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Imported Katayama fever: Clinical and biological features at presentation and during treatment

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Summary *Objectives*: To investigate the characteristics of imported Katayama fever (acute schistosomiasis) as well as evolution and outcome under treatment.
Methods: Between April 2000 and September 2004, we included prospectively all patients with confirmed diagnosis of Katayama fever. Follow-up was maintained at least until 6 months after symptoms resolved. Praziquantel (PZQ) was given as soon as the diagnosis was probable, most of the time with steroids.
Results: Twenty-three patients were diagnosed with Katayama fever by *Schistosoma* egg detection and/or by seroconversion. Clinical features were non-specific, with mainly respiratory and/or gastrointestinal symptoms. Diagnosis was confirmed at presentation in 17/23 (74%) patients, of whom 15 by serology. Immediate clinical exacerbation occurred in five of nine patients not given steroids concomitantly with PZQ. After initial resolution, fever recurred in five (22%) patients. When compiling initial and recurrent episodes ($n=28$), respiratory symptoms tended to occur at an earlier stage after exposure, while abdominal complaints were more frequent later. All patients were completely cured, sometimes after repeated treatments.
Conclusions: Clinical presentation of Katayama fever is non-specific and involves respiratory and abdominal symptoms. Recurrence of fever is not unusual despite anti-helminthic treatment. Optimal therapeutic strategy remains to be defined to prevent recurrence.

Introduction

Katayama fever (or acute schistosomiasis) occurs as an early manifestation of infection with

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Schistosoma species, in non-immune individuals exposed to cercariae-infested water in endemic regions. This syndrome is characterized by an acute febrile stage, often associated with pulmonary and/or abdominal symptoms, and may develop 2–10 weeks after the initial infection. Because fever is not always present, some experts find more appropriate to call Katayama syndrome all clinical manifestations associated with acute schistosomiasis, including also angio-oedema, respiratory symptoms and even fatigue. The symptoms of Katayama are thought to be due to an allergic reaction to various antigens released during larval migration and early oviposition, with production also of circulating immune complexes.[1,2] Symptoms are often mild and transient, and the syndrome may go unrecognized in settings unfamiliar with tropical pathology.[3] In some cases, the illness follows a more severe clinical course.[4–6] Many outbreaks among tourists returning from endemic areas have been reported in the last decades, reflecting probably the increase of exposure to freshwater during outdoor activities. Most publications described clusters of patients with Katayama from a single location of infection.[2,4–12] Optimal therapy of Katayama fever remains controversial, and evolution and outcome under treatment are poorly documented. We report on all patients diagnosed with Katayama fever during a 4.5-year prospective study on imported fever.

Patients and methods

From April 2000 onwards, all patients presenting with fever ($\geq$38 °C) and attending the in- or outpatient departments of the Institute of Tropical Medicine, Antwerp (ITMA) and of the University Hospital, Antwerp (UHA) are included in a prospective study investigating the aetiology of febrile diseases after a stay in the Tropics. All patients with a confirmed diagnosis of Katayama fever until September 2004 were further analysed for this presentation. Diagnosis of Katayama fever was confirmed when a febrile disease (study inclusion criterion) was associated with eosinophil count $>500/mm^3$ and with parasitological and/or serologic evidence of *Schistosoma* sp. infection at first presentation or during follow-up, after recent primary exposure with fresh surface water in an endemic region.

For all included patients, we recorded prospectively their history, symptoms, signs and laboratory findings at presentation, as well as relevant information regarding response to treatment and outcome. Follow-up was extended until at least 6 months after clearing of symptoms.

Concentration methods were used for egg detection in faeces and urine. Urine concentration method consisted in centrifugation of 20 ml urine after discarding supernatant, in 40–80 ml of urine sample left to stand for >1 h. Stool samples were examined by mean of the SAEX method (xylol–acetic acid extraction) after homogenization of 5 g faeces in 45 ml 1% formol–saline solution.

Two methods were used for serological testing: (1) In house enzyme-linked immunosorbant assay (ELISA), using a *S. mansoni* egg antigen extract, mixed with *S. mansoni* adult worm extract, imported from Egypt, and (2) indirect hemagglutination (IHA), using a *S. mansoni* adult worm extract (commercial test, Fumouze SA, France), with titration and cut-off at 1/80 (positive at $\geq$1/160). Sensitivity and specificity of these tests have been described elsewhere.[13] Sensitivities of the IHA test at this cut-off value in detecting chronic *S. mansoni* infection, chronic *S. haematobium* infection, and clinical Katayama fever are 88, 80 and 70%, respectively, with a specificity of 99%. Reported sensitivities of the ELISA test are, respectively, 93, 92 and 50% with a specificity of 98%. Combination of both IHA and ELISA tests gives sensitivities of 99, 96 and 80%, respectively, with also a high specificity (97%).

Treatment consisted in at least a single oral dose of praziquantel (PZQ) at a dosage of 40 mg/kg/day, associated in severe cases (at physician's discretion) with methylprednisolone 0.5 mg/kg/day during at least 3 days. A second course of PZQ was administered systematically after 1–2 months, to eradicate any residual schistosomes after maturation.[3]

Statistical analysis was performed with the SPSS program, version 12.0 (SPSS Inc., Chicago, IL, U.S.A.). Differences were compared using Student's *t*-test or Mann–Whitney *U*-test, when appropriate, for continuous outcomes, and chi-squared and Fisher's exact tests for categorical outcomes. *P* values of less than 0.05 were considered to indicate statistical significance.

Results

Epidemiology

Among the 1640 fever episodes included during the study period, 28 (1.7%) were due to confirmed Katayama fever, and occurred in 23 patients (18 males and five females). Five episodes were

due to recurrence of Katayama fever after the initial episode had subsided. All patients were native of European countries (22 travellers and one expatriate), with a mean age of 31 years (range: 18–52 years). Countries of infection were all located in sub-Saharan Africa (Table 1). Mean delay between exposure and onset of fever was 4.5 weeks (range: 1.5–9 weeks). During the same study period, six other patients, including companions of travel of confirmed cases, presented with fever and eosinophilia after recent primary exposure to fresh water in endemic areas, and had no evidence of alternative helminthic infection. Since diagnosis of Katayama fever could not be confirmed (two had no paired sera, and four did not seroconvert within 6 months), they were not included in this presentation.

Features at presentation

Median delay between onset of fever and consultation at the ITMA or UHA was 7 days (range: 1–40 days). Before consultation, 10 patients had first consulted another physician, but only two were directly referred. Six patients had previously received inadequate treatment (anti-malarials and/or antibiotics).

At the first visit, all 23 patients reported fever (=entry criterion) and most (18/23, 78%) reported also headache and/or myalgia. Half of the patients (12/23, 52%) had respiratory complaints (cough and/or dyspnoea and/or wheeze). Abdominal pain, nausea/vomiting and diarrhoea were less frequently reported, but at least one of these symptoms was present in 10 (43%) patients. High grade fever ($\geq 39\,^{\circ}C$) was rather uncommon. Urinary complaints (mictalgia, hematuria) were mentioned by only two (9%) patients (Table 2).

Laboratory examination was performed within 3 weeks after onset of fever in all but one patient. At presentation, mean eosinophil count was 2637/μl (range: 840–10 340/μl). Almost all patients had an eosinophil count $\geq 1000/\mu l$, and nearly half had $\geq 2000/\mu l$. Other abnormal laboratory findings are reported in Table 2. Chest X-rays were performed in all 12 patients with pulmonary symptoms, but lung infiltrates were detected in only three of them. Abdominal ultrasonography was performed in all patients presenting with gastrointestinal and urinary complaints ($n=12$), but revealed few abnormalities (splenomegaly in two, and hepatomegaly in one).

Table 1 Katayama fever: Regions of exposure ($n=23$)

	n	%
West Africa	11	48
East Africa	5	22
Central Africa	4	17
Southern Africa	3	13
Total	23	100

West Africa: Mali (5); Senegal (5); Ghana (1). East Africa: Kenya (2); Tanzania (2); Ethiopia (1). Central Africa: Republic Democratic of Congo (4). Southern Africa: Malawi (1); Zambia (1); Mozambique (1).

Diagnostic procedure

At presentation, diagnosis of Katayama was confirmed by egg detection in five patients (*S. haematobium*=2; *S. mansoni*=3, with an incubation time of 5–10 weeks), and by serology only in 12 other patients (both IHA and ELISA in six; IHA only in six). Seroconversion occurred in six additional cases within 4 weeks after the first contact (both tests in five, and IHA only in one). One patient diagnosed with *S. mansoni* infection by egg detection did not seroconvert within 6 months. At presentation, four patients were diagnosed concomitantly with another infection (*Shigella flexneri*=1, *Campylobacter jejuni*=1, *Giardia lamblia*=1, *Chlamydia trachomatis*=1).

Treatment and outcome

Two patients required immediate hospitalization for high fever and dyspnoea. Patients were given PZQ as soon as the diagnosis became likely, and after concomitant infections were adequately treated, within 1 week after presentation for 16 of them, and within 2 weeks for all 23. Steroids were administered the same day as PZQ in 14 (61%) patients, and none of them experienced exacerbation of the Katayama symptoms during the following days. In contrast, clinical condition worsened immediately in five of the nine remaining patients who preferred to defer the steroids ($P=0.018$). Three of them required steroids on the 2nd or 3rd day of PZQ treatment, but none had to be hospitalized.

Fever recurred in five of 23 (22%) patients after the initial episode subsided. It occurred 1–8 weeks after steroids were interrupted (mean interval=3.5 weeks), corresponding to 7–15 weeks after exposure (mean=10 weeks). All five patients were diagnosed with recurrence of Katayama fever. All had fever $<39\,^{\circ}C$, abdominal pain and/or nausea/vomiting, and eosinophils $\geq 1000/\mu l$, but none reported cough or dyspnoea. In comparison with first and/or single

Table 2 Symptoms, physical findings, and laboratory investigations at initial presentation ($n=23$) and at recurrence ($n=5$) of Katayama fever

	Initial presentation ($n=23$)	Recurrent episode ($n=5$)	*P*
Signs and symptoms			
Myalgia	17	5	NS
Headache	13	3	NS
Cough	12	0	NS (0.052)
Abdominal pain	8	4	NS
Fever ≥ 39 °C	8	0	NS
Nausea/vomiting	5	4	0.026
Diarrhoea	5	2	NS
Dyspnoea	3	0	NS
Urinary symptoms	2	0	NS
Wheeze	2	0	NS
Splenomegaly	2	1	NS
Hepatomegaly	1	0	NS
Laboratory findings			
WBC $\geq 10\,000/\mu l$	9	1	NS
Eosinophils $\geq 2000/\mu l$	10	2	NS
Raised ALT (>70 IU/l)	5	2	NS
Raised LDH >670 IU/l (21/28 tested)	10	2	NS
CRP >1 mg/100 ml	18	3	NS

Katayama presentation, prevalence of cough and nausea/vomiting differed at the time of recurrence (Table 2). Also, if these recurrent episodes were included in the analysis ($n=28$ episodes), Katayama fever occurring within 6 weeks after exposure tended to present more often with respiratory complaints, while gastrointestinal symptoms predominated later (Table 3).

One patient with recurrent fever had to be admitted. All five patients required a second course of steroids and all were given a supplementary dose of PZQ. They all reported a protracted fatigue lasting for more than 3 months, in contrast with two of 18 patients without recurrent flare ($P<0.001$). One patient experienced two additional recurrent episodes within 3 months after the first one, flaring up each time steroids were discontinued.

No clinical or biological features at first presentation (fever ≥ 39 °C, eosinophil count, delay before onset of symptoms, delay before treatment, use of steroids) could predict subsequent recurrence, apart from a significant rise in mean eosinophil count within 3–4 weeks after the initial treatment ($+3377/\mu l$ vs. $+261/\mu l$ in Katayama patients who did not recur; $P=0.015$). However, these data were not available for all patients (3/5 vs. 7/18).

Discussion

Most publications on imported Katayama fever have described outbreaks of schistosomiasis from a single source, in homogenous groups of travellers, where active tracing of patients was triggered by an index case.[2,9,10,12] This study presents prospective data on features and outcome of 28 confirmed

Table 3 Main symptoms according to delay after exposure, for initial episodes only ($n=23$) and for all episodes ($n=28$)

	Initial episodes only ($n=23$)			All episodes, including recurrences ($n=28$)		
	≤ 6 Weeks ($n=14$)	>6 Weeks ($n=9$)	*P*	≤ 6 Weeks ($n=14$)	>6 Weeks ($n=14$)	*P*
Respiratory complaints[a]	9	3	NS	9	3	NS (0.054)
Gastrointestinal symptoms[b]	4	6	NS	4	11	0.021

[a] Cough and/or dyspnoea and/or wheeze.
[b] Abdominal pain and/or nausea-vomiting and/or diarrhoea.

Katayama fevers occurring in 23 travellers, being one of the largest series of sporadic imported cases.

As reported elsewhere, schistosomiasis is nowadays almost exclusively acquired in sub-Saharan Africa.[14,15] In our experience, Katayama fever ranks third among febrile tropical diseases occurring in travellers returning from Africa, after malaria and rickettsial infections.

In other series describing patients with Katayama syndrome, fever is not universally considered as a defining criterion. In this study, clinical presentation may be more severe because we have limited inclusion only to patients presenting with fever as well. The percentage of patients developing Katayama fever after primary infection with *Schistosoma* sp. remains imprecise, ranging from 50 to 90%.[2,9,12,16] Probably at least 30% remain asymptomatic after primary infection, but when symptoms develop, fever is a prominent feature in most series.[2,3,10,17,18]

Katayama symptoms are usually mild, transient and non-specific. Diagnosis is easily overlooked when exposure is not properly considered. Dry cough is often reported, mimicking a minor respiratory tract infection or a flu-like illness. Diffuse abdominal pain is another frequent but non-specific complaint. In addition, physical examination contributes little. Hypereosinophilia ($>1000/\mu l$) is the key element towards diagnosis and must trigger appropriate investigations in exposed patients.

Definite diagnosis of Katayama fever relies on detecting *Schistosoma* sp. eggs or antibodies in previously unexposed patients. However, these may not be detectable at the time of the first contact, as it takes a few weeks before oviposition and seroconversion to occur. Therefore, a careful follow-up is required. As such, in this study, only confirmed cases were included and diagnosis was established by serology (IHA with or without ELISA) in the majority (65%) of the patients at first presentation, and by ova detection in only 22% (Table 4). Seroconversion was observed in the 6 (26%) additional cases within 4 weeks, but failed to occur within 6 months in one treated patient whose diagnosis was initially confirmed by egg detection in faeces. This may be due to the sub-optimal sensitivity of IHA to detect clinical Katayama fever, estimated at around 70–80%,[13] or to early parasitic elimination following treatment with PZQ. Of note, ELISA was of no additive value to IHA (no case detected by ELISA only), probably because ELISA contains mainly egg antigen rather than adult worm antigen.

Although this strategy is controversial, PZQ was given as soon as the diagnosis of Katayama was likely. PZQ is highly effective against adult schistosomes, but less so against immature schistosomules. There are no evidence-based recommendations for optimal treatment. Some experts advocate to delay PZQ treatment after the acute phase resolves and all larvae have matured in adult worms, while suppressing the symptoms with steroids if needed.[2] Other teams recommend earlier use of PZQ to decrease the worm load, and thus symptoms related to oviposition, as well as to reduce the risk of erratic localization. In this option, concurrent

Table 4 Results of diagnostic tests according to onset of fever and exposure

Delay after onset of fever (weeks)	1 ($n=12$)	2 ($n=6$)	3 ($n=3$)	>3 ($n=1$)	Total ($n=23$)
Egg *S. haematobium* in urine (22 tested)	1	0	1	0	2
Egg *S.mansoni* in faeces (20 tested)	0	2	0	1	3
IHA $\geq$160 (22 tested) 1st visit (seroconversion during follow-up)	8	3 (1)	3	1 (5)	15 (6)
ELISA+(22 tested) 1st visit (seroconversion during follow-up)	4	2 (1)	2 (1)	1 (5)	9 (7)

Delay between exposure and consultation (weeks)	3-4 ($n=4$)	5 ($n=3$)	6 ($n=7$)	7 ($n=4$)	8 ($n=3$)	>8 ($n=2$)	Total ($n=23$)
Egg *S. haematobium* in urine (22 tested)	0	1	0	0	0	1	2
Egg *S. mansoni* in faeces (20 tested)	0	1	1	0	1	0	3
IHA $\geq$160 (22 tested) 1st visit (seroconversion during follow-up)	2	1 (1)	4	4 (1)	3 (1)	1 (3)	15 (6)
ELISA+(22 tested) 1st visit (seroconversion during follow-up)	1	1 (1)	2 (1)	2 (1)	2 (1)	1 (3)	9 (7)

administration of steroids is recommended to avoid clinical deterioration, to be followed by a second course of PZQ after 2–3 months to eradicate any surviving schistosomes.[3] Our findings confirm that PZQ-triggered exacerbation occurs frequently (56%) in patients not given steroids concomitantly,[19–21] while patients immediately treated with steroids were probably those with more serious symptoms. As observed here, dual infections are not unusual in travellers; therefore, other pathogens, especially strongyloidosis and bacterial disease, should be excluded before starting steroids. The place of artemether, recently found to be effective against schistosomules and in a lesser extent against adult schistosomes, is not yet defined in the treatment of acute schistosomiasis.[22,23]

Nearly one quarter of all patients experienced a recurrent fever episode after initial symptoms resolved and this was independent of steroid co-treatment. To our knowledge, very few series ever mentioned such a phenomenon.[2,5,16] The precise immunopathogenesis of acute schistosomiasis is not yet fully elucidated. In contrast with chronic schistosomiasis, the worm burden (estimated by egg counts) is poorly correlated with disease severity.[4,6,18,24] Host reactivity plays an important role, through a variety of mechanisms. Clinical manifestations of the acute schistosomiasis involve type I (immediate hypersensitivity) reactions against antigens produced by the parasites and the ova, as reflected by the high levels of eosinophils and IgE, as well as type III (serum sickness-like) reactions, as confirmed by elevated levels of circulating immune complexes.[17,18,25] A transient control of these immuno-allergic reactions by a too short course of steroids is a possible explanation for some early recurrences but not for other cases which recurred up to 2 months later. Another plausible reason may be an insufficient larval eradication due to the sub-optimal efficacy of PZQ, possibly even decreased by the concomitant administration of steroids lowering its blood concentration.[26] Differences in clinical manifestations between initial and recurrent episodes as well as early and late Katayama might be due to changing larvae localization or reflect an immune reaction to different larvae/adult worm/egg antigens. At this stage, concomitant enteric pathogens were not observed any more and did not influence the clinical presentation. Our observation suggests that Katayama symptoms may evolve according to schistosome maturation even in the same patients. Katayama with predominant pulmonary symptoms has been already observed early after exposure.[4,12] Predominance of abdominal symptoms in late onset Katayama and in recurrent episodes has not been clearly mentioned so far.

No single clinical or biological feature at presentation was of any value to identify patients at risk of recurrent course. Though this was not measured in all patients, an increasing eosinophil count within 1 month following PZQ treatment was predictive for such a complicated course, but the sample was too small to allow definite conclusions.

Treatment of recurrent Katayama is not defined. We administered empirically a prolonged course of steroids and an additional PZQ treatment. Fever did not recur, except in one patient, but protracted fatigue was constantly noted.

In conclusion, Katayama fever has protean and non-specific manifestations, leading to frequent misdiagnosis. Although self-limiting, its course is incapacitating and sometimes severe, giving sense to early aetiological treatment. In this therapeutic option, steroids should be systemically associated to avoid clinical exacerbation. For reasons yet unclear, recurrence of Katayama symptoms is not unusual after standard PZQ treatment, and complicates the medical management. Clinical features are rather different than in initial presentations. A rising eosinophil count within 3–4 weeks after the anti-helminthic treatment might predict recurrent course. Further studies are also needed to define the optimal treatment options.

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