Clinical Aspects of Visceral Leishmaniasis in Albanian Adults

Healthcare

Keywords: V.L. (Visceral Leishmaniasis), Leishmania Donovani, sand fly, Albania.

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Abstract

Visceral Leishmaniasis is still a public health concern in Albania, a former communist country in Southeast Europe which is undergoing a rapid transition from a rigid centralized system towards a market-oriented economy. VL in Albania has been very widespread and known before World War II, but data were scarce. To the general public the disease is known as "spleen disease". Aim of this study is to evidence clinical manifestation of VL and epidemiological evaluation for referral, early diagnosis and treatment of the diseases. Methods: We analized clinical aspects using descriptive statistics included reporting of minimal and maximal values, ranges, mean values, standard deviations and standard errors. T-test and chi-square tests were employed to compare respectively the mean values or the proportions between groups. Upon hospitalization in our study, the disease was mainly manifested with full signs, which means that generally our cases were hospitalized during the second period of the VL that is the anemic phase, considering late. Results: The study highlighted that clinical manifestation of VL in adults are fever in 100% of cases, pancytopenia in 97.3% , anaemia in 100%, The study showed that VL in adult clinically manifested by fever in 100% of cases, anemia in 100% of cases, 73.9% weight loss, sweating 84.9%, enlargement of the abdomen 89.04%, enlarge the liver and spleen in 100% of cases, phenomena hemorrhagic 21.9%, body weakness 90.4%, paleness 75.3%, oedema 5.4%, lymphadenopathy 24.6%, 27.3%, gastrointestinal disorders, chills 61%.

Background and Introduction

VL in Albania has been known before World War II, but the first records are from Dr. Karagjozi, who reported 30 cases in 1937. Fico reported one case in 1938. Xh. Frasheri reported 15 cases in 1942, whereas Jorgoni reported 32 cases in 1953. A special acknowledgment for the recognition of this disease goes to Prof. S. Bekteshi, who has diagnosed and treated systematically the disease in the pediatric hospital since 1950. J. Adhami et al. reported 112 cases in the period 1958-75 in Kruja district and 84 cases in Gjirokaster. Cerhozi reported 146 cases in Kruja district for the period 1962-1981. Likewise, all doctors of the hematological and clinical service of paediatrics, infectious disease service and clinical laboratory of University Hospital Center "Mother Teresa" have diagnosed and treated this disease for many years and have gathered a large experience that have spread throughout the country.

According to the pathological changes in all clinical types of diseases, in the tissues invaded by leishmania occurs an accumulation of mononuclear phagocyte cells of the rethiculoendothelial system. It is this rethiculoendothelial hyperplasia that follows the infection from Leishmania Donovani which affects the spleen, liver, bone marrow, lymph-glands, gut mucosa and other lymphoid tissues that cause the increase and damage. Pathologic changes reflect the balance between the multiplication of the parasite, and degenerative changes in the patient's immune response. Due to the activation of B lymphocytes, a hyperglobulinemia mainly of polyclonal immunoglobulin type occurs, which is nevertheless something common.

Clinical features of Visceral Leishmaniasis

VL caused by parasites of L. Donovani complex displays the most important clinical features including related data. Generally, it is thought that in the endemic areas, the disease occurs in its chronic form, while in sporadic cases it appears in acute form; on the other hand, some authors distinguish a sub-acute form of the disease, which in some countries occurs more often.

The incubation period varies, so it is not yet cleared and fixed. It ranges from 10 days, several weeks, several months, to 2-9 years. On average, the incubation period is 3-6 months.

In order to investigate the history of the disease, as well as clinical and laboratory data, we included in our study 73 VL cases in adults hospitalized at the Infectious Diseases Service of the University Hospital Centre in Tirana These patients were followed according to a strict protocol compiled in collaboration with the Hematology Service.

We assessed the anamnesis data, objective and clinical examination, different laboratory data collected before the specific treatment against VL, as well as data collected after the treatment. Bone punction according to the age of the patients was conducted at the iliac crest and tibia. Colouring was conducted via the Gimsa method which was assessed for leishmaniasis and next for mielogram.

These examinations were conducted upon hospitalization of the patients, next after 15 days of the start if the treatment and in selected cases after 45 days after the start of the treatment. Furthermore, we used data related to identification of the parasite through the lineal punction as well.

Descriptive statistics included reporting of minimal and maximal values, ranges, mean values, standard deviations and standard errors. T-test and chi-square tests were employed to compare respectively the mean values or the proportions between groups.

Presentation of the study results

History of the disease

History of the disease includes data collected from adult patients' interview with regards to the time and mode of onset of the disease. Complains and objective signs of the disease, time of seeking care from the onset of the disease, complains and/or clinical signs, etc. It was obvious that the disease had started with a whole range of complains and clinical manifestations which make difficult the early diagnosis of this disease.

Time of onset of the disease and clinical signs

The time of onset of complains and clinical signs until the time of hospitalization and subsequently confirmation of the diagnosis of VL in adults the onset of the disease ranged from 5 days to 1 year, with an average of 9 weeks. Of the 73 adult cases included in our study, only in 6 of them (8.2%) there were suspicions for the presence of VL. In all the other cases, patients were hospitalized with other diagnoses based on single symptoms or groups of symptoms as described below in Table 1.

Table 1. Diagnosis in hospitalization of cases with VL in adults

DIAGNOSIS	CASES	PERCENT
Chronic febrile syndrome	48	65.8
Acute febrile syndrome	2	2.7
Progressive anaemia	8	10.9
Hepato-renal syndrome	3	4.2
Methrorrhagie	1	1.4
Pneumonia	2	2.7
Suspect Tuberculosis	1	1.4
Suspect abdominal typhoid	2	2.7
Suspect VL	6	8.2
TOTAL	**73**	**100**

From the table above, it's clear that the largest number of hospitalized cases refers to patients with chronic febrile syndrome and cases with progressive anaemia. The mode of onset of the disease in adult cases was gradual.

According to some authors, the minimal time of the onset of disease is considered about 4 weeks for the acute type of VL, whereas for the sub-acute type the time of onset of the disease is considered to be amount up to 5 months. Upon hospitalization in our study including adult patients and children, the disease was mainly manifested with full signs, which means that generally our cases were hospitalized during the second period of the VL that is the anaemic phase.

According to the data collected we conclude that 46 (63.5%) VL cases in our study consisted of the sub-acute type, whereas 27 (36.5%) cases consisted of the acute type of the disease. These findings are compatible with reports from different authors who state that the disease is mainly found in its sub-acute form. Because in none of the cases the disease exceeded 6 months, we consider that the chronic type of VL was absent among patients included in our study. These results support the conclusion that the type of disease with slow progress has a sub-acute character and very rarely a chronic form which in turn is more frequent among adults. On the other hand, several authors do not accept the existence of the sub-acute form of VL, but refer only to the acute and chronic forms of this disease.

In our study we had evidence of a higher rate of the sub-acute form of VL compared with its acute form. We believe this finding relates to the fact that in our study we were able to diagnose more correctly the disease; especially we have been focused carefully in their anamnesis.

Mode of initiation of the disease, main clinical symtoms

The initiation of the disease in our study included a wide range of complains and symptoms upon admission. However, in no cases included in our study there was evidence of skin changes related to vector bites. This is compatible with the statements from different authors who claim that it is difficult to find skin changes in the site of vector bite, due to the long incubation period of the disease.

A few authors claim that in few cases it is possible to detect primary Leishmanioma, a small papule which contains leishmania 4-6 months before the manifestations of the symptoms.

In our sample, we had evidence of a gradual initiation of the disease in 66.9% of the cases, whereas in 33.1% of the cases the diseases had a rapid initiation. The acute forms with slow progression were mainly the sub-acute forms of the disease.

The clinical signs in these cases were quite generic including weakness, sub-febrile temperature, sings related to the digestive system such as anorexia, stomach-ache, or sometimes vomiting.

These signs were evident in the majority of cases with slow initiation, whereas in few cases there was evidence of infection of the upper respiratory system with coughing, which posed difficulties to differentiate VL with pulmonary infections.

The signs and symptoms of the digestive and pulmonary systems mentioned above had duration of 10 days to 2-3 weeks and we believe that this corresponds to the prodromal period or the first phase of the disease, as it has been described by different authoritative authors in this field.

In these cases, during this period of the disease, the fever is not the main issue since it is either normal or only slightly higher than the normal values.

Other authors claim that at this stage there is evidence of a sub-febrile temperature, which can even be as high as 38^{o} C. After this period, there was evidence of clearer signs including paleness, fever, etc. which relate to the second phase of the disease.

In our cases, in the acute evolution of the disease, the signs of the prodormal period were absent and the disease started with symptoms of the second period.

We believe that this is due to the fact that the first period was either absent or very short and therefore was not possible to identify from the patients and/or their relatives.

Symptoms and clinical signs manifested by the patients are presented in Table 2. These data were drawn after a careful and rigorous interviewing of adults patients included in this study. The symptoms and signs described below relate to the early initiation of the disease until the time of hospitalization of the patients.

Fever was present in all adult cases include in our study. In 49 (80.3%) cases, the fever was irregular, whereas only in 28.7% of the cases the reaction towards anti-pyretic drugs was positive with a decrease of the temperature.

Table 2. Main clinical symptoms of cases with VL in adults

No.	Clinical signs	Number of cases	Percent
1	Fever	73	100
2	Shiver	34	61
3	Sweat	62	84.9
4	Weakness (weight loss)	54	73.9
5	Asthenia	66	90.4
6	Paleness	54	75.3
7	Exanthema	3	4.2
8	Abdominal enlargement	65	89.04
9	Oedema	4	5.4
10	Hemorrhagic phenomena	16	21.9
11	Gastrointestinal disorders	20	27.3
12	Liver enlargement	73	100
13	Spleen enlargement	73	100
14	Lymphadenopathia	18	24.6

As described in the table above, the main symptoms/signs were fever, anorexia, weakness, paleness, sweating, weight loss, and abdominal enlargement. High temperatures were evident in 73 cases, or (100%) adults. Fever is the main complain which is almost always present. In some cases there was evidence of a sub-febrile state, followed by febrile events. In many cases, however, the temperature from the very beginning was 38-39ºC. In 64 (55.6%) cases, based on a detailed anamnesis, there was evidence that the temperature had risen 2-3 times within 24 hours and, when it was stabilized back to normal values it was followed by heavy sweating and thirstiness. Furthermore, in 32% of the cases the temperature remained high for several weeks (up to 4-6 weeks); subsequently, the temperature was irregular, characterized by days with high temperature, days with normal values, and days with sub-febrile values. We believe this finding relates to the periodicity of the fever which has been described by different authors.

Anorexia and weakness was present in 64 cases, or 79.3% of them; both signs were present at the very early stage of the disease.

Paleness, though an important manifestation, appears later and in our sample it was evident in 75,3% of the adults.

Sweating was reported frequently, in 84,9% of the adults. In some cases, sweating was related to the infection and/or the sharp decrease of the temperature. In some cases, sweating was substantial and accompanied with thirstiness, which in turn was reported by 36.5% of the cases.

Among adults, weight loss was present in 73,9% of the cases. We think that the weight loss is a consequence of anorexia, vomiting, high temperatures, sweating, diarrhoea (is a few cases) and the direct effect of the parasite in the human organism.

Vomiting and diarrhoea were not very frequent, we find it in 27,3% of the cases. These symptoms were related to the digestive system and according to some authors these symptoms are connected to secondary infections of gastrointestinal system and from the damages related to the presence of leishmania parasite.

Stomach-ache was evident in 27.8% of the cases. We think that this symptom as a consequence of digestive system damage, or liver and/or spleen enlargement. According to some authors, in some cases (3% of them), the severe and acute abdominal pain may help to diagnose the disease.

Abdominal enlargement was evident in 89.04% of the cases among adults; basically we explain this symptom as a consequence of extreme enlargement of the liver and/or the spleen.

The other complains such as dry coughing, restlessness, lymph nodular enlargement, hemorrhagic phenomena, or oedemas were less evident in our study. Our findings collected from the anamnesis of the patients have been also described by other authors. An authoritative expert has reported the fever as the main symptom (in 100% of the cases), whereas abdominal enlargement was evident in 99.1% of the cases. Another author has reported the temperature in 93.3% of the cases, anorexia in 61.3% of the cases, paleness in 56% of the cases and general weakness was evident in 37.3% of the cases.

Symptoms identified upon hospital admission

Symptoms identified upon hospital admission were drawn from the examination conducted immediately upon admission and after 24 hours of admission. Signs and symptoms consisted of a whole range of characteristics, as described below in Table 25. The most important ones included the enlargement of the liver and/or spleen, paleness, fever, and enlargement of the abdomen.

In the majority of the cases, (100% in adults), there was evidence of fever. This is compatible also with findings from other authors who have reported that fever is the main symptom of VL. In our sample, fever was mainly irregular, with a long duration, of different types and with unstable features. Fever reached levels of 38-40º C, it was intermittent, remittent, or alternated. Decrease of high temperature in our sample was associated with sweating and, therefore, in some cases it was coupled with thirstiness. Use of different anti-pyretic drugs was effective upon hospital admission: in 44 cases (60% of the total) there was evidence of a febrile state, in 29 cases (40%) there was evidence of sub-febrile state.

Paleness of the skin was evident upon hospital admission in 75.3% of the cases among adults. Paleness is an important sign whose appearance completes the mosaic of signs and symptoms of the second phase of the disease. Skin colour, according to our findings, consists of paleness and in 10% of the cases it consists of a sub-icteric nuance. In Mediterranean countries, it has been reported that, at the early onset of the disease, the skin is pale like the phosphorus; other authors report that the skin has a colour similar to the old wax. At a later stage of the disease, several authors have reported a yellow colour of the skin. It has been convincingly argued that changes of the skin colour are related to the presence of anaemia and its severity.

Spleen enlargement and liver enlargement, according to our findings, consist of an important sign. We had evidence of this sign in all cases in adults, and it was of different severity degrees. Spleen was enlarged in 100% of the cases from 1 cm to 10 cm below the coastal arch, hence occupying the left half of abdomen. On average, the spleen was enlarged by 6 cm among adults.

In the majority of the cases (58.2%), the spleen is above 5 cm. Its enlargement in some cases has reached the umbilicus level and occasionally it was found up to the iliac crest, thus occupying the left half of abdomen. Often times, it was possible to touch its incisures. In the majority of the cases (67.8%), spleen had a strong consistency, whereas in 26% of the cases it had a moderate consistency. In few cases (4.2%), spleen consistency was normal.

Spleen enlargement as a major sign of the disease is compatible with the reports from many other authors. Thus, several authors have reported the prevalence of spleen enlargement in 100% of VL patients. In our study, we have noted the greatest enlargement of the spleen among patients with a slow and sub-acute progress of the disease and we had evidence of the fact that the larger the times span until diagnosis of the disease, the greater the enlargement of the spleen. According to some authors, spleen enlargement starts within 24 hours of the disease. Enlargement of the spleen occurs in all directions, but more frequently in the lower part. With the progress of the disease, spleen reaches up to the iliac crest. In the direction of diaphragm, the spleen enlarges to a lesser degree. Some authors have reported the lower bound up to the seventh coast. Some other authors report that a much enlarged spleen may exhibit the phenomena of the hyper-spleen which bears negative mechanical consequences for the other abdominal organs as well as the respiratory system.

Diagnosis of Visceral Leishmaniasis

For the diagnosis of VL, in addition to epidemiological, clinical, biochemical data, hemogram etc. to be discussed in our material, nowadays is widely in use the sero-immunological diagnosis, based on immunological changes that VL causes to the affected host.

No doubt that the final diagnosis is made by finding of the parasite (especially amastigote form) in preparation stained with Giemsa of the aspirations from the bone marrow, spleen, skin or lymph nodes. In practice, a wider application has found the detection of Leishmania in the puncture of red bone marrow. It is rare and an opportunity to identify the parasite in the patient's peripheral blood. Our experience in this area is lacking.

The aspiration of red bone marrow is the most common procedures. According to some authors, marrow positive aspiration test ranges from 54-86%.The aspiration of the enlarged spleen is also an alternative method to identify leishmania. Aspiration or lymph node biopsy can be applied in cases when the lymph nodes are enlarged.

Laboratory diagnosis of VL – hematological data

Criteria for definition of pancytopenia include decrease of erythrocytes, leucocytes, and thrombocytes below the accepted norms. It was present in 95.7% of the cases. Changes in the peripheral blood are manifested in three series, in two series, or in one series only. There was evidence in our study of three series in 39 (53%) cases, with a decrease in the number of erythrocytes, leucocytes and thrombocytes. The two series change was evident in 24 (32.2%) cases. One series changes were evident in 8 (10.5%) cases consisting mainly of a decrease of leucocytes or thrombocytes.

***Anemia**:* is the main clinical symptom that is present in the course of the disease.
Anemia is related to the decrease in the number of erythrocytes, hemoglobin concentration, or both.

***Erythrocytes**:* the majority of cases in our study were associated with a decrease in the number of erythrocytes. In 91.78% of adults, there was evidence of different degrees of anemia.

Hemoglobin: There was a decrease in the hemoglobin levels in 69 (94.8%) cases. The lowest hemoglobin level was 3.8 gr%.

***Reticulocytes**:* reticulocytes were above the norm in 42 cases (57.7%). Mainly, there was evidence of a moderate increase of reticulocytes from 15-30 per 1000 in 33 cases and above 30 per 1000 in 12 cases.

***Leucocytes**:* Our findings indicate that of 73 patients with VL the leucopenia was present in 100% of them.

Parasite detection

Parasite detection is of vital importance for the diagnosis of VL. Parasite can be detected through bone puncture, spleen puncture, and liver puncture.

Bone puncture and myelogram

Bone puncture and marrow aspiration was conducted for two main reasons: to confirm the diagnosis as well as to observe the bone changes related to development of VL disease.

In our study including adult patients, the VL diagnosis via sternum puncture was confirmed in 50 patients (89.3%) out of 56 who underwent this type of examination. In 6 cases (10.79%), the sternum puncture was negative for the leishmania parasite

Spleen puncture

We applied the spleen puncture in 9 cases out of 73 VL patients in adults (12,33%). In all 9 cases (100%) the parasite resulted positive.

Liver puncture

Liver puncture was applied in one case only where the first bone puncture resulted negative. This was the case of a 6 year old child with enlarged liver

Conclusions

In the endemic VL areas, the clinical signs such as prolonged and irregular fever, paleness, gradual weight loss, general weakness, liver and spleen enlargement coupled with laboratory findings such as anemia, leucopenia, increase of erythro-sedimentation, hypergamaglobulinemia and decrease of albumin level, are all indications for the presence of VL. The final diagnosis, however, depends on the identification of the amastigotes in the isolated tissues, cultivation of the parasite, or evidence of anti-leishmania antibodies in the serum.

VL is spread all over Albania, but is mainly found in Tirana region due to demographic changes occurring in Albania. VL affects mainly children, but is becoming a common disease also in adults. This indicates that Albania is an endemic area for the VL disease.

Important hematologic data for the diagnosis of VL include pancytopenia, anemia with decrease of erythrocytes and hemoglobin, leucopenia with absolute decrease of neutrophils and relative increase of

lymphocytes, as well as increase of erythro-sedimentation which is a function of duration of disease and decrease of thrombocytes.

The final diagnosis of VL is based on the identification of the parasite via bone puncture, spleen puncture, or liver puncture and/or positive serologic confirmation. If the parasite is found in the peripheral blood, the diagnosis of VL is considered definitive.

References

1.Abdalla S.H Weather all D.S.: "Hemaological features of Kala – azar" ne "Manson's tropical iseases" by Manson- Bahr P. E. C, Ball D.R. Boilliere Tindall-London Philadelphia 1987 pp.954, 972.
2. Adams A. "Clinical tropical diseases" 1979, 169 Oxford, London, Edinburg, Melbourne, Blawell, Scientific, Publication.
3. Agaeva R.K e bp: "Dinamika imunomorfollogiceski reaksis pri eksperimentalnom kozhnom leishmanioze u selimi mishej" Medicin. Parazit i parazitarni boleni Nr.1, 1977.
4. Andreol A.Cambia M; Mansoni D; Bonra G; Gargantini G; Giaracuri G; Perleti L: "Desuription of a case of visceral leishmaniasis. Epidemiologic diagnosiç and therapeutic considerations" Minerva-Pediatrica:1985 Jun 30: 37 (11 - 12) pp. 479-87
5. Bauer D. "Clinical laboratory mehods" The C.V. Mosby Cowpani Saint- Luis 1974, p.405.
6. Badaro R: Leishmania Donovani: An Opportunistic Microbe Associated with Progresive Disease in thre Imunocompromised Patiens, Lancet, 1985, 1: pp. 647-51.
7. Badaro R, Falcoff E: Badar F.S;Carvalho EM; "Treatment oi visceral leishmaniasis with pentavalent antimony and interferon gama" N-Engl-J-Med: 1990 Jan 4 :322(1) pp. 16-21.
8. Bastin R., Chamot G., Frottier J. Vilde J.L.Leishmaniosis in Malattie Infettie e Parassitare, 1982, pp. 256-8.
9. Berkow R. "Leishmaniasis" The Merch Manual of diagnosis and Therapi. Merc. And Co. J. N. C. 1992 pp. 206-210.
10. Berman B.D. Wyler D.J. "An invitro model for investigation of chemotherapeuic in Leishmaniasis. The Journ.of.Infect disease 1970 vol.142, Nr.1, pp. 83-86.
11. Bouree P: Anciaux Ml: Tangoudean P. "Methylglucamine antimoniate and Sodium stibogluconate in the tretment of leishmaniasis. Study of 16 cases" Pathol. Biol (Paris):1985 Jun: 33 (5 Pt 2): pp. 607-10.
12. Bosseti D: Leishmaniasis in Terapia Ragionata delle Malattie Infettive, 1985, pp.181-3.
13. Cerhori H.,Dollaku B.:Leishmanioza e organeve ne te rritur. Revista Mjekesore 1989, 5: pp. 39-42.
14. Coombs R.R e bp: "Clinical aspects imunollogy".Blockwell Scientific Publications.Oxford. London. Edinburg. Melbourne 1975, pp. 155, 157, 159, 165.
15. Dushniku N: "Leishmanioza viscerale" ne semundjet infective" Pjesa II Tirane, Shtëpia botuese "8 Nentori" 1974, pp.146-48.
16. Fabri J: "Manuale di terapia medica" Martinicci Napoli 1988 p.1138.
17. Farinella E.,Ochino: Consideracioni cliniche su due casi di Leishmaniosi Viscerale nell adulto, Inf.Trop. 1985, 4: pp. 89-9.
18. Gace A. etj"Diagnoza laboratorike e leishmaniozes viscerale tek femijet. Referat ne sesionin shkencor te pediatrise 1989.
19. Goodman L.S : "The Farmacological Basis of therapeuic" Macmilan Publishing Company Inc.New-York 1975, p.928.
20. Hervai Di B.L.,Berman . D: Recommandations for Treating Leishmaniasis with Sodium Stiboglukonate (Pentosam). and Reviee of Pertitent Clinic Studies, Ann.J.Trop.Med. Hyg., 1992, 46; pp.296-301.