Visceral leishmaniasis in Malta—an 18 year paediatric, population based study

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Abstract

Background—Visceral leishmaniasis (VL) is a chronic parasitic infection that infects approximately 400 000 individuals annually, with a predilection towards early childhood.

Aims—To study the epidemiology of VL in childhood.

Methods—VL is endemic in Malta, a small archipelago of islands in the centre of the Mediterranean with a total population approaching half a million. Notification of human cases of leishmaniasis is compulsory. Case records of all 81 paediatric patients with VL between 1980 and 1998 were analysed.

Results—The annual incidence of VL declined for all cases of VL, and declined significantly for paediatric cases ($p = 0.01$). For 1994 to 1998, the overall incidence of VL was 0.9 per 100 000 total population and the paediatric incidence was 2.5 per 100 000 population. Median age at presentation was 34 months. Common features at presentation were splenomegaly, hepatomegaly, fever, and pancytopenia with high lymphocyte and monocyte counts. The diagnostic sensitivity of isolated immunofluorescent antibody testing was equivalent to bone marrow aspiration (95%). Blood transfusions for anaemia were required in 93% of patients. Eleven per cent had intercurrent infections. All patients were cured, and were initially treated with intravenous sodium stibogluconate. Defervescence occurred after a median of six days of treatment, and patients continued to be treated on a day case basis. Nine relapsers were retreated with sodium stibogluconate, achieving a cure rate of 94%, but five patients required additional drug therapy. There were no permanent sequelae associated with VL or its treatment.

Conclusions—The decreased incidence is attributed to the eradication of stray dogs which are the disease reservoir.

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Keywords: leishmaniasis; epidemiology; antiprotozoal agents; antimony; sodium stibogluconate; retrospective study

Visceral leishmaniasis (VL) is a parasitic infection caused primarily by *Leishmania donovani* in the Old World, and by *Leishmania amazonensis* in the New World.¹ VL is also known as kala azar (Hindu name meaning black poison), and is found in tropical and subtropical

regions. VL is a chronic illness that is characterised by irregular fever, hepatosplenomegaly, anaemia and leucopenia, and progressive weakness and emaciation which can result in death if left untreated. The vector is the female sandfly, and in most regions, the dog is the reservoir. The causative organism was first isolated in 1903.² In vertebrates, the parasites are found intracellularly in the reticuloendothelial system as the amastigote form, which is aflagellate, round, and 2–4 µm in diameter (Leishman–Donovan body, LDB). Infection results in notable proliferation of the reticuloendothelial system. In the vector, the promastigote form is flagellate, spindle shaped, and 15–20 µm long.¹ It is estimated that globally approximately 400 000 individuals are infected annually.³

VL is rapidly becoming an important opportunistic infection in areas where it coexists with HIV, particularly in southern Europe where 25–70% of adult VL cases are associated with coexistent HIV, and 1.5–9.5% of individuals with HIV suffer from newly acquired or reactivated VL.^{4–6} Paediatric cases have been reported in which both organisms have been isolated.⁷ Therefore studies dealing with the epidemiology and treatment of VL are important for the allocation of finite health resources.

The Maltese Archipelago comprises the islands of Malta, Gozo, and Comino, and is situated in the centre of the Mediterranean Sea, 93 km south of Sicily and 288 km north of North Africa. VL is endemic in the circum Mediterranean region, including in Malta. As in most endemic areas, the vast majority of affected cases occur in the childhood population.⁸ Notification of human cases of leishmaniasis was made compulsory in Malta in 1946,⁸ making this country an ideal location for an epidemiological study of VL in childhood.

The diagnosis of VL was first made in Malta in 1911,⁹ and the cutaneous form of leishmaniasis is also found.¹⁰ The local sandfly vector is the species *Phlebotomus perniciosus*.¹¹ The local parasite subspecies is *L. donovani* infantum¹² and the reservoir is the dog.⁹ In a single veterinary practice, immunofluorescent antibody testing (IFAT) for leishmaniasis in 252 asymptomatic or oligosymptomatic dogs was positive in 31.1%.¹³ In an animal sanctuary where asymptomatic or oligosymptomatic stray dogs were collected from all over Malta, 47.5% tested positive.¹³

We present our experience in the management of 81 paediatric patients who presented with VL over the period 1980–1998, with successful outcome of treatment.

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Methods

PATIENTS

All Maltese cases of VL notified between 1980 and 1998 were identified from Malta Health Division notification registers. Paediatric patients were defined as those aged 14 years or under. Case notes of paediatric cases were retrospectively examined, and a form detailing presentation, diagnosis, treatment, and complications thereof was filled in for each patient. Data were then entered into a spreadsheet for processing. At least one non-Maltese paediatric patient contracted VL during a brief visit to Malta.¹⁴ Such patients were not included.

DEFINITIONS

A case of VL was defined as a patient with classical features of VL and a positive bone marrow or a positive IFAT for VL. A positive bone marrow aspirate was defined as a bone marrow sample which showed the intracellular amastigote forms (LDBs). IFAT was performed using Bio Merieux substrate slides and Binding Site FITC conjugate. A strongly positive test was taken as one positive at a dilution of at least 1/180 (St Luke's Pathology Laboratory definition in conjunction with test manufacturers). In an extremely small minority of patients who presented with a clinical picture of VL but had a negative bone marrow aspirate in the era prior to the availability of IFAT, treatment for VL was instituted empirically, and confirmation of VL was reinforced by response to treatment. Relapse was defined as above.

Judgement of cure was based on clinical criteria, and in more recent years, confirmed by a negative IFAT eight to 12 months after cessation of treatment. In the data presented, numbers may not tally, on occasion, because of incomplete information from case notes.

POPULATION

Population totals and paediatric population totals for 1980–1998 were obtained from official Maltese Government publications.¹⁵

STATISTICS

Medians are used extensively, in addition to means, as some data variables were moderately skewed. In order to compare means, *t* tests were used. Fisher's exact and χ^2 tests were used to compare proportions. The Mann–Whitney U test was used to compare distribution of non-parametric data. Pearson correlation was used to calculate correlations. Seasonal variation was analysed using Edward's method of cyclic variation.¹⁶ The quadratic equations of Fleiss were used to calculate 95% confidence intervals (CI) for sensitivity and for population rates.¹⁷ A *p* value of 0.05 or less was taken to represent a statistically significant result.

Results

EPIDEMIOLOGY

Case notes were available for confirmation of diagnosis and examination for 81 of the 83 notified paediatric patients, and analysis of paediatric patients is restricted to these 81 individuals. Over the period 1980 to 1998, a total of 145 individuals were notified as having

Table 1 Incidence of visceral leishmaniasis (VL) in Malta for the period 1980–1998

Year	Total cases	Paediatric cases	VL per 100 000 total population	VL per 100 000 childhood population
1980	9	8	2.8	10.4
1981	18	11	5.5	13.9
1982	4	3	1.2	3.8
1983	4	3	1.2	3.8
1984	7	5	2.1	6.2
1985	4	1	1.2	1.2
1986	8	5	2.3	6.1
1987	6	4	1.7	4.8
1988	16	8	4.6	9.6
1989	14	7	4.0	8.4
1990	15	5	4.2	6.0
1991	13	6	3.6	7.4
1992	10	3	2.8	3.6
1993	2	2	0.5	2.4
1994	3	3	0.8	3.7
1995	2	0	0.5	0.0
1996	3	3	0.8	3.7
1997	3	2	0.8	2.5
1998	6	2	1.6	2.5

VL (table 1). Of these, 81 patients (35 boys and 46 girls) fell in the paediatric age group. The annual incidence of VL ranged from 0.5 to 5.5 per 100 000 for the total population. For the paediatric population, the annual incidence ranged from 0 to 13.9 per 100 000 paediatric population (table 1). An overall decline in incidence can be noted. This decline was not statistically significant for the entire cohort ($r = -0.35$, $p = 0.14$). However, the decline was significant for the paediatric cohort alone ($r = -0.56$, $p = 0.01$). For the five year period 1994 to 1998, the overall incidence of VL was 0.9 per 100 000 total population (95% CI: 0.5 to 1.5 per 100 000). For the same period, the paediatric incidence was 2.5 per 100 000 population (95% CI: 1.3 to 4.7 per 100 000).

The adult cases are excluded from further analysis. Median age at paediatric presentation was 34 months, with a skew towards a younger age at presentation. No seasonal variation was found ($p = 0.6$).

PRESENTATION AND DIAGNOSIS

The median duration of fever was 4.8 weeks. Maximum recorded fever was 41.1°C for two patients, with an overall mean and mode of 39.4°C. Three patients had no fever, or history of fever, at presentation.

Symptoms at presentation included anorexia (56%), abdominal pain (32%), weight loss (27%), and rigors (19%). Clinical signs at presentation included splenomegaly (96%), hepatomegaly (66%), pallor (96%), respiratory signs (35%), bruising (5%), and lymphadenopathy (4%).

Table 2 shows haematological and biochemical indices at presentation. Common haematological features included a hypochromic, microcytic anaemia, leucopenia with a low neutrophil count, high lymphocyte and monocyte count, and thrombocytopenia. Common biochemical features included a very mildly increased serum bilirubin and hypoalbuminaemia. The erythrocyte sedimentation rate was invariably raised.

IFAT for VL has been available in Malta since 1989, and this test became widely used in the paediatric age group from 1990. Serology was positive in 21 cases and negative in one

Table 2 Haematological and biochemical indices at presentation

	Median	Mean	SD	Minimum	Maximum	Normal values
Haemoglobin (g/l)	76	79	18	47	179	105–145
Mean cell volume (fl)	70	68.8	13.2	7.1	88	78–94
Mean cell haemoglobin (pg)	23	23.8	3.5	17	34	23–30
Total white count ($\times 10^9/l$)	4	4.8	2.9	1.1	14.5	6–17.5
Neutrophil count (%)	24	25.6	11.3	9	66	54–62
Lymphocyte count (%)	66	64	13.1	21	87	25–33
Monocyte count (%)	7.5	9.5	6.4	1	40	3–7
Platelet count ($\times 10^9/l$)	111	121.1	53.2	25	292	150–400
Erythrocyte sedimentation rate (mm/h)	95	89	34	10	150	0–13
Bilirubin ($\mu\text{mol/l}$)	15	15	7	5	50	<10
Alkaline phosphatase (U/l)	227	263	138	26	683	100–350
γ -glutamyltranspeptidase (U/l)	10	15	22	1	124	<40
Alanine aminotransferase (U/l)	27	49	100	2	680	0–35
Total protein (g/l)	74	74.2	10.5	56	95	57–80
Albumin (g/l)	31	30.3	7.7	2.7	45	33–47
γ globulin (g/l)	22.2	23.6	17.1	1.8	70	17–38

case of VL who had a positive bone marrow, an overall sensitivity of 95.1% (95% CI: 87.2 to 98.4%). Bone marrow aspirate failed to show LDBs in only four of the 81 cases, a sensitivity of 94.7% (95% CI: 86.2 to 98.3%). All four had repeated bone marrow aspirates which were negative, but the clinical picture was highly suggestive of VL in all four. Treatment of VL was instituted in two cases (year of presentation 1996) who had positive IFAT. In two other cases, treatment for VL was instituted without a positive bone marrow owing to the unavailability of a serological test (year of presentation 1980). All four responded to treatment (see below). In four other cases, an initial bone marrow aspirate was negative, with subsequent positive bone marrow aspirates. There was no significant difference between the sensitivity of the two tests ($p = 1.0$). The sensitivity of combined bone marrow aspiration and IFAT was 97.5% (95% CI: 90.5 to 99.6%).

TREATMENT

All patients were initially treated with intravenous sodium stibogluconate (Pentostam, Wellcome) at a mean dose of 22.9 mg/kg/day (range 10–40 mg/kg/day). Prior to 1991, the treatment protocol consisted of a slow build up in the dose of Pentostam over a mean of

five days. In 1991, the protocol changed with a very short build up in the dose of Pentostam, or just a test dose, followed by the full dose of treatment. Furthermore, prior to 1991, the majority of patients were treated with steroids and antibiotics empirically. From 1991, steroids have not been used and antibiotics used only to treat intercurrent bacterial infections.

Blood transfusion was administered to patients with haemoglobin concentrations less than 8 g/l as our experience in the management of VL has shown that haemoglobin concentrations continue to drop well into the first two weeks of treatment. Blood transfusions were required in 93% of patients ($n = 75$), and 23% ($n = 19$) of patients required transfusion on more than one occasion during treatment. There was no significant difference in requirements for blood transfusion between the two eras 1980–1990 and 1991–1998 ($p = 0.5$). Defervescence occurred after a median of six days (mean 6.4 days, SD 3.9). Again, there was no significant difference between the two eras ($p = 0.8$). Infected individuals were treated as inpatients for only a few days after establishment of a diagnosis of VL, and daily treatment with Pentostam through an indwelling intravenous cannula continued to be given on the ward on a short, day case basis.

Relapse of VL occurred in nine of 60 patients presenting up to 1991, and in none of 21 patients presenting after 1991, but this difference was not significant ($p = 0.1$). The overall relapse rate was 11%. Four patients responded to further courses of Pentostam and the remaining five required additional drugs. In total, 94% (95% CI: 86 to 98%) of patients were cured with Pentostam alone.

Table 3 summarises the clinical course of the relapsers. The mean total cumulative volume of Pentostam given for the initial course of treatment was 0.26 ml/kg (equivalent to 26 mg/kg of pentavalent antimony). There was no significant difference in cumulative dose of Pentostam given between the relapsers and non-relapsers ($p = 0.6$).

There were no permanent sequelae associated with VL or its treatment. Complications of treatment included derangement of liver function tests ($n = 1$), microscopic haematuria ($n = 1$), and proteinuria ($n = 1$), all of which resolved very soon after stopping treatment. One patient also had prolonged thrombocytopenia requiring platelet transfusion; the platelet count recovered five weeks after stopping treatment. One other patient developed diabetic ketoacidosis and relapsed (see table 3). A relatively minor but painful inconvenience was the frequent need to resite intravenous cannulas because of thrombophlebitis in all patients, with eventual difficulty in achieving intravenous access in some patients.

Nine patients had intercurrent infections. These included urinary tract infections ($n = 5$), bronchopneumonia ($n = 1$), otitis media ($n = 1$), croup ($n = 1$), unilateral thoracic herpes zoster ($n = 1$), and a Gram negative septicaemia ($n = 1$).

Table 3 Outcome of nine patients who relapsed

Year of presentation	Remarks
<i>Cured with Pentostam alone</i>	
1980	Relapsed twice, and on both occasions treated with Pentostam
1981	Relapsed five weeks after stopping treatment—afebrile but had splenomegaly. Responded to second course of Pentostam
1983	Relapsed five weeks after stopping treatment. Responded to second course of Pentostam—this time for three weeks
1984	Relapsed one week after stopping treatment. Responded to second course of Pentostam—this time for four weeks
<i>Required other drugs in addition to Pentostam</i>	
1981	Slow response to treatment. Bone marrow at two weeks showed LDBs. Pentostam increased to 25 mg/kg/day, with poor response. LDBs still present in bone marrow, so treated with pentamidine, successfully
1981	Relapsed six times. First five times treated with Pentostam. Last relapse treated with pentamidine and cotrimoxazole
1987	Relapsed four weeks after stopping treatment, and presented in diabetic ketoacidosis. Given Pentostam for three weeks but relapsed after six weeks. Given metronidazole and rifampicin for four weeks but relapsed after eight weeks. Given Pentostam for 12 weeks but remained unwell and LDBs were detected in bone marrow at one year. Successfully treated with aminosidine
1989	Relapsed at 12 weeks and treated with a combination of Pentostam and pentamidine
1990	No response to eight weeks of Pentostam. Responded to intramuscular pentamidine, a total of 15 doses on alternate days

Discussion

EPIDEMIOLOGY

The incidence of VL in Malta has decreased over the 18 year period studied. This decrease is even more impressive when one considers that the number of cases of VL notified in the late 1940s was around 200 per annum.⁸ This decline is attributed to the virtual eradication of stray dogs and the putting down of infected dogs, and the increasing urbanisation Malta.¹⁵ Outdoor activities are more popular in the typical, hot Mediterranean summer, and seasonal analysis was undertaken as increased outdoor exposure, coupled with scantier clothing, may have caused an increased number of summer infections. No seasonal variation was found. However, seasonal variations in infection rates are easily masked by the organism's long incubation period.

PRESENTATION AND DIAGNOSIS

Presentation in the paediatric age group was characteristic, with pallor, fever, and splenomegaly and hepatomegaly. The high rate of intercurrent infections is attributed to a depressed immune status while harbouring VL.¹ Haematological and biochemical indices were typical, with pancytopenia associated with high lymphocyte and monocyte counts, hypoalbuminaemia, and an increased erythrocyte sedimentation rate.

The availability of sensitive and specific serological tests naturally tempts clinicians to forego more invasive testing, such as bone marrow or splenic aspiration.¹⁸ Our data confirm the high sensitivity of IFAT, and show no significant difference in sensitivity between IFAT and bone marrow aspiration, with both having a sensitivity of approximately 95%. Our available data preclude calculations of specificity. The highest sensitivity of laboratory diagnosis is naturally with a combined IFAT and bone marrow aspirate, approaching 100%. A recent paediatric study failed to identify LDBs in 22% of patients, a much higher failure rate than ours at 4.9%.¹⁹ HIV testing did not need to be carried out in any of our patients owing to their response to treatment.

TREATMENT

Specific treatment for leishmaniasis was first instituted by Caronia of Catania in 1914, using a mixture of sodium antimony tartarate.²⁰ Pentostam has been used for the treatment of leishmaniasis since the 1940s,²¹ and the current recommended dose of Pentostam is 20 mg/kg/day for 30 consecutive days.²² Our results show that treatment for VL in the paediatric age group with antimonials, a relatively inexpensive class of drugs, is safe and curative, with a low relapse rate as reported by other authors.¹⁹ This may be because of a very low resistance to this drug by the organism in Malta. No permanent sequelae were associated with the disease or its treatment.

The ultimate aim is prevention of VL, and an ideal way of achieving this is by the eventual development of an effective vaccine.²³ This goal is particularly important in view of the emerging resistance to antimonial drugs in some parts

of the world,²⁴ which has led to treatment with drugs other than pentavalent antimonials,²⁵ or the use of pentavalent antimonials in combination with other drugs.²⁶ Until such time as a vaccine will be available, the development of safe and effective oral treatment would be preferable to intravenous treatment.²⁷

CONCLUSIONS

In Malta, we have found a falling incidence of VL. Serological testing for VL is as sensitive as bone marrow aspiration. Treatment for VL in the paediatric age group with Pentostam, a relatively inexpensive drug, is safe and effective. To date, there appears to be very little resistance to this drug in Malta, and all patients were cured, with no disease or treatment related permanent morbidity or mortality. More expensive drugs, such as liposomal amphotericin B, should be reserved for cases which are resistant to treatment or which relapse after treatment.

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Epidemiology of Perthes' disease

The incidence of Perthes' disease varies considerably from place to place. Low rates of around 5 or 6 per 100 000 have been reported from British Columbia, Massachusetts, and rural Wessex whereas rates of between 11 and 15.6 per 100 000 have been found in Liverpool and industrial Merseyside. It has been suggested that the disease is related to the urban environment and social deprivation. A report from Northern Ireland (WDC Kealey and colleagues. *Journal of Bone and Joint Surgery* [Br] 2000;**82-B**:167–71) has stressed the second of these over the first.

Northern Ireland has a high incidence of Perthes' disease (11.6 per 100 000). Over a period of 7 years the diagnosis was made in 313 children and data on area of residence was available for 311. For successive quintiles of population density (lowest to highest) the annual incidence was 11.2, 12.3, 11.6, 10.4, and 12.2 per 100 000. Similar figures for deprivation (Townsend Deprivation Index quintiles, least to most deprived) were 8.3, 10.8, 11.4, 13.2, and 13.1 per 100 000. In rural areas the incidence was 7.1 per 100 000 in the least deprived and 16.1 per 100 000 in the most deprived. In cities it was 11.1 (least deprived) and 12.7 (most deprived).

In Northern Ireland deprivation rather than population density affects the incidence of Perthes' disease. The specific causal factors associated with deprivation remain to be demonstrated.

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