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Microsporidiosis after liver transplantation: a French nationwide retrospective study

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AIDS: acquired immunodeficiency syndrome

LT: liver transplantation

PCR: polymerase chain reaction

SOT: solid organ transplant

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Jérôme Dumortier had the idea of the project and participated in analysis and interpretation of data.

Jérôme Dumortier, Meja Rabodonirina and Philippe Poirier participated in writing of the manuscript.

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Accepted Article

Abstract

Background: Microsporidiosis has been largely reported in patients with acquired immunodeficiency syndrome, but emerged as a cause of persistent diarrhea in solid organ transplant patients.

Methods: Through the French Microsporidiosis Network and the Groupe français de recherche en greffe de foie, we collected all microsporidiosis cases identified in liver transplant patients between 1995 and 2020 in France.

Results: We identified 24 liver transplant recipients with microsporidiosis. Sex ratio was balanced and median age was 58.8 (3.5-83.5) years (there were 4 children). Microsporidiosis occurred at a median time of 3.9 (0.1-18.9) years post-transplant. Median duration of diarrhea before diagnosis was 22 days (12-45). Therapeutic care included immunosuppressive therapy changes in 20 patients, as follows: stop cyclosporine or tacrolimus (n=2), dose reduction of cyclosporine or tacrolimus (n=12), stop MMF (n=5), dose reduction of corticosteroids (n=1). In addition, 15 patients received specific therapy against microsporidiosis: fumagilline (n=11) or albendazole (n=4). Median duration of treatment was 14 days (8-45 days). Finally, 7 patients had IS treatment tapering only. Microsporidiosis was complicated by renal failure in 15 patients, requiring dialysis in 1 case. Two patients had infection relapse. No patient presented proven rejection within the 3 months after microsporidiosis. None of the patients died within the 3 months after microsporidiosis.

Conclusions: Microsporidiosis is a very rare infection after liver transplantation but can induce severe dehydration and renal failure. Therefore, it must be systematically sought in any case of persistent diarrhea after first line screening of frequent infectious causes.

Introduction

Microsporidia are spore-forming eukaryotic and opportunistic intracellular pathogens related to fungi^{1,2}, which are known to infect both invertebrates and vertebrates hosts. In most human cases, microsporidia are orally transmitted by waterborne or foodborne spores from excreta, and by interindividual contacts; presentation as small epidemic is possible³⁻⁶. Of the species infecting humans, *Enterocytozoon bieneusi* is the most frequent and, to a lesser degree, *Encephalitozoon intestinalis*, *Encephalitozoon hellem* and *Encephalitozoon cuniculi*^{1, 7, 8}. Since the late 1980's, microsporidia have been mostly known as a cause of chronic and wasting diarrhea in patients with acquired immunodeficiency syndrome (AIDS)⁹. Since the late 1990's, a limited number of cases of microsporidiosis have been reported in solid organ transplant (SOT) and bone marrow transplant (BMT) recipients, including less than 20 cases after liver transplantation (LT)^{7, 10-13}. Some rare cases of donor-transmitted infections have been reported^{14, 15}. Related to the two most prevalent species, *E. bieneusi* and *E. intestinalis*, diarrhea is the most common presenting symptom, but other clinical manifestations include ocular, renal, pulmonary, cardiac, liver, and central nervous system involvement during microsporidia infection, especially in AIDS patients with low lymphocyte counts^{2, 7}. *E. bieneusi* and *E. intestinalis* can disseminate to the hepatobiliary system leading to cholangitis. During the past decades, diagnostic methods evolved so that detection and identification of microsporidia species can now be made by specific polymerase chain reaction (PCR), in addition to microscopic detection methods². This has probably led to better recognition of cases in recent years.

In France, a microsporidia national network has been set up in 2018 to provide data on the epidemiology of human microsporidiosis. The aim of the present retrospective study was to collect information on history, treatment, and outcome of microsporidiosis in LT recipients in France.

Patients and methods

Study population

The French Microsporidiosis Network was set up in 2018, in order to provide public health authorities with data on the incidence and epidemiology of human microsporidiosis in France. Through the French Microsporidiosis Network and by contact with the French Groupe de recherche français en greffe de foie (GReF²), we retrospectively collected all microsporidiosis cases identified in LT recipients between 1995 and 2020. Cases were defined by the presence of persistent diarrhea (ie, ≥ 3 liquid stools per day for more than 2 weeks) and detection of microsporidia spores by a microscopic examination of fecal smears after Van Gool and/or Weber and/or immunofluorescent staining and/or molecular methods. Identification to the species level was achieved by using species specific antibodies or PCR ⁷.

We retrospectively collected clinical information regarding the patient, the transplant, induction and maintenance immunosuppressive regimens, clinical presentation, environmental characteristics, treatment, and outcome.

According to French law (Loi Jardé), anonymous retrospective studies do not require Institutional Review Board approval.

Statistical Analysis

Continuous variables are described as means (\pm standard deviation) and/or medians (range) and categorical variables are presented as numbers and frequencies (percentages).

Results

Study population

Twenty-four LT recipients who developed microsporidiosis between 1995 and 2020 in France were identified, from 10 transplant centers. The patient characteristics are reported in Table 1.

Sex ratio was balanced and median age was 58.8 (3.5-83.5) years at the time of microsporidiosis diagnosis. Four patients were younger than 18 years. Three patients received combined kidney and liver transplant. None of the patients had additional immunodepression favoring microsporidiosis such as congenital immune deficiency or HIV infection. Three patients received steroids boluses for the treatment of acute rejection in the 3 months prior to diagnosis of microsporidiosis. We found epidemiological information that could be associated with the occurrence of microsporidiosis in 6 patients, including 3 cases during a local epidemic (waterborne outbreak in an artificial lake ⁶), 2 cases in 2 children sisters ¹² and 1 case traveled recently in low sanitary area.

Clinical Characteristics

Microsporidiosis occurred at a median time of 3.9 years (0.1-18.9) post-transplant. It occurred within 6 months post-transplant in 4 cases. Median duration of diarrhea before diagnosis was 22 days (14-45). Diagnosis was made from stool analysis in all cases, by direct methods in 9 cases or PCR in the 15 others. None of the patients had coinfection. None of the patients had recognized associated extraintestinal location. Hospitalisation was required in all cases except one. In one case, the patient was admitted in Intensive Care Unit, due to the need of transient dialysis (the patient was not a combined liver/kidney recipient). Median hospital stay was 15 days (4-36). Weight loss (79.2%) and dehydration-related acute kidney failure (62.5%) were frequent.

Treatment and Outcome

After diagnosis of microsporidiosis, immunosuppressive therapy was modified in 20 patients, as follows: stop cyclosporine or tacrolimus (n=2), dose reduction of cyclosporine or tacrolimus (n=12), stop MMF (n=5), dose reduction of corticosteroids (n=1). In addition, 15 patients received specific therapy against microsporidiosis: fumagilline (n=11), or albendazole (n=4). Median duration of treatment was 14 days (8-45 days). Finally, 7 patients had IS treatment tapering only. Outcome was favorable in all cases, but 2 patients relapsed (1 patient had 2 relapse episodes). No systematic stool screening was done after treatment. Relapse cases were identified because of recurrent symptoms.

No patient presented proven rejection within the 3 months after microsporidiosis. None of the patients died within the 3 months after microsporidiosis.

Accepted Article

Discussion

Although recently attached to the Fungi group, microsporidia are ubiquitous unicellular microorganisms with an obligate intracellular stage, like some parasites (these microorganisms were classified as protozoa for a long time). Most cases of microsporidiosis were first described during the AIDS pandemic, highlighting its opportunistic skills¹. During the 21st century, incidence has currently decreased in this population. Nowadays, SOT recipients are considered as a risk group for microsporidiosis; nevertheless, no more than 100 cases have been reported in SOT by now, mainly in renal transplant recipients^{12, 13}. We therefore report herein the largest cohort of cases in LT recipients, based on a retrospective nationwide study. We believe that this series is probably not entirely exhaustive, except in the very recent period, after the creation of the French Microsporidiosis Network in 2018. In summary, we identified approximately one case per year in France during the last 25 years. Nevertheless, it cannot be excluded that mild cases of microsporidiosis, diagnosed or not, which did not lead to hospitalization, may have not been captured by the present survey.

Diagnosis of microsporidiosis has been established between 1 month and 28 years after LT, and this confirms that infection can occur at any time after a transplantation, even in the very long term. As in our patients, *E. bienersi* has been involved in the majority (almost all) of reported cases. The existence of microsporidia asymptomatic carriers has been supported, especially in the immunocompromised host¹⁶. Asymptomatic carriers could therefore disseminate the infection. Gastrointestinal microsporidiosis can be diagnosed using stool microscopy of at least three stool samples with chromotrope and chemofluorescent stains or immunofluorescence^{2, 17}. More recently, in house and commercialized PCR assays for detection and identification to the species level exhibit excellent diagnostic performance, and some of them allow simultaneous detection of *Cryptosporidium* sp^{2, 18-20}.

Infection with *E. bienersi* is usually restricted to the intestinal tract, and is a major cause of acute or persistent diarrhea. Clinical manifestations also include weight loss, nausea, and abdominal pain². No case of disseminated microsporidiosis or biliary involvement was reported in our cohort. Nevertheless, severe profuse diarrhea can be complicated by renal failure as illustrated in many of our cases. Gastrointestinal disorders, and especially diarrhea, in SOT recipients may have various origins including immunosuppressive drugs and infections. Microsporidiosis is undoubtedly a rare cause of diarrhea, but not exceptional. In the prospective study by Moniot and coll., among 82 French kidney transplants presenting with diarrhea, microsporidiosis and

cryptosporidiosis accounted for 2.4 % and 7.3%, respectively ¹⁹. However, prevalences were probably underestimated as this work did not distinguish between infectious and non-infectious diarrhea. Deltombe and coll. prospectively assessed the infectious causes of diarrhea in adult kidney and/or pancreas transplant recipients patients, with a specific focus on cryptosporidiosis and microsporidiosis, in France ²¹. During a 12 months period, all patients who presented with diarrhea had an exhaustive stool sample analysis. Out of 73 enrolled patients, 36 had infectious diarrhea (49.3%), including 2 cases of co-infection, 1 to 321 months after transplantation. Viruses ranked first (17/36), followed by parasites and fungi (11/36) and bacteria (5/36). Cryptosporidiosis was the most common parasitic/fungal disease (n=6, 16.7%) but there were 4 cases of microsporidiosis (11.1%). The estimated prevalence of cryptosporidiosis and microsporidiosis in the global cohort of 1624 recipients was 0.37 and 0.24%, respectively.

Therapeutic options in microsporidial infections are limited. Efficacy strongly depends on the causal species. The best criteria of therapeutic success should be the resolution of the clinical manifestations and negative samples (absence of spores), which is not always available in all cases. At the present time, albendazole and fumagillin are the most effective compounds against *E. intestinalis* and *E. bienersi*, respectively. The use of these two drugs depended in our cohort on identification of species and/or availability (fumagillin was not available at the time of oldest cases). In SOT recipients, reduction of immunosuppression is part of the treatment, as much as possible, that was the case in the vast majority of our patients. A very recent study evaluated the efficacy and safety of fumagillin in a real-life setting in France, as required by the French Medicine Agency ²². All patients receiving fumagillin between 2007 and 2018 were enrolled in a prospective study to evaluate its efficacy and safety. There were 166 patients (including 6 children) and 84% were transplant recipients. Serious adverse events were reported in 41 patients (25%), mainly thrombocytopenia (15%) and neutropenia (5%), with two haemorrhagic events leading to one death. Severe thrombocytopenia (<50 G/L) developed in 50 patients (29.6%), neutropenia (<1 G/L) in 20 patients (11.8%) and severe anaemia (<8 g/dL) in 21 patients (12.4%). Such hematological side-effects are of great clinical relevance in SOT recipients, because these are frequent side-effects of some immunosuppressive drugs. At the end of treatment, 94% of patients with available stool examination (n = 132) had no spores detected; among 99 patients with available follow-up after the end of treatment, three cases of relapse were documented. After initial favorable outcome, infection relapse is probably rare (2 cases in the present series, *i.e.* 8.3%).

In conclusion, when persistent diarrhea occurs in SOT patients, microsporidiosis infection can induce severe dehydration and must be searched systematically using specific conventional and molecular tools. Diagnosis can therefore lead to rapid treatment adapted on causal species.

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Table 1. Characteristics of the study population (n=24)

Baseline characteristics	
Age: median (range), y	58.8 (3.5-83.5)
Sex ratio (female/male)	12/12
Type of organ transplantation	
Liver only	21
Liver/Kidney	3
First transplant	24
Adults/Children	20/4
Initial liver disease	
Alcoholic liver disease	8
Viral liver disease	4
other	12
Initial immunosuppressive regimen (induction)	
Anti-CD25	9
OKT3	2
Anti-thymocyte globulin	0
Maintenance immunosuppressive regimen	
Corticosteroids	10
Tacrolimus	17
Median trough level at time of diagnosis of microsporidiosis (range), ng/mL	7.6 (5.5-18.9)
Cyclosporin	6
Median trough level at time of diagnosis of microsporidiosis (range), ng/mL	126 (32-280)
MMF	14
Sirolimus/everolimus	0
Organ rejection before microsporidiosis (in last 3 mo)	3
Clinical and biological presentation of microsporidiosis	
Median duration of microsporidiosis symptoms before diagnosis, d	22 (14-45)
Median time interval between transplantation and infection (range), y	3.9 (0.1-18.9)
Symptoms	
Diarrhea	24
Fever	1
Nausea	1
Abdominal pain	3
Blood in stool	0
Stool's nb/d	4 (3-20)

Weight loss	19
Weight loss (kg)	4 (0-17)
Acute renal failure (> 20% decrease of GFR)	15
Biological characteristics at diagnosis	
Median lymphocyte count, /mm ³	760 (200-2700)
Lymphopenia <500/mm ³	5
Microsporidia species	
<i>Enterocytozoon bieneusi</i>	19
unknown	5

ATG, antithymoglobulin; MMF, mycophenolate mofetil.

Data are n unless otherwise indicated.