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Editorial

Human fascioliasis emergence risks in developed countries: From individual patients and small epidemics to climate and global change impacts

Riesgos de emergencia de fascioliasis humana en países desarrollados: desde pacientes individuales y pequeñas epidemias hasta los impactos de los cambios climático y global

Fascioliasis is a zoonotic parasitic disease caused by two helminthic trematode species: *Fasciola hepatica* of almost worldwide distribution in mild and cold environments, and *F. gigantica* in parts of Africa and Asia mainly in warm lowlands.[1] This rural disease uses livestock species as reservoirs, mainly sheep, goats and cattle in Europe, to which the pig is added in Latin America, and the buffalo in Africa and Asia.[1] Its geographical distribution is linked to the one of their specific vectors, freshwater snails of the family Lymnaeidae whose classification needs molecular techniques due to their morphoanatomical similarities.[2]

Until the 1990s, fascioliasis was considered a disease of secondary importance in humans,[3] and analyzed human infection characteristics as a simple extrapolation of animal infection characteristics. Today it is well known that human fascioliasis pronouncedly differs from animal fascioliasis. From the 1990s onwards, studies began to change this conception owing to: the increasing number of human infection reports; description of human fascioliasis endemic areas in many countries; increased knowledge on pathology in humans including demonstration of the pathogenicity of the disease chronic phase; new information about human infection sources and its epidemiology; impact of climate change on disease transmission; and effects of global changes on its spreading capacities. All this led WHO to include fascioliasis within the group of foodborne trematodiases among the list of most important Neglected Tropical Diseases (NTDs).

Until quite recently, *F. hepatica* was considered the most frequent and pathogenic fasciolid infecting humans. Only very secondary importance was given to *F. gigantica*. This scenario is rapidly changing with the increasing description of human fascioliasis situations caused by *F. gigantica* and the demonstration of its higher pathogenicity related to its bigger size.[4]

Human infection takes place by ingestion of metacercariae, in which the snail-released cercariae transform. Human fascioliasis infection sources were recently analyzed. The high diversity of infection sources underlie the large epidemiological heterogeneity of human fascioliasis throughout and in great part explains the differences between human and animal fascioliasis.[5] These infection sources include foods, water and combinations of both. Ingestion of freshwater wild plants proved to be the main source, with watercress and secondarily other vegetables. However, freshwater cultivated plants, terrestrial wild plants, and terrestrial cultivated plants also appeared involved. The sale of vegetables in uncontrolled markets and traditional local dishes made from sylvatic plants explain urban infections. Raw liver ingestion may also be the infection cause in given religious traditions. Other previously neglected infection souces were highlighted: drinking of contaminated water, beverages, juices and soups; and also washing of vegetables, fruits, tubercles and kitchen utensils with contaminated water. All this becomes crucial in anamnesis interpretation and may be of great help in guiding physians to a correct diagnosis.[5]

The recent drive to “go green” as a healthy approach to the modern artificial lifestyle in today developed societies poses evident problems. This recent fashion has shown to underlie an unprecedented increase in the consumption of fresh, raw/green fruits and vegetables.[5] In Switzerland, a correlation with ingestion of sylvatic watercress was suspected in 22 cases diagnosed within a 2-month period in 2009. This epidemic demonstrated the growing fascioliasis incidence, and the importance of locally acquired infections.[6]

Clinically, the main focus was traditionally given to the migratory or acute phase, corresponding to the initial 3–4 month long migration of the juvenile flukes issued after metacercarial hatching at duodenal level and intestinal wall crossing up to the liver through the abdominal cavity. This phase frequently shows pronounced symptomatology which leads patients to look for healthcare. This explains why fascioliasis diagnosis usually occurs during this phase and why serological tests are preferred in developed countries, given that fasciolid eggs cannot yet be found in coprological examination.[7] However, surveys have shown that in human endemic areas the rule is to detect infected subjects in the chronic or biliary phase, in which flukes are already located in the biliary ducts or gallbladder and producing eggs detectable in stools. This means lack of detection during the acute phase, whether due to an asymptomatic or mild transitory symptomatology during the

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migratory phase not requiring healthcare or leading to diagnostic confusion, or people, mainly children, not attending health centres in remote rural areas. We know today however that an exacerbation of pathogenicity may occur along the chronic or advanced chronic phase, which in humans may last up to 13.5 years.[8] Indeed, lithiasis originated in long term infections led to surgery in many undiagnosed patients in Argentina.[9]

Although neurological and ocular affections due to fascioliasis have been reported from all continents, most of such cases were in developed countries, mainly France and Spain. These important pathogenic aspects of fascioliasis were markedly overlooked in the last decades. A wide review furnished the necessary baseline for such affections.[8] The terms of neurofascioliasis and ophthalmofascioliasis were restricted to the rare cases with a migrant ectopic fluke directly affecting the central nervous system or the eye. Cases in which neurological and ocular disorders are indirectly caused at distance by flukes in the liver are refered to as fascioliasis with neurological or ocular affection. Impressive clinical pictures comprising puzzling polymorphisms, manifestation multifocality, disease evolution changes, sequelae and mortality, were highlighted in patients presenting with neurological, meningeal, neuropsychic, and ocular disorders. Physicians may not be aware about the potential relationship between liver fluke infection and neurological implications, and such cases may remain misdiagnosed, even in developed countries.

It has recently been suggested that numerous plasminogen-binding proteins of the *F. hepatica* excretome/secretome may underlie blood-brain barrier leakage whether by many simultaneously migrating, small-sized juvenile flukes in the acute phase, or by breakage of encapsulating formations triggered by single worm tracks in the chronic phase. Blood brain barrier leakages may subsequently occur due to a fibrinolytic system-dependent mechanism involving plasmin-dependent generation of the proinflammatory peptide bradykinin and activation of bradykinin B2 receptors. Inflammation and dilation of blood vessels was additionally suggested to be linked to contact system-dependent generation bradykinin.[10]

A study proved that immune response modulation occurs in advanced chronic fascioliasis, additional to the immune response downregulation during the acute phase. A persistent immune suppression was observed in the advanced chronic infection.[11] A consequence is the suppression of immune responses directed against concurrent infections by other pathogenic parasites and bacteria.

Climate change is proving to be another driver of fascioliasis, with modifications of prevalences and intensities and also spread of the disease. Fascioliasis gathers all crucial features needed to be strongly influenced by climate change: (i) three life cycle phases (egg-miracidium, intramolluscan larval stages, cercaria-metacercaria) directly depending on the climatic and external environmental conditions; (ii) poikilothermic invertebrate vector-borne disease; (iii) many amphibious freshwater snails as vectors; (iv) r-strategist vectors with selfing reproduction capacity and fast high multiplication rates; (v) zoonotic disease; (vi) numerous domestic and sylvatic animal reservoir species involved due to the very low specificity at definitive host level; (vii) lack of buffer effect at definitive host level because of premunition absence; and (viii) adult stage of long life span and high egg laying capacity by both autofecundation and crossing.

Fascioliasis incidence has been related to air temperature, rainfall and/or potential evapotranspiration. These factors affect the snail host population dynamics and the parasite population at the level of both the free living larval stages of egg and metacercaria and the intramolluscan parasitic larval stages.[12] Increases of human fascioliasis incidence have been reported after a period of intense rainfall in Europe. Climatic seasonality defines the disease transmission seasonality. There are areas where fascioliasis is biseasonal, as Europe, whereas others are monoseasonal.

Anthropogenic and environmental modifications included in the broad term of "global change", such as construction of dams, irrigation canals and water reservoirs, may also modify fascioliasis seasonality in an endemic area. Irrigation system management has been proved to modify a monoseasonal fascioliasis transmission pattern into a biseasonal with a peak related to rainfall and another peak related to man-made irrigation.[13]

Animal transport inside countries, and import/export between countries or even different continents is another influencing factor included in global change.[1] A watercress culture contamination due to disease spread by an introduced South American sylvatic reservoir animal as the nutria appeared related to the emergence of human fascioliasis in concrete areas of France. This fascioliasis emergence was described as the first epidemic due to the ingestion of cultivated watercress.[14]

The main tools for diagnosis in humans are stool and blood techniques, which have been improved in recent years. Present availabilities for human diagnosis were reviewed focusing on advantages and weaknesses, sample management, qualitative and quantitative diagnosis, antibody and antigen detection, post-treatment monitoring, and post-control surveillance. The pronounced difficulties of diagnosing fascioliasis in humans were emphasized given the different infection phases and parasite migration capacities, clinical heterogeneity, immunological complexity, different epidemiological situations and transmission patterns. It was concluded that no diagnostic technique covers all needs and situations. A combined use of different techniques, at least including a stool technique and a blood technique, was advised.[7]

A coproantigen-detection test, combined with a new diluent developed for preservation of *Fasciola* coproantigens, has been one of the most useful recent progresses. It allows for high sensitivity and specificity, fast large mass screening capacity, detection in the chronic period, early detection of treatment failure or reinfection in post-treated subjects, and usefulness for surveillance programmes.[15] However, it is useless for fasciolid species differentiation and fluke burden evaluation.

Blood eosinophilia is extremely useful in guiding towards a fascioliasis diagnosis in developed countries, although cases have been reported in which eosinophilia was lacking.

Additional helpful non-invasive diagnostic techniques include radiology, radioisotope scanning, ultrasound, computed tomography and magnetic resonance. However, images seen on ultrasound and CT may sometimes be confusing. Imaging techniques showing abnormal bile ducts or liver lesions may be misdiagnosed as cholangiocarcinoma or another malignant process, leading the patient to undergo unnecessary, complex liver surgery.

The most useful diagnostic tool for viewing the bile ducts is cholangiography by endoscopic retrograde cholangiopancreatography (ERCP), and more recently, by magnetic resonance cholangiopancreatograpy (MRCP). Some technical limitations make bile duct detail obtained by ultrasound, CT or MRCP imaging methods inferior to that obtained with ERCP. ERCP is therefore considered the gold standard for bile duct imaging and the first choice in patients in the chronic phase. In biliary obstruction, ERCP and sphincterotomy have been used to extract parasites from the biliary tree by balloon or basket.

In developed countries, fascioliasis is also diagnosed in different kind of travellers. Business travellers, tourists, immigrants, expatriated workers, military personnel, religious missionaries, refugees and internationally adopted children have been involved in human infection reports. Europe is the continent where more imported cases have been reported. In the Americas, most of the reports concern cases diagnosed in USA.

Because of the lack of awareness of the physicians in developed countries, patients may undergo multiple, unnecessary investigations and treatments, sometimes for years, even including surgery, before a correct diagnosis is made.[6,9]

Postprandial administration of triclabendazole is the treatment of choice nowadays. Triclabendazole is the unique drug which is efficient against both migratory juvenile flukes and biliary adult flukes.[16] It has moreover no important side effects and is therefore used by WHO for preventive chemotherapy by yearly mass treatments in human endemic areas. Two doses of 10 mg/kg separated 12 or 24 h is the standard for individual patients. An additional 10 mg/kg has been in need only in rare cases. Hospitalization is recommended in cases in which more than 400 eggs per gram are found in the patient' faeces, to avoid the possibility of colic due to secondary bile obstruction by accumulation of dragged killed flukes.

Triclabendazole resistance has been reported in livestock of different countries. All indicates that resistance appeared in animals due to bad dosification, drug misuse or the use of local uncontrolled generic drugs. In developed countries, triclabendazole resistance in humans has been reported but in a few cases in Europe. In developing countries, resistance in humans has been so far reported only in Chile, Peru and Turkey. There are no data suggesting triclabendazole resistance to have the capacity to spread. This means an independent appearance in each endemic area.

There is no good alternative drug. Praziquantel, the drug of choice for other trematodiases, is usually useless in fascioliasis. Nitazoxanide has shown to be useful in cases of low burdens, but no efficiency has been reported in a European patient showing triclabendazole resistance.[17]

Treatment success usually refers to disappearance of symptoms, disappearance of eggs in stools and/or negativization of serological tests. For total recovery, anyway, diagnosis and treatment should be performed as precociously after patient infection as possible. Patients not completely recovered due to persistent hepatic lesions have been reported many years after having been appropriately treated despite initially considered not problematic infections.[18] In clinically severe cases, liver fluke infections may even leave handicapped subjects behind.[8]

One of the main problems posed by fascioliasis is that it is not a reportable disease. Senior health professionals may slowly get the idea that this disease does not more exist in their working area and young physicians do not think at it because never having faced a fascioliasis patient. In the useful review of 166 cases diagnosed in Spanish hospitals between 1997 and 2014, an amount of 166 cases were analyzed, without including patients who could be diagnosed outside hospitals.[19] When looking at the published reports of human fascioliasis in Spain during the same period, only around 32 patients could be counted. Even if some of them were perhaps reported in secondary publications which may have been overlooked, it is evident that the difference in patient number is very high.

In the present situation in which climate and global changes follow an increasing trend and allow for the emergence of other trematodiases in developed countries of the northern hemisphere,[20] there is an evident need to increase awareness on human infection by *Fasciola*. Control measures in livestock reservoirs may decrease burdens but are not able to eliminate fascioliasis in animals. In humans, prevention mainly concerns measures to avoid individual infection by considering the different human infection sources, for which chemical agents acceptable in food appear so far useless to kill metacercariae and physical tools do not appear to be easily applicable.[5]

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References

1. Mas-Coma S, Valero MA, Bargues MD. Fasciola, lymnaeids and human fascioliasis, with a global overview on disease transmission, epidemiology, evolutionary genetics, molecular epidemiology and control. Adv Parasitol. 2009;69:41–146.
2. Bargues MD, Artigas P, Khoubbane M, Flores R, Glöer P, Rojas-García R, et al. Lymnaea schirazensis, an overlooked snail distorting fascioliasis data: genotype, phenotype, ecology, worldwide spread, susceptibility, applicability. PLoS ONE. 2011;6:e24567.
3. Chen MG, Mott KE. Progress in assessment of morbidity due to Fasciola hepatica infection: a review of recent literature. Trop Dis Bull. 1990;87:R1–38.
4. Valero MA, Bargues MD, Khoubbane M, Artigas P, Quesada C, Berinde L, et al. Higher physiopathogenicity by Fasciola gigantica than by the genetically close *F. hepatica*: experimental long-term follow-up of biochemical markers. Trans Roy Soc Trop Med Hyg. 2016;110(Special Issue):55–66.
5. Mas-Coma S, Bargues MD, Valero MA. Human fascioliasis infection sources, their diversity, incidence factors, analytical methods and prevention measures. Parasitology. 2018;145(Special Issue):1665–99.
6. Perrodin S, Walti L, Gottstein B, Kim-Fuchs C, Candinas D, Banz V. Fasciola hepatica in a country of low incidence: a tricky diagnosis. HepatoBiliary Surg Nutr. 2019;8:597–603.
7. Mas-Coma S, Bargues MD, Valero MA. Diagnosis of human fascioliasis by stool and blood techniques: update for the present global scenario. Parasitology. 2014;141(Special Issue):1918–46.
8. Mas-Coma S, Agramunt VH, Valero MA. Neurological and ocular fascioliasis in humans. Adv Parasitol. 2014;84:27–149.
9. Mera, Sierra R, Agramunt VH, Cuervo P, Mas-Coma S. Human fascioliasis in Argentina: retrospective overview, critical analysis and baseline for future research. Parasit Vector. 2011;4:104.
10. Gonzalez-Miguel J, Valero MA, Reguera-Gomez M, Mas-Bargues C, Bargues MD, Simon-Martin F, et al. Numerous Fasciola plasminogen-binding proteins may underlie blood-brain barrier leakage and explain neurological disorder complexity and heterogeneity in the acute and chronic phases of human fascioliasis. Parasitology. 2019;146:284–98.
11. Gironés N, Valero MA, García-Bodelón MA, Chico-Calero MI, Punzón C, Fresno M, et al. Immune suppression in advanced chronic fascioliasis: an experimental study in a rat model. J Infect Dis. 2007;195:1504–12.
12. Mas-Coma S, Valero MA, Bargues MD. Climate change effects on trematodiases, with emphasis on zoonotic fascioliasis and schistosomiasis. Vet Parasitol. 2009;163:264–80.
13. Afshan K, Fortes-Lima CA, Artigas P, Valero MA, Qayyum M, Mas-Coma S. Impact of climate change and man-made irrigation systems on the transmission risk, long-term trend and seasonality of human and animal fascioliasis in Pakistan. Geospatial Health. 2014;8:317–34.
14. Mailles A, Capek I, Ajana F, Schepens C, Ilef D, Vaillant V. Commercial watercress as an emerging source of fascioliasis in Northern France in 2002: results from an outbreak investigation. Epidemiol Infect. 2006;134:942–5.
15. Ubeira FM, Muiño L, Valero MA, Periago MV, Pérez-Crespo I, Mezo M, et al. MM3-ELISA detection of Fasciola hepatica coproantigens in preserved human stool samples. Am J Trop Med Hyg. 2009;81:156–62.

16. Gandhi P, Schmitt EK, Chen CW, Samantray S, Venishetty VK, Hughes D. Triclabendazole in the treatment of human fascioliasis: a review. Trans Roy Soc Trop Med Hyg. 2019;113:797–804.
17. Zumaquero-Rios JL, Sarracent-Perez J, Rojas-Garcia R, Rojas-Rivero L, Martinez-Tovilla Y, Valero MA, et al. Fascioliasis and intestinal parasitoses affecting schoolchildren in Atlixco, Puebla State Mexico: epidemiology and treatment with nitazoxanide. PLoS Negl Trop Dis. 2013;7:e2553.
18. Rondelaud D, Dreyfuss G, Vignoles P. Clinical and biological abnormalities in patients after fasciolosis treatment. Méd Malad Infect. 2006;36:466–8.
19. Guerrero Espejo A, Bernad Anso A. Incidencia y distribución geográfica de pacientes hospitalizados con fascioliasis en España. Enferm Infecc Microbiol Clin. 2019, http://dx.doi.org/10.1016/j.eimc.2019.08.004.
20. Boissier J, Mone H, Mitta G, Bargues MD, Molyneux D, Mas-Coma S. Schistosomiasis reaches Europe. Lancet Infect Dis. 2015;15:757–8.

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