

Cercarial Dermatitis, a Neglected Allergic Disease

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Abstract Cercarial dermatitis (swimmer's itch) is a common non-communicable water-borne disease. It is caused by penetration of the skin by larvae (cercariae) of schistosomatid flukes and develops as a maculopapular skin eruption after repeated contacts with the parasites. The number of outbreaks of the disease is increasing, and cercarial dermatitis can therefore be considered as an emerging problem. Swimmer's itch is mostly associated with larvae of the bird schistosomes of *Trichobilharzia* spp. Recent results have shown that mammalian infections (including man) manifest themselves as an allergic reaction which is able to trap and eliminate parasites in the skin. Studies on mammals experimentally infected by bird schistosome cercariae revealed, however, that during primary infection, parasites are able to escape from the skin to the lungs or central nervous system. This review covers basic information on detection of the infectious agents in the field and the clinical course of the

disease, including other pathologies which may develop after infection by cercariae, and diagnosis of the disease.

Keywords Cercariae · Cercarial dermatitis · Schistosomes · *Trichobilharzia*

Introduction

Cercarial dermatitis is a water-borne allergic disease caused by penetration of human skin by larvae (cercariae) of schistosome flukes. The infection manifests as a strong maculopapular skin eruption which is accompanied by intensive itching. In a temperate climate, cercarial dermatitis is a seasonal disease which is diagnosed mainly during summer months when both the release of cercariae from snails and the number of people swimming in natural waters reach peak levels [1].

Schistosome flukes are characterized by a two-host life cycle (Fig. 1). The free-swimming cercariae develop in and are released from various aquatic or amphibious snails (intermediate hosts), and after they penetrate into the skin of specific (compatible) definitive hosts (birds and mammals, including man), they develop to adult flukes producing eggs which are released to the external environment. Schistosome cercariae are also able to penetrate the skin of non-compatible accidental hosts (e.g. the infection of humans by bird schistosomes), in which they die early after the infection.

Except for Antarctica, the disease is reported from all around the world. Usually, it is recorded from land lakes, and cercariae of avian schistosomes are the most-reported causative agent. However, cercarial dermatitis can be acquired also in the sea or brackish waters, and recent findings of new genera and species indicate there is a broad spectrum of causative agents of the disease with different life cycles, host specificity and pathogenicity.

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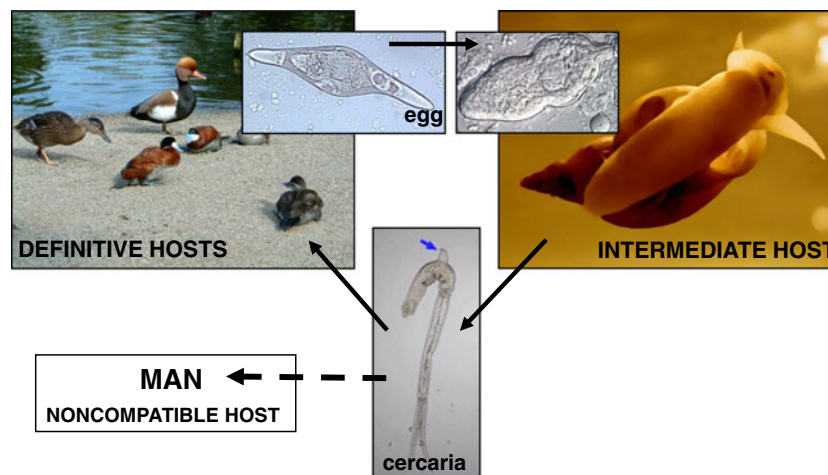


Fig. 1 Life cycle of bird schistosomes: In definitive hosts (mostly waterfowl), the parasite matures and produces eggs which are released in host excrements. When the eggs get to water, larva (miracidia) hatch and actively search for specific intermediate hosts. Within these hosts,

a complex of larval development ending by release of larvae (cercariae) takes place. Free-swimming cercariae are able to wait for a vertebrate host in typical (resting) position, during which they are fixed by a ventral sucker (blue arrow) to the water surface

The Causative Agents of Cercarial Dermatitis

The symptoms of cercarial dermatitis were first described in Japanese rice planters by Fujii in 1887 [2]. The causative agent—schistosome cercariae—was recognised by Cort in 1928 in North America [3]. Soon, the disease was reported in the UK [4] and France [5] and since then has been noted in many other countries and described under different names, e.g. *zerkarien-dermatitis* [6], *dermatite des nageurs* [5], *bouton de canicule des baigneurs* [7], *kabure itch* or *koganbyo* [2], *sawah itch* [8] and *water mange* [9]. The most common name at present, swimmer's itch, was used for the first time by Christensen and Green [10]; direct translation of the term is frequently used in other languages, e.g. *sundmannakláði* in Icelandic [11].

Cercariae of the majority of known genera of schistosomes develop in specific freshwater snails (Table 1). *Bilharziella* Looss, 1899, *Jilobilharzia* Liu et Bai, 1976, and *Trichobilharzia* Skrjabin et Zakharrow, 1920, then mature in birds, while the definitive hosts of *Heterobilharzia* Price, 1929, *Schistosoma* Weiland, 1858, *Orientobilharzia* (syn. *Schistosoma*), Dutt et Srivastava, 1955, and *Schistosomatium* Tanabe, 1923, are mammals. The larval development of avian schistosomes of *Austrobilharzia* Johnston, 1917, and *Ornithobilharzia* Odhner, 1912, takes place in salt or brackish waters; larval stages of various species of *Gigantobilharzia* Odhner, 1910, were found in marine, brackish and freshwater snails.

At present, *Trichobilharzia* cercariae are frequently recognised as the causative agent of cercarial dermatitis, and the fact that the parasite life cycles are dependent on freshwater snails explains why cercarial dermatitis is commonly associated with swimming in land lakes all over the world. However, outbreaks reported from salt/brackish waters were also reported

(Table 1), and they were mostly associated with cercariae of the genus *Austrobilharzia* Johnston, 1917, but representatives of the other genera such as *Ornithobilharzia* Odhner, 1912, and *Gigantobilharzia* Odhner, 1910, might be of similar importance [12]. The definitive hosts of all of these flukes are various species of birds. The intermediate hosts of the bird schistosomes of *Allobilharzia* Kolářová, Rudolfová, Hampl et Skírnisson, 2006, *Dendrobilharzia* Skrjabin et Zakharrow, 1920, and of the mammalian genera of *Macrobilharzia* Travassos, 1922, and *Bivitellobilharzia* Vogel et Minning, 1940, are still unknown.

Cercariae (Fig. 2a) do not feed, and therefore, their life-span is short; for European *Trichobilharzia szidati*, about 1–1.5 days at 24 °C [13]. The larva is composed of the body and tail with furcae; the total length is about 1.2 mm. In the first half of the body of bird schistosomes, e.g. of *Trichobilharzia* sp. and *Bilharziella* sp., two pigmented spots are present. The anterior end is occupied by a head organ which contains ducts (=cellular projections) and openings of the glands (of which the most visible are two pairs of circum- and three pairs of post-acetabular penetration glands). They are able to actively find and penetrate into the skin of various vertebrates and cause cercarial dermatitis.

Studies on the host-finding behaviour of schistosome cercariae revealed that the parasites exhibit a wide range of behavioural adaptations which are used for recognition of and invasion into vertebrate skin. Positive phototactic and negative geotactic behaviour, response to shadow, water turbulence and temperature are characteristic patterns in *Trichobilharzia ocellata*/*T. szidati*. Cercariae are also able to respond to some compounds released by vertebrate skin [14–16]. Chemo-orientation of cercariae of *T. szidati* and *Schistosoma mansoni* induces movement towards and attachment to the host skin, prolongs contact with the skin,

Table 1 The time course of development of cercarial dermatitis during initial infection and reinfections in humans primarily infected or sensitized by previous contact with the cercariae of bird schistosomes, respectively

Genus	Distribution	Intermediate host	Definitive host
Freshwaters			
<i>Heterobilharzia</i> ^v	North America	Pulmonata	Carnivores, rodents
<i>Orientobilharzia</i> ^v	Asia, Europe ^b	Pulmonata	Subungulates, carnivores
(Syn. <i>Schistosoma</i>) ^{v, a}		Pulmonata,	Mammals, including man
<i>Schistosoma</i> ^{vn, a}	Cosmopolitan	Prosobranchia	
<i>Schistosomatium</i> ^v	North America	Pulmonata	Rodents
<i>Bilharziella</i> ^{v, e, a}	Northern Hemisphere	Pulmonata	Birds
<i>Trichobilharzia</i> ^{vn, e, a}	Cosmopolitan	Pulmonata	Birds
<i>Jilobilharzia</i> ^v	Asia	Pulmonata	Birds
Salt or brackish waters			
<i>Austrotilharzia</i> ^{v, a}	Cosmopolitan	Prosobranchia	Birds
<i>Ornithobilharzia</i> ^{v, e}	Northern hemisphere	Prosobranchia	Birds
<i>Gigantobilharzia</i> ^{v, e, a}	Cosmopolitan	Pulmonata	Birds
		Opisthobranchia	
Complete life cycle unknown			
<i>Bivitellobilharzia</i> ^v	India, Africa?	Unknown	Elephants
<i>Allobilharzia</i> ^v	Northern hemisphere	Unknown	Birds
<i>Dendrotilharzia</i> ^v	Cosmopolitan	Unknown	Birds
<i>Macrobilharzia</i> ^v	Cosmopolitan ^b	Unknown	Birds

The disease can be caused by visceral as well as nasal schistosomes, and depending on the species, acquired in fresh-, brackish or salt waters. Therapy is only symptomatic: in mild cases, abirritant powders, and in serious cases, systemic antihistaminics (tablets or better in gels) or mild corticosteroids should be considered

^a Cercariae were confirmed as the causative agent of human infections (cercarial dermatitis) [11, 45, 70, 71, 75–95, 97, 98]

^b Except for Hungary [9], where only adult schistosomes were detected, larval stages were confirmed as the causative agents of human cercarial dermatitis mainly in Russia and Asia [112]

^v The genus includes parasites which migrate from the skin via the bloodstream to the visceral organs of definitive hosts where they mature [45]

^{vn} The genus includes visceral as well as nasal species; the studies on nasal *T. regenti* showed that the parasites are able to escape from the skin and migrate further through the CNS to the nasal area of the definitive host [45]

^e Experimentally confirmed partial development of visceral or nasal bird schistosomes in mammalian hosts during primary infection (after exposure to cercariae) [35, 40, 45, 49, 53–56, 100]

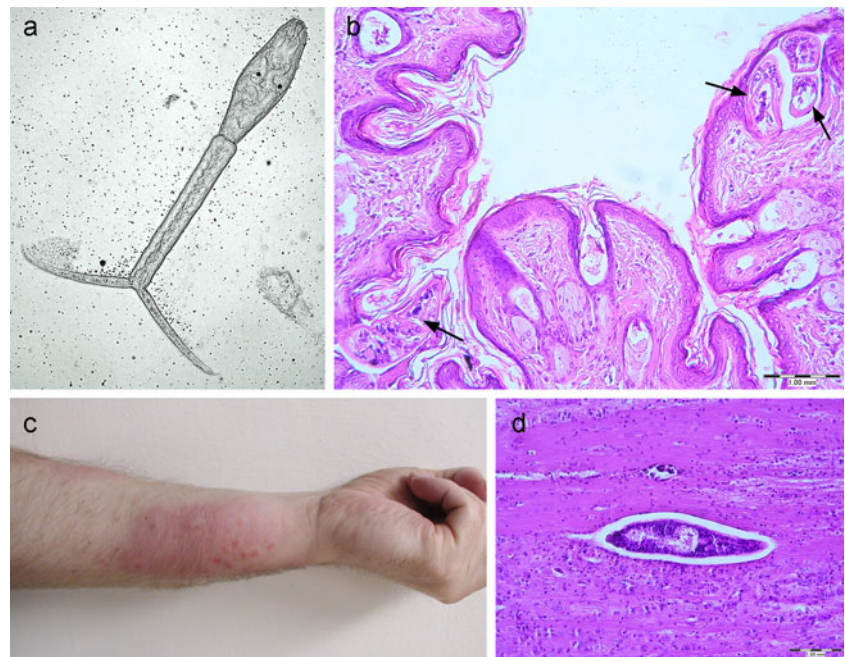
aids creeping movement to entry sites, penetration, shedding of the tail, secretion of acetabular gland contents and orientation within the host's tissues [17–22].

Cercariae of *T. szidati* prefer to penetrate via wrinkles and hair follicles, whereas *S. mansoni* cercariae prefer invasion of smooth skin areas as their main site of entry [23]. Invasion into the skin is fast; *S. mansoni* and *T. szidati* were able to penetrate into the tissue within 94 and 83 s, respectively [23]. The penetration process of *T. szidati* and *S. mansoni* is enabled by the enzymatic activity of the contents of the acetabular glands. The main penetration enzyme of *S. mansoni* is thought to be a serine protease—elastase [24], while in *Schistosoma japonicum*, *T. szidati* and *Trichobilharzia regenti*, it was suggested that serine-protease cathepsin B-like cysteine proteases may act as the main penetration enzymes [25–30]. The immunohistochemical studies of Dolečková et al. [31, 32]

revealed the presence in skin of a protease-cathepsin B2 (named TrCB2) derived from the post-acetabular penetration glands of *T. regenti*. It was documented that recombinant TrCB2 is able to degrade skin, serum and nervous tissue components in vitro, and therefore, Dolečková et al. [31] suggested that the enzyme might have a similar histolytic role as the serine protease—elastase expressed by *S. mansoni* and *Schistosoma haematobium* larvae, but not detected in *S. japonicum*.

During penetration into the skin, cercariae transform to schistosomula (Fig. 2b). The studies on *T. szidati* showed that the process is accompanied not only by shedding of the tail and emptying of penetration gland contents, but also by creation of a different parasite surface through the disappearance of lectin and antibody targets on the surface of schistosomula. These adaptations appear to be a means by which schistosomula evade host immune response [33].

Fig. 2 **a** Cercaria of *Trichobilharzia* sp.—larval stage of a bird schistosome; **b** *Trichobilharzia* sp. schistosomula (arrows) in the mouse skin during initial infection (4 h p.i.); **c** cercarial dermatitis caused by *Trichobilharzia* sp. on day 2 p.i. (photo by L. Mikeš); **d** *T. regenti* schistosomula in the mouse spinal cord on day 3 p.i.



Subsequent escape of schistosomula of *T. szidati* and *S. mansoni* from the skin to internal organs of compatible as well as non-compatible hosts is believed to be stimulated by some chemo-attractive compounds which are recognised by both parasites. It has been observed that soon after transformation, schistosomula of *T. szidati* respond to chemical signals in mouse skin (L-arginine, L-arginine-containing peptides, and D-glucose) [18]. In comparison with *S. mansoni*, *T. szidati* schistosomula migrate faster in human skin, and this feature might be a consequence of adaptation of these parasites to ducks as hosts because the skin of the webbed feet of ducks has a thicker keratinized surface layer than the human skin. A greater vulnerability of human skin might explain frequent infections of humans in natural water bodies where snails releasing bird schistosome cercariae are present [23].

After leaving the skin, the behaviour of schistosomula differs in various schistosome species/genera. Except for *S. haematobium* maturing in the vesical plexus, most immature flukes of *Schistosoma*, *Bilharziella*, *Austroilharzia*, *Ornithobilharzia* and *Trichobilharzia* [34–37] migrate through the bloodstream via the lungs to visceral organs of definitive hosts (Table 1). After reaching the final location, the parasites, which feed on blood, mature and lay eggs that are released to the lumina of the intestine or the bladder in the case of *S. haematobium*.

Worms of nine schistosome species have been found to reside in the nasal area of their definitive hosts (Table 1). Except for one representative of the genus *Schistosoma* (*S. nasale*), the others all belong to the genus *Trichobilharzia*—*T. arcuata*, *T. australis*, *T. aureliani*, *T. duboisi*, *T. nasicola*, *T. regenti*, *T. rodhaini* and *T. spinulata* [38]. Details regarding the migration route from the skin to the nasal tissues are

only available for *T. regenti* [39, 40]. Similarly to visceral schistosomes, *T. regenti* cercariae transform to schistosomula in the host skin, but prior to taking up residence in the nasal cavity of the definitive avian host, the immature flukes migrate through the peripheral nerves to the spinal cord and brain [39, 40]; during the migration through the central nervous system (CNS), the parasites feed on the host nervous tissue [41].

Studies on bird schistosomes have shown that the development and migration routes of immature flukes in non-compatible hosts (mammals, including man) are similar to those in compatible hosts. In mammals, however, the parasites do not reproduce and die at various intervals after infection. Under certain circumstances, contact of mammals with cercariae leads to dermatitis, but other pathologies may also develop.

Clinical Symptoms and Signs

Human cercarial dermatitis (Fig. 2c) represents a maculopapular skin eruption associated with intensive itch. The time course (Table 2) and severity of the disease depend on the number and duration of exposures to cercariae and on host immune status, i.e. previous history of swimmer's itch and individual susceptibility to the infection [42]. Massive infections may also cause fever, limb swelling, nausea and diarrhoea. From the diagnostic point of view, it is noteworthy that skin lesions occur only on parts of the body that were in contact with cercariae, including parts under swimming suits. The itching can range from negligible to unbearable, potentially causing insomnia [42].

Table 2 Development of human cercarial dermatitis during initial infection and reinfections (i.e. primarily infected or sensitized people, respectively)

Clinical symptoms and signs	Time p.i.	Note
Primary infections^a		
Macules (1–2 mm in diameter) can be replaced by inconspicuous papules. Contrary to weak infections that are usually without reaction or linked to only mild reactions, strong infections are accompanied by itching.	12–48 h	In some patients, a delayed formation of small papules (as late as 8 days p.i.) can be noted.
Reinfections of sensitized humans		
Transitory macules up to 10 mm in diameter; occurrence of primary itching (prickling sensation) which can persist for up to 1 h	4–20 min	In some patients, local urticarial reactions characterized by small discrete and indurated papules that reach 1–5 mm in diameter
Disappearance of macules	2–10 h	
Macules are replaced by distinct and indurated papules (3–5 mm in diameter) accompanied by intense itching (secondary itching).	10–15 h	Around the papules, erythematous zones with central punctum may develop. During massive reinfections, papules become confluent, and the whole exposed area may be elevated and oedematous.
Formation of vesicles (1–2 mm in diameter) on papules; these vesicles can often rupture by scratching.	2–3 days	
Regress of papules	By day 4	
Disappearance of papules which leave pigmented spots (1–4 mm in diameter) that persist for a month or longer	By day 10	Sporadic and intermittent pruritus may accompany skin eruption; it tends to disappear within several days.

The disease can be caused by visceral as well as nasal schistosomes. Depending on the species, the infection can be acquired in fresh-, brackish or salt waters. Therapy is only symptomatic: in mild cases, abirritant powders can be applied onto the skin, whereas systemic antihistaminics (tablets or better in gels) or mild corticosteroids should be considered in serious cases [42–45]

^a Weak infections usually do not manifest as cercarial dermatitis

In strongly sensitized hosts, papules may occur within 1 h post infection (p.i.). They usually have vesicles, increase up to 3–8 mm in diameter and are associated with erythema (10–100 mm in diameter), oedema and intensive pruritus. Symptoms may persist at least for 20 days [43]. Erythema starts to regress by day 3 p.i. Bacterial superinfection may lead to formation of pustules. A generalized skin reaction (rash) may start by day 2 p.i. and persist for 2 days in some infected patients [44]. Rashes are characterized by small (about 2 mm), hard and pink papules which are mildly and intermittently itchy. Papulo-vesicular eruptions accompanied by sloughing and injury of the skin were described by Oda [2] on dorsal parts of the hands and fingers in Japanese rice planters who were repeatedly exposed to a high number of cercariae.

It seems that all representatives of the genus *Trichobilharzia* and other non-human schistosomes produce similar symptoms when infecting humans [45]. No significant differences between swimmer's itch acquired in fresh- and salt water bodies were found [46]. According to Olivier [44], the sensitized state may persist in humans for years. Few data are available on the development of host desensitization as a consequence of repeated contacts of host with bird schistosome cercariae; only Macfarlane [47] reported cercarial dermatitis exclusively in children and not in adults who probably had the disease in the past. It seems that human schistosomes

usually induce milder skin reactions [34]. According to observations on human volunteers by Haas and Haeberlain [23], sensitization by human schistosomes seems to disappear in the course of time, as the senior volunteer developed no immediate cercarial dermatitis, although, in his history, he had acute schistosomiasis *mansoni* three times. Generally, it is difficult to distinguish whether the skin reactions were caused by either bird or human schistosomes. In tropical and subtropical areas where bird and human schistosomes are co-endemic, similarity in symptoms underlines the necessity to assume all travellers to be positive for schistosomiasis if the symptoms of cercarial dermatitis were acquired after contact with a freshwater body.

Host Immune Response

Until now, it was generally assumed that a strong skin reaction is due to the death of bird schistosome cercariae soon after they have infected a non-compatible host (mammals, including man). Studies on various species of the bird genera *Trichobilharzia*, *Gigantobilharzia*, *Bilharziella* and *Ornithobilharzia* revealed, however, that under some circumstances in experimentally infected mammals, the parasites are able to escape from the skin and migrate further [35, 39, 47–55]. Schistosomula of visceral *Trichobilharzia*

species were found in the lungs of various mammals [35, 39, 50–52]. Additionally, some parasites were detected in other organs such as liver, kidney, heart and intestine [51]. *Trichobilharzia regenti* schistosomula (Fig. 2d) were found in the mouse CNS [39, 40, 50, 52]. Immature *Trichobilharzia* were found to survive for several days and even weeks in non-compatible hosts and cause damage to the host tissues [35, 48, 50, 54, 56]. Severity of organ pathologies was closely related to immune reactivity in host skin. Whereas repeated infections led to strong skin inflammatory reactions which were able to entrap parasites in the skin and prevent their further migration, the most severe tissue injuries in the mammalian lungs and CNS were associated with primary infections in which parasites had escaped from the skin and migrated further in the mammalian body [48, 53, 54, 57].

In mice experimentally re-infected (four times) by *T. regenti*, Kouřilová et al. [54] observed more rapid killing of parasites in the skin compared to that in mice after initial exposure (Fig. 3). Published data on the fate of the parasites in human skin are at present scanty. Intense inflammation that was found around worms in the skin from humans with cercarial dermatitis (i.e. from sensitized subjects) was probably taken from sections of biopsies of sites with a papula [45]. The most comprehensive study of Haemmerli [58] on the time course of skin infection by *Trichobilharzia* describes a three-phase cellular response (leucocytic, lymphocytic and histiocytic). Soon after the penetration of cercariae during the leucocytic phase (3–9 h p.i.), the parasites were intact. By 24 h p.i., the tegument of the parasite started to degrade (lymphocytic phase), and schistosomula were completely destroyed during the histiocytic phase (36–52 h p.i.). The process was accompanied by perivascularitis and spongiosis of the area surrounding the parasites. Tissue repair (72 h p.i.) was accompanied by parakeratosis with reduced perivascular infiltration in the surrounding tissue, after which cell melanotic pigmentation occurred (100 h p.i.).

Gay et al. [59] suggest that the progression of skin reactions described above may be determined by the degree of host sensitization. Only a mild human reaction to *T. ocellata* and *T. szidati*, comprising only leucocytic vascularitis with perivascular dermal infiltrates of lymphomonocytic and polynuclear cell types, was typical for patients with a low degree of sensitization. However, a strong reaction characterized by lymphocytic vascularitis with lymphocytic dermatitis that occurred as early as 10 h p.i. was noted in sensitized patients. This was also confirmed in 2004 by Kouřilová et al. [53] with mice that were infected once or four times by *T. regenti* cercariae. Their study revealed that an initial infection with 1,000 cercariae evoked immediate oedema, thickening of the exposure site and an influx of leucocytes, including neutrophils, macrophages, CD4⁺ lymphocytes and mast cells (Fig. 3). During the initial infection, IL-1 β , IL-6 and IL-12p40 were produced, while histamine,

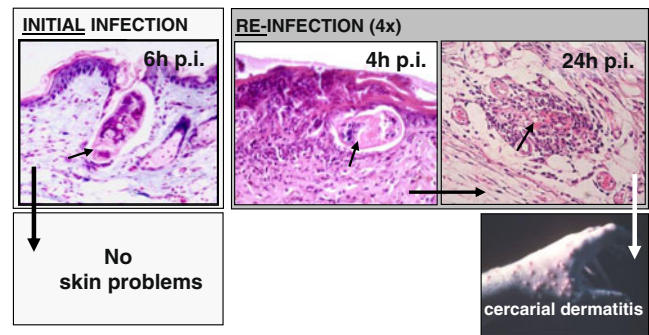


Fig. 3 During penetration into the skin, cercariae transform to schistosomula (arrow). Primary (initial) infection of mice with bird schistosome cercariae of *Trichobilharzia regenti* showed that immediate oedema, thickening of the exposure site and an influx of leucocytes, including neutrophils, macrophages, CD4⁺ lymphocytes and mast cells, occur in the skin. Analysis of antigen-stimulated lymphocytes from the skin-draining lymph nodes revealed that cells from one time-infected mice produce a mixed cytokine response (IL-1 β , IL-6 and IL-12p40) including abundant IFN- γ ; also, significant elevation of histamine, IL-4 and IL-10 within 1 h p.i. was observed. It can be assumed that during initial infection, Th17 polarization of the immune response develops. In mice four times re-infected by the cercariae, Th2-polarized immune response (elevation of IL-4 and IL-5) developed. A similar type of the reaction can also be expected in humans re-infected by the cercariae, and Th2-polarized immune response might be characteristic for maculopapular skin eruption which develops as a consequence of repeated infections by the parasites. The anti-parasite immune response during primary infection is weak, and therefore, bird schistosomes are able to escape from the skin and migrate further to the mammalian organs under certain circumstances

IL-4 and IL-10 were dramatically elevated in the re-infected mice within 1 h after infection. Analysis of antigen-stimulated lymphocytes from the skin-draining lymph nodes revealed that cells from one time-infected mice produced a mixed “Th1/Th2” cytokine response, including abundant IFN- γ , whereas cells from four time-re-infected mice were Th2 polarized dominated by production of IL-4 and IL-5. These results demonstrated that mammalian cercarial dermatitis caused by bird schistosomes was characterized by an early type I hypersensitivity reaction and a late phase of cutaneous inflammation, both associated with a Th2-type polarized acquired immune response. According to the current knowledge (e.g. [60]), however, we could assume that detection of IL 6 and IL 1 β during initial infection is rather an evidence of Th17 polarization, and Th2 response was detected only in four time-re-infected mice.

In a subsequent study, Lichtenbergová et al. [61] measured the antibody reactivity and antigen specificity of sera obtained after experimental infection of mice and natural infection of humans. Sera from mice re-infected with *T. regenti* showed a bias towards the production of antigen-specific IgM and IgG1 antibodies and elevated levels of total serum IgE. Their results thus also confirmed a Th2-polarized immune response. These authors furthermore demonstrated that cercariae are a source of antigens that

can trigger IL-4 release from basophils collected from healthy human volunteers. Elevated levels of cercarial-specific IgG were found in sera from patients with a history of cercarial dermatitis, particularly in samples collected from adults (>14 years old), although elevated levels of antigen-specific IgE were not detected.

Early phases of rodent infections by visceral bird schistosomes were characterized by the occurrence of migrating schistosomula in the lungs which was accompanied by a development of bright red, distinct and discrete superficial pulmonary lesions; sometimes deeper, larger and dark red haemorrhages with diffuse and indistinct margins developed with progression of the infection [55]. The study on gerbil infections by *Ornithobilharzia* revealed numerous whitish nodules alongside pulmonary and collateral arteries, and the peribronchial trees; some nodules were scattered in the parenchyma [49].

Chanová et al. [35], working on *T. szidati*-primoinfected mice, revealed schistosomula in the lungs between 2 and 4 days p.i.; the parasites were located extravascularly in the alveolar walls. The authors did not record any specific reaction against the parasites, but alveolar congestion, oedema and lymphocyte infiltrates in the tissue were noted. No migratory pattern similar to that in the lungs of birds (migration from the blood vessels through the blood capillaries to the lung tissue and penetration into the free air space of the lungs) was noted in mice. Nevertheless, pronounced pulmonary lesions were caused by the parasites in mice, and a potential risk of lung injury therefore exists for accidental hosts (mammals, including man).

It has been described that previously exposed mammals can develop strong immune responses against bird schistosomes. Examination of the lungs of gerbils that were re-infected with *Ornithobilharzia* showed that most parasites suffered damage to the tegument. Moreover, lymphocytic vasculitis occurred around live worms and worms that had incurred some tegumental damage. The resulting pathology was accompanied by macrophage alveolitis in the peripheral lung parenchyma [49].

Immature flukes of the bird nasal schistosome *T. regenti*, which are neurotropic and migrate through the CNS, can cause severe disorders also in mammals. The examination of mice experimentally infected by *T. regenti* cercariae showed both intact and destroyed immature flukes in the nervous tissue of these hosts [40, 54, 56]. Strong inflammatory reactions around disintegrating parasites were noted in the tissue, and establishment of the parasites in the CNS and associated pathologies may thus lead to changes in neuro-behavioral reactions of affected mammals [40].

Except for human and avian schistosomes of the genera *Schistosoma* and *Trichobilharzia*, respectively, there is little documentation showing that cercariae of other schistosomatid genera can infect man [12]. However, as schistosomes of,

e.g. the genera *Heterobilharzia* and *Bivitellobilharzia* and animal species of *Schistosoma* (including former *Orientobilharzia*), are important parasites of various ungulates, rodents and carnivores [9, 62, 63], it cannot be excluded that human infections by cercariae of mammalian schistosomes can lead to similar pathologies as those caused by bird schistosomes.

Diagnosis and Therapy

There are difficulties in differential diagnosis of cercarial dermatitis, because the skin lesions resemble those resulting from contact dermatitis, insect bites and dermatitis of bacterial aetiology [64]. Skin symptoms of swimmer's itch resemble also those of seabather's itch, a hypersensitivity reaction accompanied by intensive itching and caused by immature nematocysts of larval cnidarians such as thimble jellyfish or sea anemones. In comparison to cercarial dermatitis, however, seabather's itch is characterized by the development of smaller red papules (1 to 1.5 mm in diameter) located on the skin under swimwear or between hairs [65, 66].

Among clinical and epidemiological data of cercarial dermatitis, the most important diagnostic criteria are: (1) recent history (within the previous 96 h) of contact with a natural water body, (2) appearance of a papular skin reaction with severe itching between 12 and 24 h after exposure and (3) lesions that are distributed only on parts of the body that were immersed in water [67]. These data have to be evaluated together with the results of parasitological and immunological diagnostic methods.

Detection of schistosomulum in skin biopsies can be performed only in samples that were isolated from sites where papulae have developed, and the method can only be successful when it is performed within 24–72 h p.i. [58]. Later, the parasites are destroyed, and only eosinophilic inflammation can be observed [12]. Basic laboratory tests may reveal increased eosinophil counts in patients with cercarial dermatitis [68]. The results of Lichtenbergová et al. [61] suggest that elevated levels of total IgE may also be detected in these individuals. Laboratory tests based on the evaluation of erythema developing around injected antigens prepared from homogenized cercariae lack specificity and sensitivity [69, 70]. Moreover, erythema can also develop in patients infected by bird schistosomes and tested with antigens prepared from adult *S. mansoni* or *S. japonicum*. Methods of detecting specific antibodies against antigens of bird schistosomes include the “Cercarienhüllenreaktion”, the complement fixation test, IFAT and ELISA [45]. Although these techniques are more sensitive than skin tests, they are not specific and sensitive enough, and therefore, they are not routinely used by diagnostic laboratories. Nevertheless, a recent study of Lichtenbergová et al. [61],

focused on the development of antibody responses against antigens of *T. regenti* in experimentally infected murine hosts and humoral responses in patients with clinical expression of cercarial dermatitis, revealed that both types of sera recognised an antigenic molecule of 34 kDa. The authors suggest this might serve as a diagnostic tool.

At present, therapy of cercarial dermatitis is based solely on the symptoms. Abirritant powders may be applied to the skin, and in serious cases, use of systemic antihistaminics (tablets or better in gels) or mild corticosteroids should be considered [12].

Epidemiology

The association between avian schistosomes and cercarial dermatitis has been known for many decades. Cercarial dermatitis is reported from many countries, but there are no data on the number of afflicted persons per year. The paucity of valuable epidemiological data might be explained by a relatively low level of clinical interest in human skin infections that arise from bathing in freshwaters.

Cercarial dermatitis can be acquired in water bodies with conditions that favour parasite transmission, i.e. in places where both intermediate and definitive hosts are found. In a particular water body, various schistosome species may co-occur, and recent data show that larval and adult stages of such species can develop in the same snail or bird host (e.g. [9, 71–74]). As a consequence, cercarial dermatitis caused at the same time by several schistosome species may occur in a particular water body.

The majority of bird schistosome species develop in freshwater snails among which pulmonate snails of the families Lymnaeidae, Physidae and Planorbidae usually serve as intermediate hosts [75]. Other groups of freshwater snails, e.g. Valvatidae, Pleuroceridae, Ampulariidae and brackish or marine/littoral snails belonging to Littorinidae and Hydrobiidae, are rarely used by bird schistosomes [76]. Because definitive hosts of bird schistosomes are mostly waterfowl, it is hypothesized that the disease is predominantly distributed along the major migratory flyways and birds serve as transport of adult flukes (within the host) and perhaps also larval stages (within snails transported on bird legs) to and from nesting areas [45]. Conditions under which the parasites are transmitted to various areas remain to be explained in detail. Recently, Brant et al. [71] revealed that the Asian marine snails of the species *Haminoea japonica*, first observed in San Francisco Bay in 1999, shed schistosome cercariae of *Gigantobilharzia*. It is, however, not clear whether a trans-Pacific migratory flyway was used for transport of infective snails to the USA.

In the past [45] and also more recently, species of *Trichobilharzia* have been reported as the main etiological

agent of swimmer's itch in many countries (Table 1) [11, 71, 72, 76–96]. The prevalence of the parasite in snails of the family Lymnaeidae and Physidae differs across localities; in lakes of various countries, it ranged from 0.05 to 52.4 % [75]. It seems that prevalence rates are not dependent on geographical latitude [92, 94, 97].

With respect to outbreaks of the disease developing after swimming in salt or brackish waters (Table 1), cercariae of the avian genera *Austrotilharzia* and *Gigantobilharzia* were identified as the causative agents in Australia and North America [1, 71, 98]. In Italy, *Gigantobilharzia acotylea* was probably a source of human dermatitis in the Venice Lagoon [99].

The presence of birds is essential for establishment of a schistosome life cycle in a particular water body. Even only a transient presence of the infected birds in a particular water body can result in snail infections. Recent studies show that prevalence of adult schistosomes in birds of the orders Anseriformes and Charadriiformes is quite high all over the world. For example, in French and Icelandic aquatic birds, the prevalence was 40.3 and 35.5 %, respectively [86, 100], and Brant [101] found *Allobilharzia visceralis* in 92 % of tundra swans. Besides waterfowl, passerine birds can also serve as definitive hosts (reviewed by [75]).

The number of reports of species other than *Trichobilharzia* which may cause swimmer's itch is also increasing (Table 1). For example, schistosomes of *Schistosoma turkestanicum* which mature in cattle, sheep and other mammals have been identified as causative agents of swimmer's itch in Asia, Russia and recently also in Central Europe [9, 102].

In temperate climates, cercarial dermatitis is diagnosed usually during summer [1, 103], i.e. during the period when natural conditions favour parasite transmission. Under certain circumstances, however, the infection can be acquired during the whole year. Skirnisson and Kolářová [11] reported an outbreak of swimmer's itch during December 2003 as well as in late winter in 2004; it occurred in a slow-flowing brook with geothermally heated groundwater in Landmannalaugar, Iceland. The disease can also be acquired by cleaning an aquarium containing field-collected snails that favour avian schistosomes [104, 105].

Cercarial dermatitis can occur in any location where people come in contact with water bodies harbouring schistosome-infected snails [79]. Risk of cercarial dermatitis increases with the number of water exposures, especially in shallow water which is a typical habitat for water snails and accumulation of cercariae [106, 107].

Incidence of human cercarial dermatitis depends on the behaviour of bathers (duration of swimming), previous contact with the parasite (history of cercarial dermatitis) and, possibly, individual susceptibility to the cercariae. A multivariate analysis [42] showed that the time of day, barometric pressure, maximum air temperature and duration of

swimming activity influence not only the incidence of cercarial dermatitis, but also the number of skin lesions. The study of Neuhaus [13] showed that free-swimming schistosome cercariae were released from snails in large numbers especially on sunny days.

Cercarial dermatitis should be considered if strong skin reactions occur early after infection; both sexes can be affected equally under similar conditions, and there is no gender bias [42]. Nevertheless, some differences may be identified in different age groups; children between 5 and 9 years are at highest risk, because they spend more time in the water during recreational activities [1].

Despite the fact there are no statistical data on the incidence of the disease, cercarial dermatitis is regarded as an emerging disease at present [75]. Increased contact of people with schistosome-infested water, high eutrophication of water reservoirs [95], colonization of ponds by susceptible snails and nesting ducks and long periods of sunshine in the summer are important factors that have led to recent increases in the number of outbreaks of cercarial dermatitis in some areas.

Identification of Risky Areas

Water bodies with a risk of infection are frequently recognised during the recreational season. When outbreaks of “water-borne disease” are recorded, usually, snails are collected and examined. However, evidence of a risk of infection can be checked before the recreational season begins since the presence of both water snails and nesting waterfowl (or even transitory presence of infected birds) harbouring larval or adult schistosome stages, respectively, may indicate a potential for a later occurrence of cercarial dermatitis [108].

Cercariae are identified in water snails; all species of snails present in a water body should be examined for the presence of cercariae [108]. The commonly used methods that focus on detection of snails shedding cercariae can, however, produce false-negative results, because they ignore developing larval stages which are not shed at the time of examination. Microscopic examination of snail organs (hepatopancreas) should therefore be performed [109]. Detection of cercariae in water can be difficult due to their low concentration, even if samples are filtered. A new approach which includes concentration of suspected water samples by filtration and detection of parasite DNA by PCR has therefore been recommended [93, 110].

The search for avian schistosomes in birds commonly focuses on examination of bird faeces; this approach permits detection of visceral schistosomes, but fails to show the presence of nasal schistosomes. Birds can, however, be examined throughout the year, and valuable

results can be obtained by necropsy of birds during the hunting season. It is recommended that mainly the blood system and the surrounding tissue of the preferred organs should be examined, because visceral schistosomes and their eggs are mostly found in the intestinal wall, mesentery veins, liver, lung and heart. Nasal worms can be recovered from the nasal tissues as well as various parts of the CNS [108]. Taxonomic identification of cercariae is difficult: different species and/or genera are very similar, and thus, determination under the microscope is often impossible [111]. Besides morphological data, other supporting information, e.g. host species, location of the worms and their eggs, may help to delineate the species [108]. Molecular techniques may be applied for a precise identification and elucidation of phylogenetic relationships [72, 77, 79, 112, 113].

Control

Control of the disease has to focus mainly on interruption of the schistosome life cycle. Intervention efforts can be directed at the level of either intermediate or definitive hosts. The control of intermediate hosts [114] usually aims to eliminate snails and/or prevent snail reproduction by chemical (e.g. niclosamide), mechanical (removal of aquatic vegetation, elimination of snails by mechanical disturbance) and/or biological (e.g. application of various bacterial products) approaches [45]. With regard to definitive hosts, control measures may include prevention of bird contact with risky water bodies and chemotherapy of birds [115].

Human infections can be prevented by prohibiting access to waters that harbour snails infected by schistosome larval stages. Protection by rubbing the skin to full dryness immediately after contact with schistosome-infested water has no significant effect. To avoid infection with schistosome cercariae, various preparations (e.g. vaseline) with different effects against the parasites were developed in the past [45]. The value of protective clothing (hip boots, waders) is indisputable. Recently, niclosamide in a water-resistant sun-protecting cream was found to have a protective effect against infections caused by *T. szidati* and *S. mansoni* [116].

Conclusion

The association of schistosome larvae and cercarial dermatitis was recognised many decades ago. Studies on rodents experimentally infected by bird schistosome cercariae revealed the ability of the parasites to penetrate into mammals and cause more severe pathologies than cercarial dermatitis alone. The current paradigm of CD4⁺ T lymphocyte differentiation [60] specifies old results [53], and from the

new point of view, the belief that cercarial dermatitis is generated by allergic Th2 response only in re-infected mice is more clear. Nowadays, cercarial dermatitis is an emerging disease; cosmopolitan occurrence of bird schistosomes and frequent exposures of humans to cercariae provide an ample justification for an intensified study of clinical and pathological aspects related to bird schistosome infections of humans.

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