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Invasive Infections for Endemic Fungi in Pediatrics in Guatemala

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Abstract

Background: Invasive fungal infections are common opportunistic diseases in patients with AIDS, other conditions related to immunodeficiency and healthy infants. Most publications on this subject are related to industrialized countries, and in adult population, with limited data in Latin America (except for Brazil, Colombia, and Argentina), and especially in pediatric population. These patients present a variety of clinical manifestations representing a diagnostic and therapeutic challenge for the health system. **Objective**: The objective of the study is to describe the epidemiological and laboratory characteristics of children with invasive fungal infections in Guatemala. **Methods**: A review of the microbiology service database was carried out at Roosevelt Hospital in Guatemala. Positive cultures were taken from children under 15 years of age, in a period of seven years, from 2007 to 2014, with its corresponding medical history. **Results**: Finally, 23 isolates were documented but only 15 patients were included in the study with complete information; 10 *Histoplasma capsulatum* cases, 4 *Cryptococcus neoformans* cases and 1 *Coccidioidessp* case. The average age was 7 years old for Histoplasma and 9 years old for Criptococo, with an age range from 6 months to 14 years. Around 60% of the patients were older than 5 years, of which, more than two-thirds were HIV positive children without antiretroviral therapy, who presented an invasive fungal infection at the time of HIV diagnosis. These infections are endemic in Guatemala, so the distribution was mostly uniform. Around 80% of the patients had some disease related to immunodeficiency and 70% were infected with human immunodeficiency virus (HIV). The microbiological isolation was from blood, bone marrow, lymph nodes, cerebrospinal fluid and urine. The predominant laboratory findings were decrease in hematological

series. The most frequent clinical syndromes were fever, adenomegaly, hepatosplenomegaly, respiratory, gastrointestinal, neurological and weight loss. Mortality rate was 53% (from them, 62% were HIV positive). From these patients, an87% did not receive antifungal treatment in time due to late diagnosis of the infection. **Conclusions**: These infections should be considered when treating pediatric patients from tropical regions, with nonspecific systemic symptoms and signs, lymph node involvement and hematological alterations related to the mononuclear phagocytic system, mainly if they are patients infected by HIV in an advanced stage, infants, or children with a disease that weakens the immune system. When there is a high suspicion of a fungal infection, screening for HIV is mandatory; cultures should be taken early and together with rapid diagnostic tests. An antifungal treatment should be started immediately and then modified accordingly to laboratory results.

Keywords

Cryptococcosis, Histoplasmosis, Coccidioidomycosis, Invasive Infection, Pediatrics, Immunodeficiency, HIV (Human Immunodeficiency Virus)

1. Introduction

Along the pediatric population, there are some groups with an increased risk for invasive fungal infection (IFI). Within these risk groups, are found extremely premature newborns (especially less than 1000 g), children who require prolonged admission in intensive care units, patients with hemato-oncological diseases and patients who undergo precursor hematopoietic or solid organ transplants. Also children who have primary or acquired immunodeficiency, such as HIV infection or prolonged immunosuppressive treatment are at risk for IFI [1] [2].

Histoplasma capsulatum is a fungus acquired by inhaling thermally dimorphic microconidia (environmental mold becomes yeast at 37˚C), produced by the micellar form. There are two biotypes able to infect humans: *H. capsulatumvar-capsulatum* and *H. capsulatumvarduboissii*.

In Latin America, the prevalence ranges from 2.1% to 20% and is defined as AIDS related event in 30% - 75% cases. Lung disease is the most common presentation followed by cutaneous diseases. Dissemination occurs in more than 50% of patients, and in these cases, up to 20% are co-infected with tuberculosis. More than 7% of all HIV patients in Guatemala manifest this infection in a disseminated way [3] [4].

For the immunological diagnosis, the CD4 count is usually <150 cel/ul, although there is no threshold established in infants. It affects people immunosuppressed mainly by HIV, healthy infants from endemic regions <2 years, patients with rheumatological diseases under immunosuppressive therapy, children with acute lymphoblastic leukemia without neutropenia and patients after

undergone a solid organ transplantation [5] [6].

When IFI is in its disseminated form, the manifestations are nonspecific and systemic.

It is considered the most common endemic mycosis in the United States and Central America, causing localized epidemics related to environmental alterations such as exposure to bird droppings, bats and dust [7].

Cryptococcosis is produced by *Cryptococcus neoformans varneoformans*, which is responsible for 95% of cases, and *Cryptococcus neoformansvargattii*, mostly observed inimmunocompetent patients. This infection is the second cause of death by fungi in Latin America. This yeast is encapsulated and is acquired by inhalation and affects patients with AIDS, transplant recipients, Sarcoidosis patients, chronic lymphoproliferative and auto immunedisease patients. It has also been described in children without immunodeficiency and patients without underlying disease up to 5% - 10% [4] [8] [9].

The most common manifestation in Latin America is meningoencephalitis, and 85% of cases are produced by *C. neoformans,* of which, 80% are associated with HIV infection. Lung disease without dissemination is rare in children. This fungal infection can also affect lung, bone and skin tissues.

Coccidioides species include *Coccidioides immitis* in California, and *Coccidioides posadasii* in Arizona, Texas, Mexico, Central America and South America. In Central America, there are two endemic areas: the Motagua River Valley, Guatemala, and the Comaya Valley, Honduras. This dimorphic fungi, is acquired by inhaling the arthroconidia, which are spores that grow in warm soil in arid areas of the Americas. It is estimated that 60% of infected people do not develop symptoms or the symptoms are mild.

This infection is self-limited in more than 90% of children. Of those who do not limit the disease, 40% have flu-like symptoms, others could go up to disseminated infection (less than 5%), being immunosuppression a risk factor, even though it can affect healthy children. At lung level, it causes nodules and cavities (uncommon in children). Children with primary lung infection mainly may have fever, malaise, and chest pain, but it could affect bone and skin tissue, meninges and lymph nodes. In endemic areas, cough, fever, and cervical adenopathies are a useful triad for diagnosis [10] [11].

The incidence of these fungi infections has decreased due to antiretroviral treatment, but they continue affecting HIV infected patients in regions where the diagnosis of viral and fungal diseases is insufficient. The three fungi are endemic in Guatemala. We elaborated this review because of the poor information available on these infections in children.

2. Methodology

This retrospective descriptive study was carried out in the pediatric department of the Roosevelt Hospital, a reference center in Guatemala.

The database of positive cultures from pediatric patients for endemic fungi of

the microbiology department was reviewed. Data used was from 2007 to 2014, excluding diagnoses made by rapid tests. Enrollment was limited to pediatric patients (aged under 18 years) with newly diagnosed invasive fungi infection with medical records available.

The files were reviewed, focusing on epidemiological variables (gender, age and origin), clinical (predominant clinical manifestations and associated medical conditions), fungi (site of fungus growth) and laboratory data.

Qualitative variables were summarized using counts and proportions. Since data collected were considered as population-based, no hypothesis testing was conducted.

3. Results

1) Microbiological isolation:

For seven years, 23 isolates were documented:

a) *Cryptococcus neoformans* (12 cases)

b) *Histoplasma capsulatum* (10 cases)

c) *Coccidioides* sp. (1 case)

The study included ten patients with histoplasmosis, 4 with Cryptococcosis and 1Coccidioidomycosis case.

From the 12 Cryptococcus cultures, 8 of them, blood (1), cerebrospinal fluid (CSF) (3), urine (2), tracheal aspirate (1) and skin (1), were not included in the analysis because clinical data was not available.

2) Demographic data and associated medical conditions:

Table 1 shows patients characteristics, including the type of infection, age, and gender.

In the case of histoplasmosis, the average age was seven years old, and this infection occurred more in males (6/10).

Overall, 70% of the children were infected by HIV and one of them was coinfected by Hepatitis C virus (HCV). Other conditions were juvenile dermatomyositis under immunosuppressive therapy and two healthy infants with acute progressive disseminated histoplasmosis.

In the case of cryptococcosis, the average age was nine years old, and the distribution was equal in both genders. Two out of four patients with cryptococcosis had HIV infection. One of the patients had myelomeningocele and chronic renal failure and there was an infant with a urine isolation with no apparently underlying disease.

Regarding to coccidioidomycosis, there was a case in a 13-year-old girl with Down Syndrome.

Belonging the origin, according to regions of the country, more than half of the cases corresponded to central zone and south coast. Histoplasmosis cases had the widest distribution, although 90% of the cases were in the eastern, central and southern areas of the country.

Overall, distribution of infections was uniform throughout the country, especially in areas with tropical climate. There were no cases in the northern region.

Table1. Characteristics of children with fungal infections.

	Histoplasmosis	Cryptococcosis	Coccidioidomycosis
No. of patients	10	4	1
Average age years, (SD)	7 (5.67)	9 (4.86)	13 (0)
Gender (M/F)	6/4	2/2	1/0
HIV+	7 (70%)	2 (50%)	0
Other diseases	Juvenile dermatomyositis	Myelomeningocele and CRF (1)	Down's Syndrome
Without disease	2 cases	1 case	

SD = standard deviation, M = male, F = female, HIV = Human immunodeficiency virus.CRF = chronic renal failure.

Table 2 shows CD4 T lymphocyte count and basal viral load for HIV positive patients according to the type of fungus. From them, 89% were in stage 3 according to the CDC classification based on CD4 T lymphocite count. Only a one-year old infant was found in stage 2 [12].

Regarding to viral load, patients older than ten years had values below100,000 cp/ml while younger children had higher viral load values. These patients were not on antiretroviral therapy because they were diagnosed with HIV along with the fungal infection.

3) Symptoms and signs

According to Table 3, the most frequent symptom was fever. It occurred in half of the cases of histoplasmosis and cryptococcosis. Other frequent symptoms of histoplasmosis were cough and asthenia. Dyspnea, headache, vomiting, diarrhea, and odynophagia, were less frequently observed, without predominance of a particular infection.

Regarding the clinical signs, we observed that adenomegaly, pallor, hepatosplenomegaly, exanthema, and wasting were the most frequent in histoplasmosis. Craneal hypertension occurred in cryptococcosis and the case of coccidioidomycosis presented suppurative adenomegalias without any other location.

4) Microbiological isolation site and affected systems:

Table 4 summarizes the isolation according to the type of sample and patient. Most of the isolated fungi were obtained from blood and bone marrow culture, collectively 7 (47%), ganglion biopsy culture 4 (27%), and CSF culture 2 (13%).

Histoplasma capsulatum was found primarily in blood culture and myeloculture in 7 patients, and ganglion biopsy culture in 3 patients. In one patient, urine and pleural fluid were isolated.

Cryptococcus neoformans was isolated in the cerebrospinal fluid of 2 patients infected with HIV, and in peritoneal fluid and urine. The only case of *Coccidioides* sp. was found in a culture of a cervical lymph node biopsy sample.

The infection by *Histoplasma capsulatum* did not affect a specific organ since in all (100%) of the cases was disseminated (all patients were immunosuppressed and healthy infants); Central Nervous System (CNS) was affected in 50% of

Table 2. HIV Infection data according to infection.

	Age (years, months	CD4 (Cel/ul)	Stage according to CD4	Viral load (Cp/ml)
Histoplasma capsulatum	13	5	3	5160
	6	17	3	123,000
	2.7	35	3	153,000
	0.11	941	2	10,000,000
	14.11	6	3	3,280,134
	3.11	325	3	474,043
	8	17	3	8965
Cryptococcus neoformans	12.4	67	3	811,569
	11.6	3	3	49,667

Table 3. Clinical manifestations.

	Histoplasmosis	Cryptococcosis	Coccidioidomycosis
Clinical manifestations			
Symptom			
Fever	5/10 (50%)	2/4 (50%)	0
Cough	2/10 (20%)	1/4 (25%)	0
Dyspnea	1/10 (10%)	1/4 (25%)	0
Headache	1/10 (10%)	1/4 (25%)	0
Vomiting	1/10 (10%)	1/4 (25%)	0
Diarrhea	1/10 (10%)	1/4 (25%)	0
Sore throat	1/10 (10%)	0	0
General discomfort	1/10 (10%)	0	0
Asthenia	2/10 (20%)	0	0
Signs			
Adenomegalia	4/10 (40%)	0	1/1 (100%)
Wasting	2/10 (20%)		
Pallor	4/10 (40%)	0	0
Rash or purple	2/10 (20%)	0	0
Decreased weight	1/10/10%)	0	0
Seizures	1/10 (10%)		
Hepatosplenomegaly	3/10 (30%)	0	0
Intracranial hypertension	0	1/4 (25%)	0
Sepsis	1/10 (10%)		

Cryptococcus neoformans cases (HIV patients), and *Coccidioides* sp. affected lymph nodes in the patient infected.

5) Antifungal treatment and deaths:

According to Table 5, eight of the patients died, mostly histoplasmosis infected patients. More than half of HIV positive infection children with histoplasmosis infection died. The causes of death were related to complications such as pneumonia, septic shock, and marrow aplasia in an average of 18 days after diagnosis.

Table 4. Isolation Site and affected system.

	Histoplasmosis	Cryptococcosis	Coccidioidomycosis
Culture results			
Ganglion culture	3/10 (30%)	0	1/1 (100%)
CSF	0	2/4 (50%)	0
Blood	3/10 (30%)	0	0
Urine	0	1/4 (25%)	0
Bone marrow	1/10 (10%)	0	0
Peritoneal fluid	0	1/4 (25%)	0
Blood and bone marrow	2/10 (20%)		
Blood, pleural fluid and urine	1/10 (10%)		
Affected system			
Disseminated	10/10 (100%)	0	0
Lymph nodes	0	0	1/1 (100%)
CNS	0	2/4 (50%)	0
Urinary system	0	1/4 (25%)	0
Peritoneum	0	1/4 (25%)	0

CSF: cerebrospinal fluid. CNS: Central Nervous System.

Table 5. Antifungal treatment and information on the death of children with fungal infections.

Age (years, months)	Sex	Fungal infection	HIV +	Antifungal treatment	Death	Death after diagnosis (days)	Cause of death
13	M	*H. capsulatum*	Yes	Amphotericin Band Itraconazole	Do not	-	-
6	M	*H. capsulatum*	Yes	Amphotericin Band Itraconazole	Do not	-	-
13	F	*C. immitis*	Donot	Fluconazole	Do not	-	-
12, 4	F	*C. neoformans*	Yes	Amphotericin Band Fluconazole	Do not	-	-
1, 10	M	*C. neoformans*	Do not	Any	Yes	14	Complicated pneumonia
2, 7	M	*H. capsulatum*	Yes	Any	Yes	4	Severe anemia
11, 6	M	*C. neoformans*	Yes	Any	Yes	8	Meningitis, pneumonia
0.11	F	*H. capsulatum*	Yes	Any	Yes	16	Pneumonia, chronic diarrhea
14, 11	F	*H. capsulatum*	Yes	Any	Yes	10	Septic shock, bone marrow aplasia
3, 11	M	*H. capsulatum*	Yes	Any	Yes	80	Pneumonia, septic shock
10, 6	F	*C. neoformans*	Do not	Any	Do not	-	-
14	F	*H. capsulatum*	Do not	Any	Yes	11	Septic shock
8	M	*H. capsulatum*	Yes	Amphotericin B and Itraconazole	Do not	-	-
1, 2	M	*H. capsulatum*	Do not	Amphotericin B and Itraconazole	Do not	-	-
0.6	F	*H. capsulatum*	Do not	Amphotericin B	Yes	4	Multi-organic failure

From al the patients, 53% did not receive any antifungal treatment due to the late diagnosis of the infection. This occurred in 50% of the patients with histoplasmosis infection and two-thirds of cryptococcosis infected patients.

Histoplasma capsulatum infection was treated with Amphotericine B with or without Itraconazole, for *Cryptococcus neoformans* infection, Amphotericine B and Fluconazole and for *Coccidioides* sp. was used Fluconazole.

One of the seven patients who received antifungal treatment died, and from the eight patients that did not received treatment, seven patients died.

4. Laboratory Results

1) Hematology:

Table 6 shows data obtained from laboratory analyses, according to age, sex, and infection. According to hematology data, patients were stratified by sex and age [13].

More than a half (53%) of patients had leukopenia, 20% neutropenia and 73% of the patients had lymphopenia. More than 70% of children had anemia, and 33% had thrombocytopenia.

In general, more than 90% of the patients presented some hematological alteration, a decrease in some of the myeloid or lymphoid series. Lymphopenia and anemia were the predominant symptoms. Overall, children with HIV had lymphopenia (89%). According to the type of fungus, 70% of the cases of histoplasmosis and 75% of cryptococcosis had some hematological alteration.

Table 6. Hematology and blood chemistry results of children with fungal infections

Age (years, months)	Sex	Fungal infection	WBC (K/ul)	Neut. (mm^3)	Lymph. (mm^3)	Hb (g/dl)	HT (%)	PLT (K/ul)	GLU (mg/dl)	AF (UI/L)	LDH (U/L)	ALTTGP (U/L)	ASATTGO (U/L)
13	M	*H. capsulatum*	4.3	2.4	1.9	13.8	43.6	171	83	145	230	46	42
6	M	*H. capsulatum*	7.9	6.4	1.5	13.3	40.6	403	85	289	218	22	26
13	F	*C. immitis*	3.7	2.1	1.6	13.8	43.9	231	72	153	175	19	24
12, 4	F	*C. neoformans*	3.12	1.26	1.38	11.6	33.7	371	102	384	640	28	55
1, 10	M	*C. neoformans*	9	7.87	0.99	7.7	23.8	279	239	-	1039	-	-
2, 7	M	*H. capsulatum*	5.87	3.5	1.96	6.4	21.8	277	58	863	1088	73	129
11, 6	M	*C. neoformans*	4.56	3.99	0.47	9.9	30.3	278	110	93	-	29	54
0,11	F	*H. capsulatum*	17.14	4.14	10.14	9.7	32.3	194	104	294	1186	66	142
14, 11	F	*H. capsulatum*	0.9	0.48	0.34	4	12	1	94	269	785	13	39
3, 11	M	*H. capsulatum*	3.38	1.62	1.59	5.6	17.2	28	62	298	79	-	-
10, 6	F	*C. neoformans*	12.63	8.92	2.19	11.9	36	578	81	-	333	6	-
14	F	*H. capsulatum*	5.25	4.43	13.30	8.2	24.5	438	187	282	575	6	30
8	M	*H. capsulatum*	2.65	1.97	0.68	6.2	-	10	-	248	-	42	136
1, 2	M	*H. capsulatum*	2.20	1.2	1	7.2	-	80	-	240	-	84	125
0.6	F	*H. capsulatum*	11.29	3.16	7.1	12	36.7	4	81	117	757	85	81

WBC: white blood cells. Neut. Neutrophils. Lymph. Lymphocytes. Hb. Hemoglobin. HT Hematocrit. PLT platelets. GLU glucose. AF Alkaline phosphatase. LDH lactic dehydrogenase. ALT Alanine aminotransferase. ASAT aspartate aminotransferase.

The only case of coccidioidomycosis did not present important changes.

2) Blood chemistry:

Taking the normal value of alkaline phosphatase up to 270 UI/L, 46% of the children analyzed presented a high value. However, only one of the cases had a value greater than twice the normal value.

Taking 480 UI/L as the upper limit for lactate dehydrogenase, 58% of analyzed patients had an altered value. There was a 66% of altered results in criptococcosis infected patients and 63% of histoplasmosis infected patients.

Regarding to hepatic profile, 46% of patients presented an elevation of alanine aminotransferase (ALT) and 75% presented aspartate aminotransferase (AST) elevation.

From histoplasmosis patients, 66% of them had elevated ALT or AST values. All cryptococcosis cases presented ALT or AST elevation.

The only case of coccidioidomycosis did not present biochemical alterations.

5. Discussion

This study is the first one conducted in a reference hospital in Guatemala describing the characteristics of invasive fungal infections in the pediatric population. The total burden of serious fungal infections in Guatemala is unknown, but it is likely to exceed 268,363 cases (1.7% of the population), and cases reported in the pediatric population are not common [14].

The incidence reported in the literature of endemic fungal infections in children is lower than in adults, in which HIV infection and reactivation of past infections are predominant risk factors. Due to the rapid progression and poor prognosis of these infections in the pediatric population and the difficulty of microbiological isolation, are generally underestimated [15].

Although age range goes from 11 months to 14 years, there is a trend in children over five years old, especially in the case of HIV infected children (more than 65% are older than five years). These are children with slow progression of HIV infection that begins with reactivation of past infections, as occurs with adults. However, more than a third of the patients were under five years old, which indicates probable primary infection due to the endemicity of these pathogens in Guatemala.

The distribution by regions was uniform, due to tropical climate in the country and the predominant economic activity, consisting on agriculture and livestock, which favors the cycle of these fungi and high exposure to inocula. However, there is a trend in the central and southeast region, perhaps because of the proximity to the hospital. There were no cases in the northern region. It is possible that the access from these cities to the capital makes it difficult to detect cases. *Histoplasma capsulatum* had the widest and most uniform distribution in many regions. Regarding frequency, the most isolated fungus was *Cryptococcus,* however, due to missing files; only 4 cases could be included in the study.

In general, around 80% of the patients had some disease related to the wea-

kening of the immune system, as rheumatological disease, chronic kidney disease, and HIV infection (that occurred in 70%), and a girl with Down Syndrome. HIV infection was the most important risk factor for these infections [16].

There is a possibility of these infections in children without underlying diseases, for example, there were two cases of progressive disseminated Histoplasmosis of the infant, a condition that may go unnoticed and be confused with other diagnoses. Furthermore, there were eight lost cases of Cryptococcosis infection that were not found in the HIV database, despite being a hospital where systematic HIV screening is performed on all patients that present these infections.

Pathogens were isolated from blood, bone marrow, lymph nodes, cerebrospinal fluid, peritoneal liquid, and urine. The yield of the culture of these samples could not be determined because it was not possible to analyze all the samples requested. Although the low profitability of the microbiological isolation for these pathogens is known, Histoplasma predominated in blood, bone marrow and lymph nodes due to its disseminated presentation, and Cryptococcus predominated in fluids, mainly cerebrospinal, due to the fact that more than 90% of cases with Cryptococcosis produce meningoencephalitis in patients with advanced HIV infection.

The optimal approach requires an early and accurate diagnosis to implement the appropriate antifungal therapy and minimize the use of toxic drugs. Standard methods as culture, histopathology and microscopy often lack sensitivity and specificity. These limitations have promoted the development of non-invasive diagnostics methods for fungal antigens or genetic material detection. Such is the case of galactomannan, 1 - 3 B, D glucan or Histoplasma antigen in urine by enzymatic immunoassay. However, the first two methods are not validated or standardized in children and they are not available in most countries with limited resources. However, Histoplasma antigen has a sensitivity of 95% in disseminated disease in patients with AIDS and can cross-react with *Blastomyces dermatitidis, Paracoccidioides brasiliensis, Penicillium marneffei*, *Coccidioides immitis* and *Coccidioides posadasii* [17] [18].

The lack of specificity from clinical symptoms causes diagnosis and treatment delayed. Although more than half of the patients did not receive adequate treatment, mortality (which exceeded 50%) was higher in those who did not receive treatment. It shows a late diagnosis due to the nonspecific presentation of these infections and the difficulty of microbiological isolation. Another problem is the progress of opportunistic and underlying diseases (mainly HIV infection) since these patients are late diagnosed with HIV (89% of HIV patients were in stage three, and one was a stage two infant where the CD4 value is not predictive).

There should be caution when interpreting the CD4 T lymphocyte value in children < 5 years infected with HIV, as regards to its relationship with opportunistic infections and the cut-off point, for example for histoplasmosis it is not defined, presenting qualitative alterations rather than quantitative. Furthermore,

in children, the CD4 count to consider severe immunosuppression is different from that of adults. For example, two of the patients did not have CD4 < 150 which is the cut-off point for histoplasmosis in adults [19].

Regarding to viral load, older children had values below 100,000 cp/ml, compared to young children, due to the natural evolution of the infection since younger children have higher replication of the virus.

In general, this situation of HIV and fungal infection in children in non-industrialized countries is common; being diagnosed at the same time, with no time for antiretroviral treatment administration.

In most of the cases, signs and symptoms were nonspecific, predominating fever and constitutional systemic signs with involvement of the mononuclear phagocytic system (hepatosplenomegaly, lymphadenopathy).

This supports isolation results, mainly in Histoplasmosis due to its 100% disseminated presentation. In the case of Cryptococcosis, the classic signs of CNS involvement were isolated from CSF in patients with HIV infection [20].

The lack of specificity from the clinical findings causes the diagnosis and treatment to be delayed. Lab findings show decreased values of hematological parameters in these patients mainly for histoplasmosis and cryptococcosis. This is related to the presence of a secondary Hemophagocytic Syndrome [21].

Anemia and lymphopenia are predominant, being the last one related to the depletion of CD4 T lymphocytes in patients with advanced HIV infection, caused by the late diagnosis.

The discrete elevations of alkaline phosphatase, lactic dehydrogenase and transaminases were observed in about half of the children. The AST/ALT index of 2.5 or greater, described as a contributor in the diagnosis of disseminated histoplasmosis compared to other IFAs, was observed in three children with this entity, but not in the others. These nonspecific findings should be considered in these infections, mainly in disseminated histoplasmosis [22] [23].

The limitations of this study are that, as it is a retrospective study, some clinical histories were not available to be reviewed with the diagnosis of invasive fungal infection. The lack of some diagnostic techniques that are used today for these infections is also a limitation to our work.

In summary, in countries with tropical climates, such as Guatemala, there should be a higher index of suspicion of regional fungal infections in patients of pediatric age who present a situation of severe hematological cytopenias and neurological symptoms [24].

Although infection by regional fungi can occur in immunocompetent patients, it is necessary to perform screening for immunodeficient patients, including HIV infection, since it is the most important risk factor for IFI in this population. The prognosis of the infection may depend on early diagnosis and treatment.

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Interest Conflict

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