Delay in Diagnosis in Children with Visceral Leishmaniasis: A Single-Center Experience

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Abstract

Objective: Visceral leishmaniasis (VL) is a systemic disease characterized with irregular fever, hepatosplenomegaly, and pancytopenia. Because VL is difficult to detect, misdiagnosis is common and treatment is often inappropriate and delayed. The aim of this article defines the reasons that cause a delay in diagnosis of the disease in Western Anatolia, where VL is endemic. We hope this article helps clinicians to improve their knowledge about the diagnosis of VL and to consider of the disease better.

Material and Methods: The clinical and laboratory data records of 15 patients with VL who had been diagnosed and followed up in our hospital from August 2005 to December 2011 were retrospectively reviewed. The demographic, clinical, and laboratory features of the patients were recorded.

Results: Thirteen patients were from Western Anatolia, which is the most endemic region of Turkey. The most common complaints were pallor and fever. All patients had hypoalbuminemia, hyperglobulinemia, and cytopenia. The symptoms of the patients had begun 5–180 days before admission.

Conclusion: We concluded that VL should be considered in patients with prolonged fever, pallor, hepatosplenomegaly, and cytopenia and those who live in an endemic region. Education for general practitioners and pediatricians is necessary, and these educational efforts may reduce the delay in diagnosis.

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Introduction

Visceral leishmaniasis (VL), caused by *Leishmania infantum,* has been known to exist in the western and southeastern parts of Turkey for a long time, and it may be an important public health problem throughout the country. VL is fatal if it is left untreated. VL may present as an acute disorder with fever and hepatosplenomegaly or as a more chronic condition characterized by increasing hepatosplenomegaly and pancytopenia and has been associated with high mortality. If it is not searched in particular, diagnosis may be easily overlooked or delayed (1-5). Therefore, diagnosis of VL should always be kept in mind.

In this study, clinical, demographic, and laboratory features and diagnostic tools for pediatric VL were determined, and the factors that cause the delay in diagnosis were also evaluated.

Material and Methods

The clinical and laboratory data records of 15 patients with VL from August 2005 to December 2011 were recorded.

The age, local origin, previous complaints, symptoms, clinical and laboratory features, therapies, and duration of symptoms from onset to admission were obtained from patients' history and previous medical reports.

At the time of admission, laboratory findings such as hemoglobin, leucocyte and thrombocyte

counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum albumin and globulin, alanine (ALT) and aspartate aminotransferase (AST) values were recorded. The lower and higher levels of hemoglobin, leucocyte and platelet counts, ESR, CRP, serum albumin and globulin, ALT and AST values were defined as an age-adjusted reference range for healthy children (6). In our hospital, the diagnosis of the disease was based on the following criteria: clinical features, immunofluorescence antibody test (IFAT) at a titer of ≥1/64, and the demonstration of *Leishmania* amastigotes in Giemsa-stained bone marrow aspirates. The IFAT was performed using standard procedures, and titers ≥1/64 were scored as positive (7). Bone marrow aspirates were obtained from patients for direct examination by microscopy after staining with Giemsa.

Results

The median age of the patients was 37.0 months, ranging between 8 and 144 months. Eleven patients (73.3%) were below 5 years of age.

Thirteen (86.7%) patients were referred from Western Anatolia; seven were from rural and six were from urban areas. Moreover, five of these patients were referred from Manisa districts, which are known as one of the well-known endemic counties in Turkey. The other two (13.3%) patients were referred to our hospital from southeastern Anatolia for further investigations and treatment (Table 1). Nine of 15 patients were admitted to the hospital in February (n=3), March (n=2), and August (n=4). None of the patients had an underlying disease at admission. The symptoms of the patients had begun 5–180 days before admission (median 20.0 days) (Table 1). The most common complaints of the patients at the first admission at the other medical centers were pallor (n=14, 93.3%), fever (n=13, 86.7%), and abdominal distention (n=5, 33.3%). We observed hepatosplenomegaly in all patients.

Thirteen patients (86.7%) with fever were diagnosed with upper or lower respiratory tract infections (n=11) and sepsis (n=2) and were treated with various antibiotics by general practitioners and pediatricians for 7-180 days. Seven patients were referred to our hospital for further investigation of fever and splenomegaly, and six patients with fever and cytopenia were also referred to our hospital because of did not obtain any clinical and laboratory healings with many different therapies. Two patients were referred our hospital 5 and 20 days after for abdominal distension; however, these patients were found to have profound splenomegaly. These two patients were referred to our hospital from the medical centers of the Izmir province. The delay in diagnosis was more frequent in patients referred from rural areas (n=9) than from urban areas (n=5) (Table 1).

The mean hemoglobin levels at admission was found to be 6.5±1.8 g/dL. Thirteen patients (86.7%) had pancytopenia and one patient (6.7%) had anemia and thrombocytopenia. Hypoalbuminemia (mean 2.3±0.5 g/dL) and hyperglobulinemia (mean 4.1±1.0) were found in all patients. CRP and ESR levels were found to be high (mean 8.2±5.1 mg/dL and 73.6±39.9 mm/h, respectively).

ALT (minimum level 7 IU/L, maximum level 248 IU/L, and median 21.0 IU/L) and AST (minimum level 22 IU/L, maximum level 408 IU/L, and median 44.0 IU/L) levels were found to be variable.

We detected that *Leishmania* IFAT was positive in all patients, and *Leishmania* amastigotes were detected in bone marrow aspiration in all patients (Table 2).

We also detected a hemophagocytic syndrome based on the examination of bone marrow aspirations and other clinical and laboratory findings in two patients (patient no. 6 and 13).

All patients were cured at the end of our therapies and no relapse occurred during the 2-year follow-up.

Table 1. Demographic and clinical features of patients (*)

Case number	Age (mo)	Time for diagnosis (days)	Pallor	Fever	HSM	Local origin
1	36	90	+	+	+	WA-R
2	73	20	+	+	+	WA-U
3	54	25	+	+	+	WA-R
4	66	5	+	-	+	WA-I
5	37	180	+	+	+	EA-R
6	38	10	+	+	+	WA-U
7	26	90	+	+	+	WA-R
8	48	7	+	+	+	WA-R
9	84	20	+	-	+	WA-R
10	18	7	+	+	+	WA-R
11	17	15	+	+	+	WA-R
12	144	10	-	+	+	WA-U
13	8	20	+	+	+	WA-U
14	8	60	+	+	+	WA-U
15	22	60	+	+	+	EA-R

(*): mo: month; HSM: Hepatosplenomegaly; WA: Western Anatolia; EA: Eastern Anatolia; R: Rural; U: Urban; I: Center of the city

Table 2. Laboratory features, diagnostic tools, and treatment regimens of patients (*)

Cases	Hb (g/dL)	WBC (/mm³)	Plt (/mm³)	CRP (mg/dL)	ESR (mm/h)	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)	Globulin (g/dL)	IFAT	Amastigotes in bone marrow
1	4.5	6560	105000	12.6	87	248	364	2.0	3.8	1/512	+
2	6.8	2950	174000	2.59	93	34	63	1.9	3.1	1/320	+
3	6.8	2900	117000	4.2	14	236	408	2.5	3.3	1/64	+
4	8.7	6150	69000	6.7	109	12	41	2.3	6.2	1/256	+
5	5.7	3300	75000	5.14	104	7	22	1.6	4.1	1/1024	+
6	4.2	4000	29000	18.6	40	57	44	1.8	4.1	1/1024	+
7	5.4	2500	77000	0.76	114	30	74	1.7	5.3	1/1024	+
8	4.7	2070	129000	5.92	33	10	41	2.9	3.2	1/128	+
9	5.2	1550	95000	11.2	140	7	22	2.0	6.1	1/256	+
10	7.3	7120	108000	9.84	86	14	24	2.1	3.7	1/256	+
11	5.8	3190	67000	15.8	115	21	48	2.7	2.7	1/128	+
12	10.9	5920	293000	7.5	69	18	25	2.9	4.0	1/64	+
13	7.9	5800	136000	4.38	39	87	44	3.0	3.1	1/64	+
14	6.4	3300	52000	12.3	15	102	83	2.5	4.3	1/1024	+
15	6.7	2800	42000	5.3	46	14	84	2.4	4.6	1/1024	+

(*) Hb: hemoglobin; WBC: white blood cells; Plt: platelets; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ALT: alanine transaminase; AST: aspartate aminotransferase; IFAT: immunoflourescence antibody test

Discussion

The clinical features of pediatric VL patients in Turkey suggest that it is the Mediterranean type which is mostly observed in children younger than 5 years of age (1-3, 5, 8). Eleven of 15 patients were below 5 years of age in our study.

Leishmania infantum is endemic in Western Anatolia and the Mediterranean regions of Turkey (8-15). In this study, 13 patients were from various counties of Western Anatolia.

There is no nationwide epidemiological research about the incidence of the disease, and there are only a few case reports or limited series of childhood leishmaniasis from Turkey (11-15). It is suspected to be underreported in Turkey because of a lack of an awareness of the disease among physicians (8).

In the western regions of Turkey, between April and September, the prevalence of the disease has increased many fold because the sandflies have their highest activity during this period, and according to the duration of the incubation period, the symptoms appears from October to February. Most of our patients were admitted to the hospital in February, March, and August, thus indicating that patients were probably infected during summer and autumn, which was similar to the findings in the literature (3, 4).

Children with VL may be asymptomatic or may have mild constitutional symptoms and intermittent fever. In 25% of the children without therapy, the disease, which is also called kala-azar, proceeds to active illness within 2-8 months. In this condition, the fever is intermittent and the spleen begins to enlarge. The classic clinical features of the disease are high fever, marked splenomegaly, and hepatomegaly (1-3, 5, 8). Among our patients, pallor (93.3%), and fever (86.7%) were the most common complaints. Hepatosplenomegaly was found in all of our patients, pallor was found in 93.3% of our patients, and high fever was found in 86.7% of our patients. VL was diagnosed in a median time of 20 days from disease onset (range 5–180 days) in our patients. In 12 patients (80%), the disease was diagnosed between 15 and 180 days and we accepted them delay in diagnosis. We also found that the delay in diagnosis was more frequent in patients referred from rural areas than from urban areas.

We thought that general practitioners and pediatricians could not suspect or recognize the disease; however, they could recognize this disease when the spleen began to enlarge and/or cytopenia was detected. All the centers that referred these patients to our hospital with their medical records provided clinical and laboratory results and many probable diagnoses except VL. Similar results and conclusions were reported from Turkey. In these articles, the mean and the range of the periods of delay in diagnosis were reported from 4 days to 12 months (mean 60.7±88.5 days) (11), 10 days to 3

months (mean 29.3±9.5 days) (12), 7 to 90 days (mean 41 days) (13), and 7 days to 6 months (14).

In our patients, diagnosis of VL was established within 1-2 days of admission with laboratory examinations and detection of *Leishmania* amastigotes in bone marrow aspiration smears and positive *Leishmania* IFAT results.

Pancytopenia is the prominent feature of the disease. Hyperglobulinemia, hypoalbuminemia, and high transaminase levels are the other common findings (1-3, 5). All of our patients had anemia, and 13 (86.7%) of them had pancytopenia. Elevated ESR and CRP are also the other common laboratory findings (1-3, 5), which were observed in 14 (93.3%) of our patients.

Conclusion

VL can manifest itself with symptoms which are fairly common for other diseases. Patients from endemic areas with varied symptomatology of fever, anemia, and hepatosplenomegaly should be suspected of VL and should be referred to the centers where facilities for its diagnosis and treatment are available for early detection of disease. However, clinicians are often ill informed on the symptoms of and detection methods for VL, which may lead to an initial misdiagnosis and a delay in diagnosis and treatment. Hence, most patients are referred in the advanced stage of the disease.

VL remains a public health problem in Turkey. The disease is fatal if left untreated; thus, early detection and feasible management of complications may reduce morbidity and mortality in childhood VL.

Because of the above mentioned reasons, practitioners and pediatricians need to be informed of VL in Turkey, particularly those who work in endemic areas. Education for such practitioners and pediatricians is necessary. Education efforts about VL may reduce the initial misdiagnosis and the time from onset of symptoms to diagnosis.

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