

Epidemiology of human fascioliasis: a review and proposed new classification

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The epidemiological picture of human fascioliasis has changed in recent years. The number of reports of humans infected with *Fasciola hepatica* has increased significantly since 1980 and several geographical areas have been described as endemic for the disease in humans, with prevalence and intensity ranging from low to very high. High prevalence of fascioliasis in humans does not necessarily occur in areas where fascioliasis is a major veterinary problem. Human fascioliasis can no longer be considered merely as a secondary zoonotic disease but must be considered to be an important human parasitic disease. Accordingly, we present in this article a proposed new classification for the epidemiology of human fascioliasis. The following situations are distinguished: imported cases; autochthonous, isolated, nonconstant cases; hypo-, meso-, hyper-, and holoendemics; epidemics in areas where fascioliasis is endemic in animals but not humans; and epidemics in human endemic areas.

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Introduction

Fascioliasis, an infection caused by the liver fluke *Fasciola hepatica*, has traditionally been considered to be an important veterinary disease because of the substantial production and economic losses it causes in livestock, particularly sheep and cattle. In contrast, human fascioliasis has always been viewed as a secondary disease (1, 2).

The public health importance of human fascioliasis has, however, increased in recent years, as shown by the high number of human cases recorded over the period 1970–90: 2594 infected persons in 42 countries located on all continents (3). Previously, cases of human fascioliasis had always been linked to cases among livestock in the area concerned.

Types of human fascioliasis

Published material on human fascioliasis falls into the following broad categories (3, 4):

- the majority of articles deal only with individual case reports;

- several articles report that the incidence is significantly aggregated within family groups because the individual members have shared the same contaminated food;
- several articles have reported outbreaks not necessarily involving only family members; and
- a few articles have reported epidemiological surveys of a large number of infected persons.

Recent developments

The traditional epidemiological picture of human fascioliasis has changed markedly in recent years, as outlined below.

Geographical distribution

The numbers of reported clinical cases of human fascioliasis caused by *F. hepatica* as well as of infected persons identified during epidemiological surveys have increased significantly since 1980. A recent review by Esteban et al. (4) compiled a total of 7071 human cases reported from 51 countries over the last 25 years, distributed as follows: Africa (487 cases), America (3267), Asia (354), Europe (2951), and Oceania (12). The major associated health problems are found in Andean countries of South America, northern Africa, Islamic Republic of Iran, and western Europe. The true number of human cases is undoubtedly much greater than that reported (4).

The epidemiological and transmission characteristics of fascioliasis mean that the disease has a patchy distribution, with foci being related to the local distribution of intermediate snail host populations in freshwater bodies as well as to general physiographic and climatic conditions. It is therefore not appropriate to refer to the characteristics of fascioliasis at the country level, but rather to those in a given physiographically and climatically homogeneous area.

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Human endemic areas

Surveys in several regions indicate that there are areas with true endemic human fascioliasis, ranging from low to very high prevalence and intensity (5). Recent estimates suggest that up to 2.4 million (6) or even up to 17 million people (7) are infected with *F. hepatica* in the world. WHO (8) has stressed the large health problem caused by fascioliasis in several countries, and Hillyer & Apt (9) have underlined the situation in the Americas. These data take on great importance because of the recognized pronounced pathogenicity of fascioliasis in humans (3, 5, 10).

Global analysis of the geographical distribution of human cases shows that the expected correlation between animal and human fascioliasis occurs only at a basic level. A high prevalence in humans does not seem to correlate with areas where fascioliasis is a major veterinary problem (4). Thus, classification of fascioliasis as one of the principal tropical diseases appears warranted (11).

Prevalence of human fascioliasis

Whereas the prevalence of human fascioliasis can be negligible in areas where the veterinary form of the disease occurs, the rates vary widely in areas where the disease is endemic to humans.

Examples of very low prevalences are 0.34–3.1 cases per 100 000 inhabitants in Basse-Normandie, France (12, 13); 0.83–1.16 cases per 100 000 inhabitants in Corsica (14, 15); and 0.7% prevalence (41 cases per 5861 subjects studied) in the VII Region of Chile (16). Intermediate levels are exemplified by prevalences of 3.2% in the inner Porto region, Portugal (17); 7.3% in the Nile delta, Egypt (18); 8.7% in Cajamarca, Peru (19); and 10.9% in Corozal, Puerto Rico (20). Examples of high prevalences are provided by 15.64% in the Puno region (21) and 34.2% in the Mantaro valley (22), both in Peru. The highest human prevalences have been reported in the Bolivian Altiplano: up to 66.7% detected using coprological techniques (23–26) and up to 53% using immunological methods (23, 27–29); higher rates of 72% and 100%, respectively, have been reported by local Bolivian workers (30).

The relationship between the prevalence of fascioliasis and age differs in human endemic and human nonendemic areas. In high prevalence areas children under 15 years of age usually present the highest rates (16, 18, 19, 21, 24, 25), in contrast to the current situation in human nonendemic areas.

Human infection intensities

Among human cases low egg outputs, e.g. 1–2 eggs per g of faeces (epg) (20) and 1–4 epg (19), were until recently the most common, with an output of 440 epg (31) being considered rare. These egg outputs are, however, very much lower than those found in human endemic areas. For example, among Bolivian children, eggs in stools ranged from 24 to 5064 epg, with arithmetic and geometric mean levels of 474–1001 epg and 201–309 epg, respectively, the

highest levels thus far reported (24, 25). In Porto, Portugal, a prospective study provided a geometric mean level in stools of 233 epg (range, 25–2100 epg), although most of the subjects shed 101–300 epg (17).

Although in general the prevalence and intensity of egg outputs are higher in children (75%, 24–4440 epg) than adults (41.7%, 144–864 epg), in hyperendemic zones adults either maintain the parasites they acquired when young or can be newly infected because they live in a zone of high infection risk (25).

The parasite

Most of the areas with a high endemicity of human fascioliasis involve *F. hepatica*. However, in Asia the distribution of *F. hepatica* and *F. gigantica* overlaps, and this makes it difficult to identify the particular species involved, which is often referred to simply as *Fasciola* sp. This especially occurs in China (Province of Taiwan), Japan, the Republic of Korea, and the Philippines (32).

A similar problem occurs in Egypt, where fascioliasis has appeared as an emerging health problem (33) with some rural areas being endemic and having prevalences in the range 7–17% (34). A total of 27.7 million people are at risk, with the number infected being at least 830 000 (8). Both *F. hepatica* and *F. gigantica* as well as intermediate forms have been found, thus explaining why the fluke species involved has not been determined in most instances (4).

Both the abnormal spermatogenetic type (AST, including diploid, triploid, and mixoploid chromosome types in which no fertilization occurs) and the normal spermatogenetic type (NST) of *Fasciola* spp. have been found in several Asian countries: China (Province of Taiwan), India, Nepal, the Philippines, Thailand, and Viet Nam. AST occurs particularly in Japan and the Republic of Korea. In south-east Asia, AST flukes are sympatric with NST *F. hepatica* and NST *F. gigantica*. In Europe, South and North America, and Oceania, where mainly *F. hepatica* occurs, and in Africa, where *F. gigantica* predominates, only NST specimens have been found (35).

Japanese flukes reproduce by parthenogenesis because of their abnormal gametogenesis, regardless of whether they are diploid, triploid, or mixoploid (36). Studies have distinguished various parthenogenetic lines that have arisen independently of each other, presumably through independent hybridization between strains. The existence of such hybrids would explain the continuing taxonomic confusion regarding the taxonomic status of the Japanese liver flukes (36). Enzymatic studies have been unable to settle this issue, perhaps because the worms reproduce parthenogenetically, with the populations examined consisting of descendants of a single individual (37, 38).

Molecular techniques have, however, provided an answer to this controversy. Ribosomal DNA

(rDNA) sequence studies have shown that *F. hepatica* and *F. gigantica* are distinct, with Japanese *Fasciola* sp. having an rDNA sequence close to that of *F. gigantica* (38, 39). Very recently, Hashimoto et al. (40) have found that intermediate forms from Japan may be ascribed to *F. gigantica*, based on their mitochondrial and nuclear DNA sequences. For the time being, however, the situation is not clear for other Asian countries.

Domestic animal reservoir hosts

In the Bolivian Altiplano, prevalence and intensity surveys show that, besides sheep and cattle, pigs and donkeys are efficient reservoirs of the parasite: pigs (27.1% infected, 4–65 epg (mean, 21.6 epg), estimated number of eggs shed per host and per day, 2000–195 000); donkeys (15.4% infected, 3–101 epg (mean, 38.8 epg), estimated number of eggs shed per host and per day, 9000–808 000) (41).

Recent studies have, moreover, demonstrated that eggs shed by pigs and donkeys are viable, i.e. able to infect a lymnaeid snail, and that the metacercariae subsequently produced are infective for another definitive host (Bargues et al., unpublished data, 1999). This is the first occasion that the need to take pigs and donkeys into account in preventive and control measures against human fascioliasis has been pointed out (41).

Wild animal reservoir hosts

In Corsica, where the level of endemicity of human fascioliasis is low, habitats have been identified where lymnaeids are infected but which have no livestock present. Helminthological surveys showed that black rats (*Rattus rattus*) were repeatedly infected by liver flukes (42, 43).

Adult stage morphoanatomical (44) and isoenzyme studies (37) have revealed no significant difference between the flukes of rodents and cattle. Fascioliasis in *R. rattus* was found in different enclaves throughout Corsica. A 6-year study in a given Corsican endemiotope found a high mean prevalence (45.13%) of *F. hepatica* infection in *R. rattus*, with an *F. hepatica* adult burden per rat of 3.04 (range, 1–12). Moreover, the pathology induced by the flukes, located in the main biliary duct, did not reduce the rat life span, naturally infected rats housed in the laboratory having survived up to 22 months (Valero et al., unpublished data, 1999).

Experimental studies have demonstrated the viability of *F. hepatica* isolates from black rats, both for development of the intramolluscan larval stage (Mas-Coma et al., unpublished data, 1999) and subsequent infection of black rats with metacercariae (45). It was therefore concluded that *R. rattus* can play an important role as reservoir and participate in the geographical diffusion of the disease (46).

Intermediate snail hosts

Nuclear and mitochondrial rDNA sequence analysis has proved useful for both specific determination and

supraspecific lymnaeid phylogeny (47–50). The importance of these techniques is evident in view of the specific determination problems in Lymnaeidae snails. Moreover, especially the E10-1 helix of the V2 variable region of the 18S ribosomal RNA (rRNA) gene has proved useful in distinguishing between lymnaeid species which transmit and which do not transmit fasciolid parasites, as well as in distinguishing between those species that transmit *F. hepatica* and those that transmit *F. gigantica* (47, 48, 51).

DNA sequence and isoenzyme studies showed not only that the European species *Lymnaea truncatula* occurs also in South America but that it is the only snail species involved in transmission of fascioliasis in the Bolivian Altiplano (47, 48, 52).

Several DNA probes capable of detecting *F. hepatica* in lymnaeids have been developed (47, 48, 53–56). One such assay detects infected snails immediately after miracidial exposure and throughout the parasite's development period (55), but possible cross-reactions with other digeneans using the same snail species have not yet been evaluated. Kaplan et al. reported the development of a highly sensitive and specific probe for radioisotopic detection of *F. hepatica*-infected snails, together with an efficient DNA extraction protocol suitable for large-scale testing of field-collected snails (56). A modification that employs chemiluminescence and has an improved assay efficiency (sensitivity, 100%; specificity, >99%) detects infected snails immediately following miracidial penetration and does not cross-hybridize with DNA of other digenean species that share the same snail hosts and overlap their enzootic ranges with *F. hepatica* (57).

The first case of transmission of a *Fasciola* species by a snail not belonging to the Lymnaeidae family (*Biomphalaria alexandrina*, Planorbidae) was recently reported in Egypt (58). The importance of this discovery for the transmission of fascioliasis remains, however, to be evaluated.

Transmission

Recent studies have demonstrated that humans play a significant role in the transmission of liver flukes, at least in human hyperendemic zones such as the Bolivian Altiplano. All the necessary characteristics converge (24, 25, 59): human prevalences are sufficient and maintained over time; egg outputs in humans are sufficiently high; and parasite eggs shed with human stools have proved to be viable. For the first time, it has therefore been shown that humans participate in the transmission of the disease in those places where outdoor defecation is practised (Bargues et al., unpublished data, 1999).

Ecology

Field and laboratory studies have shown that fascioliasis has a great capacity to spread that is related to the ecological niche-widening ability of the

lymnaeid hosts and the considerable colonization and adaptation capacity of the parasite.

On Corsica, numerous different types of habitats inhabited by the only transmitting snail species (60) may be distinguished (61, 62). Several atypical habitats represent an ecological niche widening that is related to the extraordinary distribution of the disease on the island (63, 64).

The presence of fascioliasis at very high altitude (3500–4200 m) in different Andean regions is also worthy of mention. The highest prevalences and egg outputs occur in humans precisely in these very high altitude zones of Bolivia and Peru (23–27, 30). This means not only that snail and parasite were able to colonize successfully extreme conditions of very high altitude but also that they have been able to develop different adaptation strategies which permit higher parasite transmission rates (65).

Human contamination

Recent studies have shown that many freshwater plant species other than watercress may participate in human infection, depending on geographical zones and human dietary habits in the areas concerned: in France, *Taraxacum dens leonis* (dandelion leaves), *Valerianella olitoria* (lamb's lettuce), and *Mentha viridis* (spearmint) (4); in the Islamic Republic of Iran, other green leafy *Nasturtium* spp. and *Mentha* spp. (8); and in the Bolivian Altiplano, *Juncus andicola* (Juncaceae), *Juncus ebracteatus* (Juncaceae), *Mimulus glabratus* (Scrophulariaceae), *Nostoc* sp. (Cianofitas), among others (24, 27, 30).

Water has been cited as the source of human infection, whether directly by drinking or indirectly by contaminating vegetables or kitchen utensils (3, 5). Infection by ingestion of salads contaminated with metacercariae-carrying water used for irrigation has recently been reported (13). In Bolivia, 13% of the experimentally obtained metacercariae are always floating (66); this may be related to many of the human contaminations in this zone, where proper waste or sewage disposal facilities are lacking. This is consistent with understanding about human infection in the Americas in areas where people do not have a history of eating watercress (9).

Recent experimental results suggest that humans who consume raw dishes prepared from fresh livers infected with immature flukes could become infected with fascioliasis (67).

Proposed new epidemiological classification

It is evident that today we have a different epidemiological conception of human fascioliasis, with several areas in the world being endemic for the disease, and that it has a considerable capacity to expand geographically due to the high adaptability of the parasite and the substantial colonizing power of the vector lymnaeid species. Human fascioliasis can

no longer be considered merely as a secondary zoonotic disease but must be taken to be an important human parasitic disease (11).

All these data indicate the need to review current understanding on the epidemiology of human fascioliasis in areas where *F. hepatica* is present. Below we present a proposed new epidemiological classification for human fascioliasis.

- *Imported cases*: Human cases diagnosed in a zone lacking *F. hepatica* (even among animals) but which were infected in an area where *F. hepatica* transmission occurs (68, 69).
- *Autochthonous, isolated, nonconstant cases*: Humans who have acquired the infection in the area where they live and where animal fascioliasis is also present; these human cases appear sporadically, without any constancy (70).
- *Endemic*: Three types of endemic situations can be distinguished according to the prevalence in the total population obtained by coprological diagnosis (prevalence estimated from serological tests may be somewhat higher):
 - hypoendemic: prevalence <1%; arithmetic mean intensity <50 epg; high epg levels only in sporadic cases; human participation in transmission through egg shedding may be neglected; sanitation characteristics usually include latrines and waste or sewage disposal facilities; and outdoor defecation is not commonly practised (14–16, 71);
 - mesoendemic: prevalence 1–10%; 5–15-year-olds may present higher prevalences (holoendemic); arithmetic mean intensity in human communities usually 50–300 epg; individual high epg levels may occur, although intensities >1000 epg are rare; human subjects may participate in transmission through egg shedding; sanitation characteristics may or may not include latrines and waste or sewage disposal facilities; and outdoor defecation may be practised (17, 19);
 - hyperendemic: prevalence >10%; 5–15-year-old children usually present higher prevalences (holoendemic); arithmetic mean intensity in human communities usually >300 epg; individual very high epg levels are encountered, with intensities >1000 epg being relatively frequent; human cases contribute significantly to transmission through egg shedding; sanitation characteristics do not include the use of latrines; no proper waste or sewage disposal facilities; indiscriminate defecation is commonly practised (20, 22–26).
- *Epidemic*: There are different types of outbreaks according to the endemic/non-endemic situation of the zone:
 - epidemics in areas where fascioliasis is endemic in animals but not humans: outbreaks appearing in zones where previous human reports have always been isolated and sporadic; such outbreaks usually concern a very few individuals infected from the same contamination

- source (family or small group reports; contaminated wild, home-grown, or commercially grown watercress or other metacercariae-carrying vegetables) (72–74); and
- epidemics in human endemic areas: outbreaks in zones where the disease is endemic in humans; a greater number of individuals may be involved; usually related to climatic conditions that have favoured both the parasite and the snails; and epidemics can occur in hypoendemic (75–78), mesoendemic (79), or hyperendemic (27) areas.

This classification may be a useful tool for global assessment of the importance of human fascioliasis. Such a classification is also needed because, with the recent registration of triclabendazole for human use against fascioliasis (80), new opportunities are now available for the control of this parasite. ■

Résumé

Epidémiologie de la distomatose hépatique humaine : bilan et projet de nouvelle classification

Le tableau épidémiologique de la distomatose hépatique humaine a changé ces dernières années. Depuis 1980, on note une augmentation sensible des cas d'infestation par *Fasciola hepatica* chez l'homme et plusieurs régions sont désormais considérées comme de véritables zones d'endémie humaine, avec des niveaux d'intensité et de prévalence de l'infestation très variables. La prévalence de la distomatose humaine n'est pas forcément élevée là où cette parasitose pose un important problème vétérinaire. On ne peut plus considérer la distomatose hépatique humaine comme une zoonose secondaire : il

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faut désormais y voir une importante parasitose humaine. C'est pourquoi nous proposons dans notre article une nouvelle classification épidémiologique de cette maladie. Nous distinguons les situations suivantes: cas importés; cas autochtones, isolés, non constants; hypo-, méso-, hyper- et holoendémie; épidémies survenant dans des zones où la distomatose est endémique chez l'animal mais non chez l'homme; enfin, épidémies survenant dans des zones d'endémie humaine.

Resumen

Epidemiología de la fascioliasis humana: revisión y propuesta de nueva clasificación

La situación epidemiológica de la fascioliasis humana ha cambiado en los últimos años. Desde 1980 el número de notificaciones sobre personas infectadas por *Fasciola hepatica* ha aumentado considerablemente, y en varias zonas geográficas se ha señalado la existencia de verdaderas endemias humanas, con cifras de prevalencia e intensidad entre bajas y muy altas. Las zonas de alta prevalencia de fascioliasis en el hombre no coinciden necesariamente con las zonas donde la enfermedad constituye un problema veterinario de primera magnitud. La fascioliasis humana ya no puede considerarse

simplemente como una enfermedad zoonótica secundaria, sino como una enfermedad parasitaria humana importante. Por ello, en este artículo proponemos una nueva clasificación epidemiológica de la fascioliasis humana. Se distinguen las siguientes modalidades: casos importados; casos autóctonos, aislados y esporádicos; hipoendemias, mesoendemias, hiperendemias y holoendemias; epidemias en zonas donde la fascioliasis es endémica en los animales pero no en los seres humanos; y epidemias en zonas donde es endémica en los seres humanos.

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