostoma* AL3 larvae preferentially migrate to the skin causing cutaneous lesions such as migratory panniculitis or serpiginous eruptions (cutaneous gnathostomiasis). The larvae occasionally migrate to unexpected sites such as visceral organs (visceral gnathostomiasis), eyes (ocular gnathostomiasis) and/or the central nervous system (neuro-gnathostomiasis) leading

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to serious complications. Ocular gnathostomiasis is rare. Most cases have been reported only in local journals. In an extensive English literature survey of gnathostomiasis by Rusnak and Lucy in1993 [5], there were only 20 ocular gnathostomiasis cases reported. In 2006, Lamothe Argumedo reviewed gnathostomiasis in Spanish-language journals and found 60 ocular cases reported [6]. With the present study, we carried out a comprehensive review of the literature to determine the current status of ocular gnathostomiasis in the world.

Search strategy and selection criteria

References for the review were identified through PubMed searches to August, 2010, using the following search string: ("gnathostoma" and "ocular") and ("gnathostomiasis" and "ocular"). Only studies that included ophthalmological manifestations of gnathostomiasis were selected. Studies were reviewed for their relevance by the present authors. The reference lists of all papers were checked for uncited cases. Additional searches in Japanese and Chinese language literature was performed using Japana Centra Revuo Medicina (JCRM: Ichushi), Google Scholar and iLib. Some case reports appearing in local journals in Thailand were obtained from the Library of the Ratchawithi Campus of Mahidol University, Bangkok, Thailand.

List of patients

We found a total of 73 cases of ocular gnathostomiasis reported starting with the first case reported by Rhitthibaed *et al* in 1937 [7] (Table 1). All 60 cases cited by Lamothe-Argumedo in 2006 [6] were included here (Table 1). Although 61 cases were listed in his review, one case was counted twice in two papers [9,10] so the actual number of cases should be corrected to 60. All 18 cases in Japan were cited and previously reviewed by Sasano *et al* in 1994 in Japanese [48]. During 1937-2005, we found an additional 6 cases not listed in the review by Lamothe-Argumedo [6]; 4 cases in Thailand [34,35,43,53] and 1 case each in Malaysia [49] and Taiwan (a Myanmar worker) [40].We also found 7 new cases from 2006 to the present; 3 cases each from Thailand [62,64,67] and India [65,66,68] and 1 case from Bangladesh [63].

Table 1 The list of ocular gnathostomiasis cases.

No.	Year	Sex	Age	Affected eye	Country*	Parasites**	References
1	1937	M	?	R	Thailand	Yes	7
2	1941	F	17	R eyelid	Thailand	Yes	8
3	1945	M	26	L	India	Yes	9, 10
4	1949	M	?	R	Thailand	Yes	11
5	1949	F	?	R	Thailand	Yes	11
6	1949	F	?	R	Thailand	No	11
7	1949	M	42	R	Japan	No	12
8	1949	M	36	R	Japan	No	12
9	1949	M	45	L	China	Yes	13
0	1949	M	35	L	China	Yes	14
11	1950	F	40	L	Israel	Yes	15
12	1950	M	32	R	Japan	Yes	16
13	1950	M	36	?	Japan (China)	No	17
14	1950	M	37	L	Japan (China)	No	18
15	1951	M	39	L	Japan (China)	No	19
16	1952	M	36	R	Japan (China)	No	20
17	1952	M	64	R and L	Japan	No	21

No.	Year	Sex	Age	Affected eye	Country*	Parasites**	References
18	1952	?	?	?	Japan	NA	21
19	1952	?	?	?	Japan	NA	21
20	1952	?	?	?	Japan	NA	21
21	1953	M	50	R	Japan	No	22
22	1955	M	34	?	Japan	Yes	23
23	1960	M	47	R	Japan	No	24
24	1960	M	28	L	Burma	Yes	25
25	1961	?	?	?	Bangladesh	Yes	26
26	1962	M	37	R	Thailand	Yes	27
27	1962	?	?	R	Japan	Yes	28
28	1968	M	48	L	Burma	Yes	29
29	1969	M	23	L	India	Yes	30
30	1969	F	32	R	India	Yes	30
31	1970	M	35	R	Bangladesh	Yes	31
32	1970	M	27	L	Mexico	Yes	32
33	1971	F	17	L	USA (Philippines)	Yes	33
34	1974	M	25	L	Thailand	Yes	34
35	1976	F	47	L	Thailand	Yes	35
36	1976	F	29	R	Cambodia	Yes	36
37	1978	M	50	R	Japan	Yes	37
38	1979	M	60	L	Japan	Yes	38
39	1981	F	22	L	USA (Malaysia)	Yes	39
40	1984	M	27	L	Taiwan (Myanmer)	Yes	40
41	1987	F	61	L	Thailand	Yes	41
42	1987	F	32	L	Thailand	Yes	41
43	1988	M	7	L	Mexico	Yes	42
44	1990	F	24	L	Thailand	Yes	43
45	1993	F	27	R	Mexico	Yes	44
46	1993	F	29	L	USA (Mexico)	Yes	45
47	1993	F	50	L	Bangladesh	Yes	46
48	1994	F	30	L	India	Yes	47
49	1994	M	24	R	India	Yes	47
50	1994	M	26	L	Japan	Yes	48
51	1998	M	47	L	Mexico	Yes	49
52	1998	?	?	?	Mexico	Yes	57
53	1999	M	32	L	Malaysia	Yes	49
54	1999	F	34	L	India	Yes	50
55	1999	F	41	R	India	Yes	51
56	2000	F	58	R	Canada (Bangladesh)	Yes	52
57	2000	M	49	R	Thailand	Yes	53
58	2001	M	37	L	Mexico	Yes	54
59	2001	F	15	L	Mexico	Yes	55
60	2002	M	39	R	Vietnam	Yes	56
61	2002	F	42	L	Mexico	Yes	57

No.	Year	Sex	Age	Affected eye	Country*	Parasites**	References
62	2003	M	57	L	Malaysia	Yes	58
63	2004	F	32	R	Mexico	Yes	59
64	2004	F	22	R	Mexico	Yes	59
65	2004	M	50	R	India	Yes	60
66	2005	F	39	R	India	Yes	61
67	2006	F	16	L	Thailand	Yes	62
68	2006	F	32	R	Bangladesh	Yes	63
69	2007	M	21	L	Thailand	Yes	64
70	2007	F	48	L	India	Yes	65
71	2007	F	32	L	India	Yes	66
72	2008	F	37	L	Thailand	Yes	67
73	2009	F	28	L	India	Yes	68

* Country name is based on where the patient was found and treated. The country names in parentheses are the places where the patient contracted the infection.

** In patients #26 and #62, the worm was found but not surgically removed, and in patients #67 and #69, the worm was removed from the eyelid.

Epidemiology

The geographical distribution of the 73 patients is comprised of 12 countries. Four countries had more than 10 cases each: Japan, Thailand, India and Mexico (Fig 1), while the other 8 countries had 5 or fewer cases. The majority of the cases, excluding 12 cases from Mexico and Israel, were in Asian countries or among immigrants from Asia: three cases in the USA were from the Philippines [33], Malaysia [39], and Mexico [45]; one case in Canada was from Bangladesh [52]; one case in Taiwan [40] was a Chinese Burmese working in Taiwan. All the immigrant cases were counted as being from their native countries.

Of the four countries with the most ocular gnathostomiasis cases, Japan, Thailand and Mexico have a custom of consuming raw fish dishes; thousands of human gnathostomiasis cases are reported from each of these countries [4].

However, India, Bangladesh and Sri Lanka, have not been considered as endemic for human gnathostomiasis since consumption of raw fish is not a common custom in those countries. Cutaneous gnathostomiasis is rarely reported from south Asia. We found no reported cases of gnathostomiasis from India, 1 case of cutaneous gnathostomiasis in a Bangladeshi woman from Germany [69] and 2 cases of cutaneous gnathostomiasis from Sri Lanka [70]. Considering only a few cutaneous gnathostomiasis cases have been reported from travelers returning from India/ Bangladesh [71], it seems likely cutaneous gnathostomiasis is underreported in south Asia, especially in India. As for the source of infection in India, water contaminated with cyclops harboring early 3rd stage larvae (EL3) is suspected; Indians do not usually consume uncooked fish but do drink natural water. Advanced 3rd stage larvae (AL3) in fish or other paratenic hosts are usually responsible for human gnathostomiasis [1,2,72], but EL3 in the cyclops may be responsible for the infection in India. Infectivity of EL3 to mammalians has been proven experimentally [73]. EL3 may disseminate more easily via the circulation to the eyes because of the smaller size than the AL3, similar to *Toxocara* larvae causing ocular toxocariasis. This possibility needs further experimental and epidemiological studies.

Clinical features, diagnosis and treatment

Of the 73 reported cases, 37 were males, 30 were females, but in 6 cases the gender was not specified. The average age of the patients was 35.5 years with a range of 7-64 years; the majority were aged 20-50 years (Fig 2). Except for one Japanese case in which both eyes were affected, the rest were unilateral with a ratio of side of eyes infected of L:R = 31:36 (7 unknown). The majority of patients complained of visual disturbances, such floaters or blurred vision. Most of the cases were treated by surgical removal of the parasite; a definitive diagnosis was made by detection of *Gnathostoma* larvae either from the anterior chamber or from the vitreous fluid. A history of having eaten fresh- or blackish-water fish is important suggestive evidence for a diagnosis. In cases where the larva was not available, serological detection with specific antibody by ELISA and/or Western blotting is helpful, although the causative species cannot be identified by such immunological methods.

Identification of parasites

The parasites obtained from the eyes of patients can be differentiated morphologically from other parasite larvae such as the metacestoda of *Taenia* sp [74], *Angiostrongylus* sp [75], or filarial larvae [76], which are occasionally found in human eyes. The majority of ocular gnathostomiasis cases reported from Asia were identifiedas *G. spinigerum*, except for one case from Japan [48] in which the extirpated larva was confirmed as AL3 *G. doloresi* by morphology. All the cases from Mexico were infected with *G. binucleatum*.

There were a few cases in which identification of the parasite was difficult or inaccurate. In a case report from Malaysia [58], the fundoscopic exam revealed a motile whitish nematode measuring 1-1.5 disc diameters in length in the inferior temporal quadrant; this was as *G. spinigerum*.

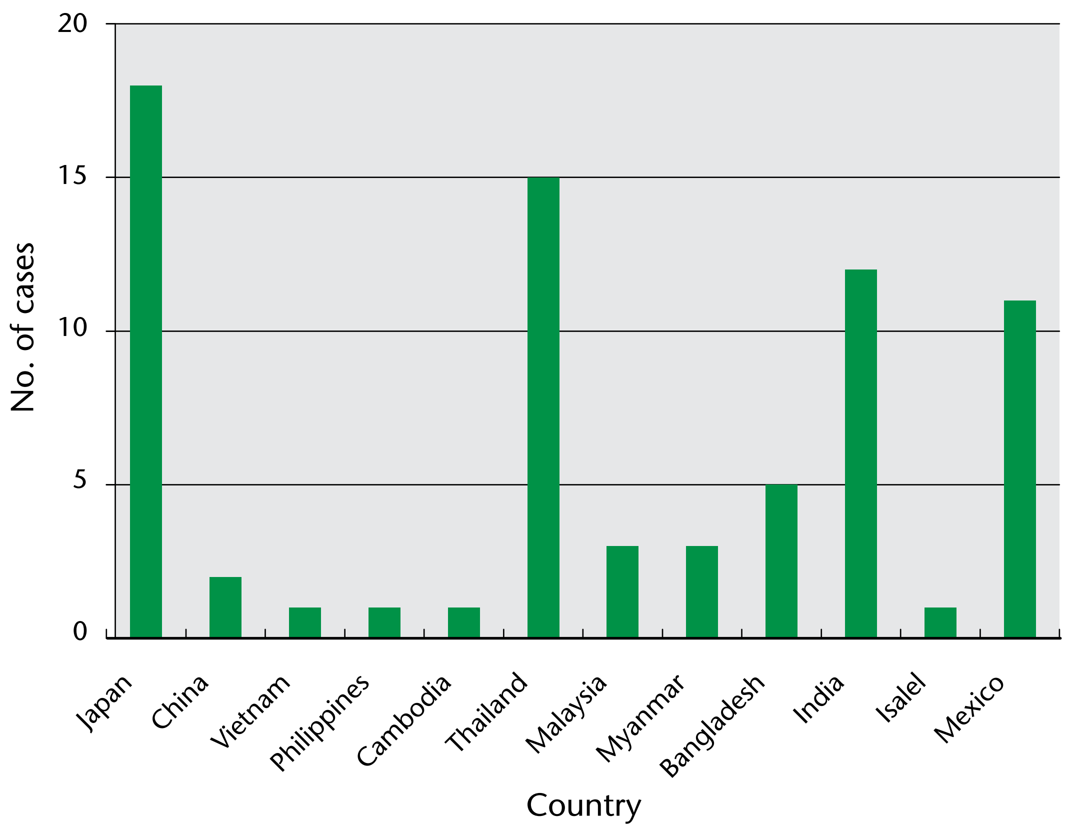

Fig 1 Cumulative number of ocular gnathostomiasis cases in each country.

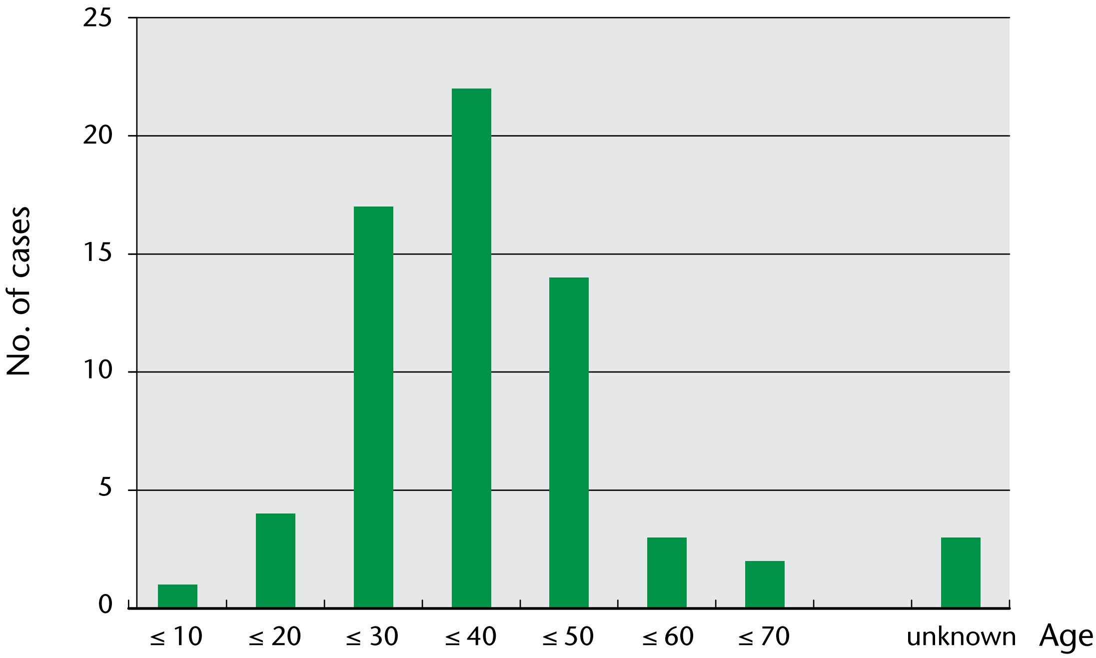

Fig 2 Age distribution of ocular gnathostomiasis patients.

However, in the figure provided with this case report, the parasite was extremely slender and had a string-like appearance with a length-to-width ratio of > 50. Such a string-like appearance is not consistent with *Gnathostoma* larvae, but rather resembles a juvenile *Angiostrongylus cantonensis*, which is often found in the eyes [75]. In a case report from Vietnam [56], the worm was no doubt the larva of a *Gnathostoma* species. However, most of the cephalic hooklets had irregular bases, similar to *G. doloresi*, but the number of cephalic hookets was the same as that of *G. spinigerum*. In that report, the authors tentatively identified the worm as an atypical larva of *G. spinigerum*. In southeast Asia, in addtion to *G. spinigerum* and *G. doloresi*, other *Gnathostoma* species, such as *G. vietnamicum* and *G. malaysiae*, have been reported [72], so the precise identification is unclear.

Another interesting but difficult identification was in a recent report from India [68]. In this report, the worm was no doubt the larva of *Gnathostoma* species, as seen by its typical head bulb with cephalic hooklets. It was identified as a male larva (L3) of *G. spinigerum*. The reported size of the larvae was approximately 1.5 to 2.0 cm in length, which is about the same size as an adult male *G. spinigerum*. The number of cephalic hooklet rows of this worm was reported to be five, which is unusual, except for 3 rows with *G. nipponicum*, all known *Gnathostoma* larvae have 4 rows of hooklets [72]. Unfortunately the figures provided with the report are not clear enough for further morphological analyse.

Conclusions

Ocular involvement is rare with gnathostomiasis. In this review, fewer than 20 cases per country were found, even in the most heavily endemic countries with human gnathostomiasis, such as Thailand, Japan and Mexico, where thousands of cumulated gnathostomiasis cases have been reported [4]. In addition to the previous 60 cases reviewed by Lamothe-Argumendo [6], we report 6 previously non-cited cases occurring before 2005 and 7 new cases eported during 2006-2010, to give a total number of reported ocular gnathostomiasis cases of 73. In one case from Malaysia [58], the identification of the larva is doubtful. If we remove this case from the list, the total number of ocular gnathostomiasis cases should be 72. All the cases listed in this review were obtained by literature survey, so there is bias due to unreported or undiagnosed cases. Interestingly, we found 13 ocular gnathostomiasis cases reported from India, where no cutaneous gnathostomiasis cases have been reported. This discrepancy needs some explanation. In general, the diagnosis and treatment of ocular gnathostomiasis is not difficult since the worm can frequently be removed surgically. However, in some cases, the identification of the worm is not easy, with some misidentification or uncertainty. Close collaboration between ophthalmologists and parasitologists is necessary to improve identification of this pathogen.

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