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RESEARCH ARTICLE

CLINICAL AND ETIOLOGICAL FACTORS OF HEPATOSPLENOMEGALY

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ABSTRACT:
Hepatosplenomegaly is a common finding in infants and children. It is a sign seen in various disease processes. It may be very easy to find the diagnosis or it may require extensive evaluation in order to distinguish benign, self- limited disease process from serious life threatening condition involving liver and spleen. An attempt is made in the present study to know the various etiological factors and clinical features of Hepatosplenomegaly.
Discussion:
This is a prospective study of ninety five consecutive cases, from One Month to twelve years of age with Hepatosplenomegaly admitted in the Pediatric wards of SVS General Hospital, from January 2014 to august 2015. Hepatomegaly was defined as when the liver edge was palpated below the right costal margin at the mid clavicular line for infants and older children and the liver span should be more than the expected for the corresponding age Infants 5-6cms; 1-5yrs 6-8cms; 5-10yrs 8-9cms; 10-14yrs 8-12cms;[1,4,16] Splenomegaly was classified into 3 grades on clinical grounds i.e., Mild (1-3cms), Moderate (4-7cms) and Massive (>7cms). A detailed study of the cases including history, thorough physical examination and necessary investigations depending on the history and clinical findings were done. Day to day progress has been observed during the hospital stay and after discharge, the cases have been followed up every month.Routine investigations like completed blood picture, peripheral smear, urine analysis, stool examination, Chest X Ray, Mantoux tests were performed in all cases. Relevant investigations like WidalTest, Pediatric HIV ELISA, Liver function tests, Bleeding time, Clotting time, prothrombin time, Hb Electrophoresis, Blood culture, X ray skull, X ray long bones were done in relevant cases, depending upon the provisional diagnosis made on history and clinical examination.Special investigations like CT scan, Sickling test, Osmotic fragility test were done in few cases wherever indicated.
Conclusion : Both sexes are affected equally with slight predominance of males. It is highest in the below 6 years age group. Fever, Pallor, Anorexia and Jaundice are the common presenting complaints. Anemia, Jaundice, Fever, Stunting, Wasting and abdominal distension are the common examination findings. The liver enlargement varied from 2.5cm to 14cm. The spleen enlargement varied from 2cm to 15cm. Infections and malignancy are the most common diagnosis found in the study. Malaria is the most common infection detected in the study. Acute lymhoblasticleukemia is the most common malignancy associated in the study. Investigations required varies with the type of case presentation. The progression of the disease varied in different conditions.Retardation of growth was noticed in majority of storage disorders and malignancy.Infections, malignancy and congestive disorders are found commonly between 4-9 years of age. Extramedullaryhematopoietic disorders (hemolyticanemias, osteopetrosis) are commonly found between 1-6 years of age.Hepatosplenomegaly with generalized lymphadenopathy is most commonly associated with malignancy in our study.
Key words: hepatosplenomegaly , infections , jaundice

INTRODUCTION

Hepatosplenomegaly is a common finding in infants and children. It is a sign seen in various disease processes. It may be very easy to find the diagnosis or it may require extensive

evaluation in order to distinguish benign, self- limited disease process from serious life threatening condition involving liver and spleen.

Liver is regarded as chemical factory of the body[1]. It performs the life giving and lifesaving exploits. It has to do manifold magic performances of complex nature but with simple structure. "It is this combination of apparent simplicity with actual complexity which is the despair of all who attempt to correlate to the structure with disorder of function of liver" (William Boyd).

An attempt is made in the present study to know the various etiological factors and clinical features of Hepatosplenomegaly in the cases admitted in SVS General Hospital from January 2014 to August 2015.

AIMS AND OBJECTIVES

To study the possible Etiology, Clinical features and Evaluation of children presented with Hepatosplenomegaly.

MATERIALS AND METHODS

PATIENTS AND METHODS

This is a prospective study of ninety five consecutive cases, from One Month to twelve years of age with Hepatosplenomegaly admitted in the Pediatric wards of SVS General Hospital, from January 2014 to august 2015.

Those children presented with pushed down liver due to various causes are excluded by measuring liver span for that particular age. Hepatomegaly was defined as when the liver edge was palpated below the right costal margin at the mid clavicular line for infants and older children and the liver span should be more than the expected for the corresponding age Infants 5-6cms; 1-5yrs 6-8cms; 5-10yrs 8-9cms; 10-14yrs 8-12cms;[1,2,3] Splenomegaly was classified into 3 grades on clinical grounds i.e., Mild (1-3cms), Moderate (4-7cms) and Massive (>7cms)

A detailed study of the cases including history, thorough physical examination and necessary investigations depending on the history and clinical findings were done according to the proforma given later. Day to day progress has been observed during the hospital stay and after discharge, the cases have been followed up every month.

Routine investigations like completed blood picture, peripheral smear, urine analysis, stool examination, Chest X Ray, Mantoux tests were performed in all cases.

Relevant investigations like WidalTest, Pediatric HIV ELISA, Liver function tests, Bleeding time, Clotting time, prothrombin time, Hb Electrophoresis, Blood culture, X ray skull, X ray long bones were done in relevant cases, depending upon the provisional diagnosis made on history and clinical examination.

Special investigations like CT scan, Sickling test, Osmotic fragility test were done in few cases wherever indicated.

Hematologic investigations:

Peripheral smear: Helpful in the diagnosis of several haematological disorders.

- In hemolyticanaemia's, pencil shaped cells, Tear drop cells and polychromasia were seen.
- Bone marrow examination was done to diagnose storage disorders.
- In Sickle cell disease, sickle cells were seen.
- Peripheral smear was most valuable diagnosis of infections like malaria.

- Hb Electrophoresis: It was done to confirm the diagnosis of hemolyticanaemia's like Beta Thalassemia, Sickle cell anaemia etc.,

Biopsy:

- Liver biopsy was performed in cases of storage disorders.
- Lymphnode biopsy was done to diagnose Glandular tuberculosis if required.

Radiological investigations:

- X-Ray skull was done to see the "hair on end" appearance in Hemolyticanaemias.
- X-Ray spine and hands were done in cases of Mucopolysaccharidosis.
- USG Abdomen was done to correlate the clinically diagnosed liver size, spleen size, free fluid and to note the portal vein size.

RESULTS

RESULTS AND STATISTICS

A Total of 95 patients were studied

Table 1 : Distribution of cases based on age

Age in Yrs	No of Cases	Percentage
< 1 year	9	9.5
1-3 years	21	22.1
4-6 years	37	38.9
7-9 years	23	24.2
10-12 years	5	5.3
Total	95	100

In the present study it was observed that out of 95 patients majority of patients 38.9 % were in the age group of 4 – 6 yrs followed by 24.2% cases were in the age group of 7 – 9 yrs.

Figure 6: Distribution of cases based on age

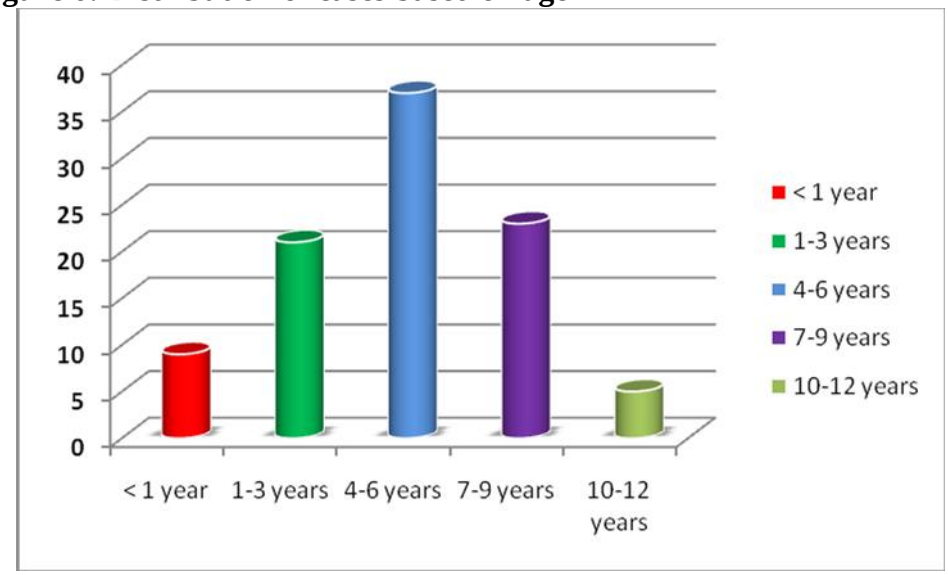

Table 2 : Distribution of cases based on sex

Sex	No of Cases	Percentage
Males	53	55.8%
Females	42	44.2
Total	95	100

Of the 95 Children 53 Patients (55.8 %) were males and 42 patients (44.2 %) were females. In our study male to female ratio of cases is 1.26:1. There was no significant difference in the gender distribution in the present study.

Figure7: Distribution of cases based on sex

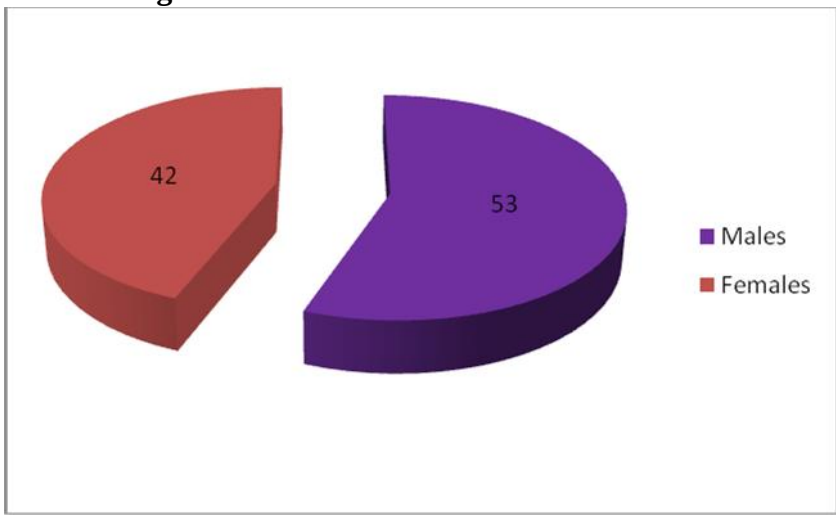

Table 3: Complaints associated with Hepatosplenomegaly

Complaints	No of Cases	Percentage
Fever	74	77.8
Pallor	70	73.7
Loss of appetite	45	47.4
Loss of weight	26	27.4
Abdominal distension	19	20
Jaundice	17	17.9
Petechiae	10	10.5
Pedal edema	5	5.3

In the present study it was observed that most common complaint was fever 77.8 % followed by pallor 73.7%.

Figure 8: Complaints associated with Hepatosplenomegaly

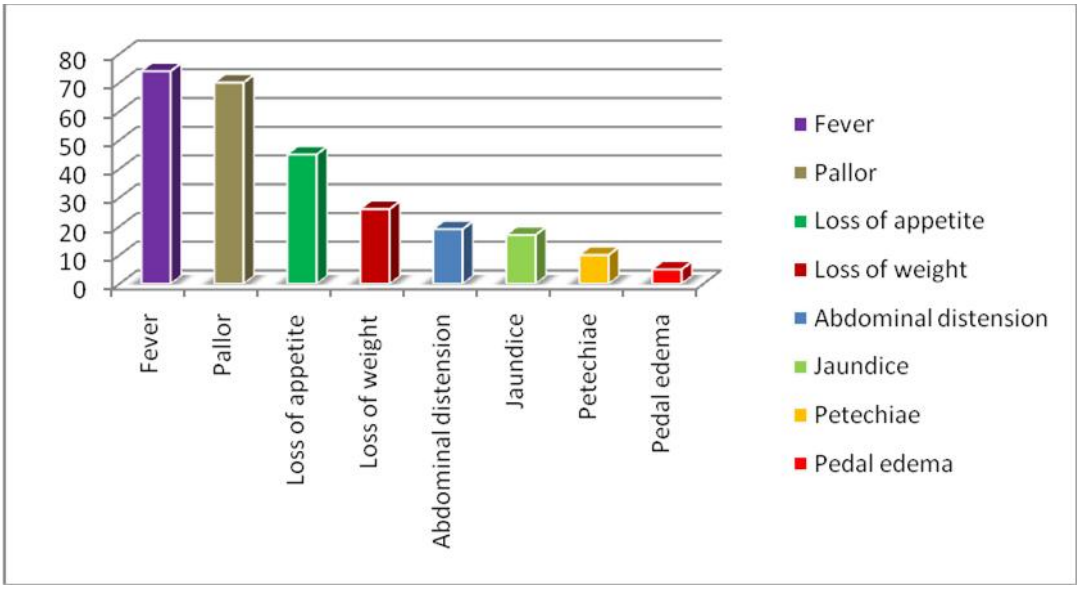

Table 4: Findings present on Physical Examination

Alterations	No of Cases	Percentage
Pallor	70	73.7
Fever	74	77.8
Wasting	20	21
Generalized lymphadenopathy	22	23.1
Stunting	14	14.7
Ascites	17	17.9
Petechiae	10	10.5
Pedal edema	5	5.3

In the present study it was observed that most common presentation on physical examination was fever 77.8 % followed by pallor 73.7%.

Figure 9: Findings present on Physical Examination

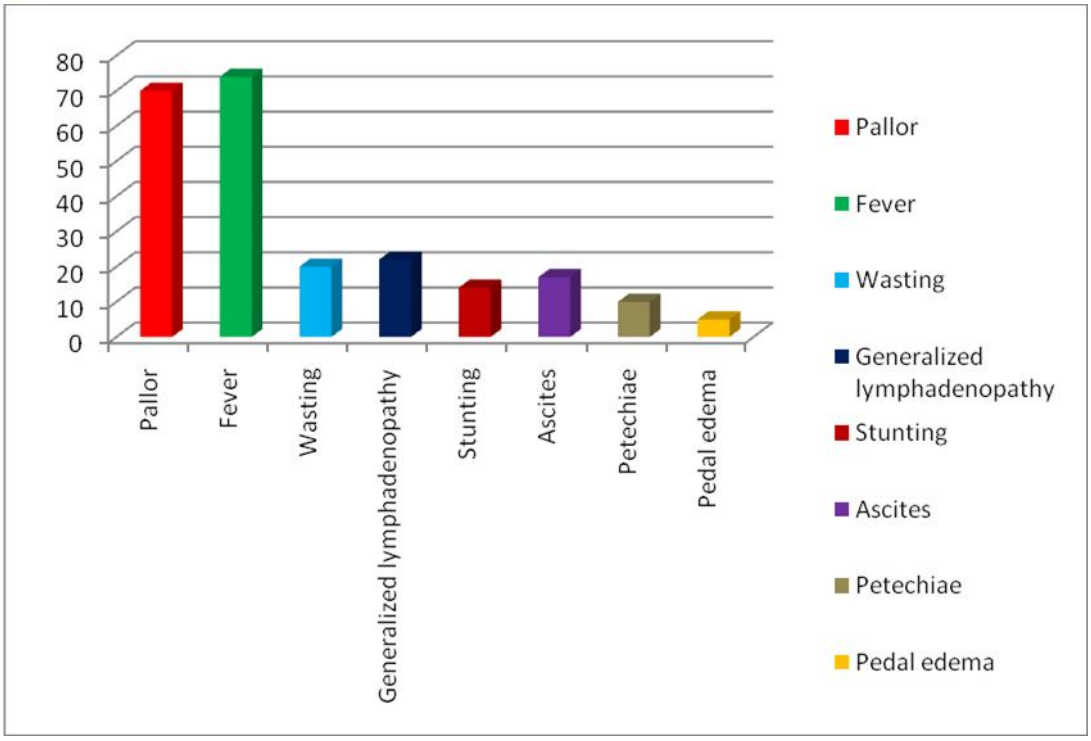

Table 5: Diagnosis associated with Hepatosplenomegaly

Diagnosis	No of Cases	Percentage
Infections	35	36.8
Malignancy	20	21
Storage Disorder	8	8.4
Extramedullary haematopoiesis	16	16.8
Congestive	6	6.3
Others	10	10.5
Total	95	100

In the present study it was observed that 36.8 % of patients who presented with hepatomegaly had infection as the diagnosis followed by 21 % patients had malignancy, 16.8% cases had extra medullary hematopoiesis, 8.4% had storage disorder, 6.3% cases had congestive etiology.

Figure 10: Diagnosis associated with Hepatosplenomegaly

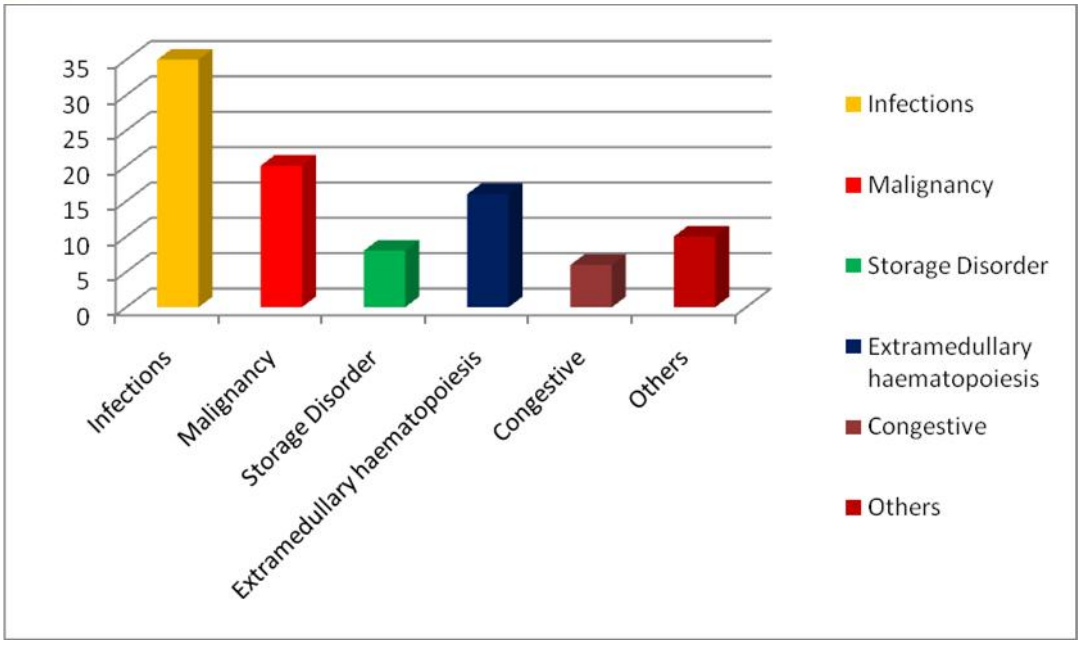

Table 6: Distribution of cases with Infections as etiology (35 cases)

Infections	No.of Cases	Percentage
Malaria	11	31.4
Viral hepatitis	5	14.3
Tuberculosis	5	14.3
Enteric fever	4	11.4
Torch infection	3	8.5
Septicemia	3	8.5
Idiopathic Neonatal hepatitis	2	5.7
HIV	1	2.9
Infectious mononucleosis	1	2.9

In the present study malaria was the most common cause of infection seen in 31.4 % cases followed by viral hepatitis and tuberculosis which constituted 14.3 % cases each with diagnosis of infection.

Figure11: Distribution of cases with Infections as etiology (35 cases)

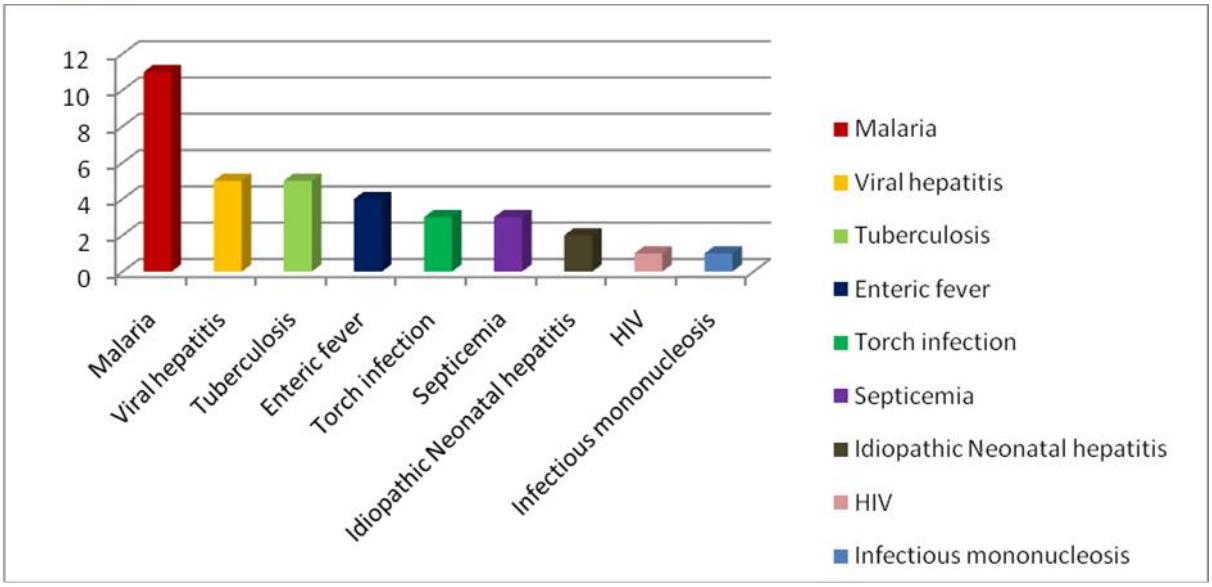

Table 7: Distribution of cases with malignancy as etiology (20 cases)

Malignancy	No. of cases	Percentage
Acute lymphoblastic leukaemia	12	60
Hodgkins lymphomas	5	25
Non Hodgkins lymphoma	1	5
Acute myeloid leukaemia	2	10

In the present study acute lymphoblastic leukaemia was the most common cause of malignancy seen in 60 % cases followed by hodgkins lymphoma seen in 25 % cases with malignancy.

Figure12: Distribution of cases with malignancy as etiology (20 cases)

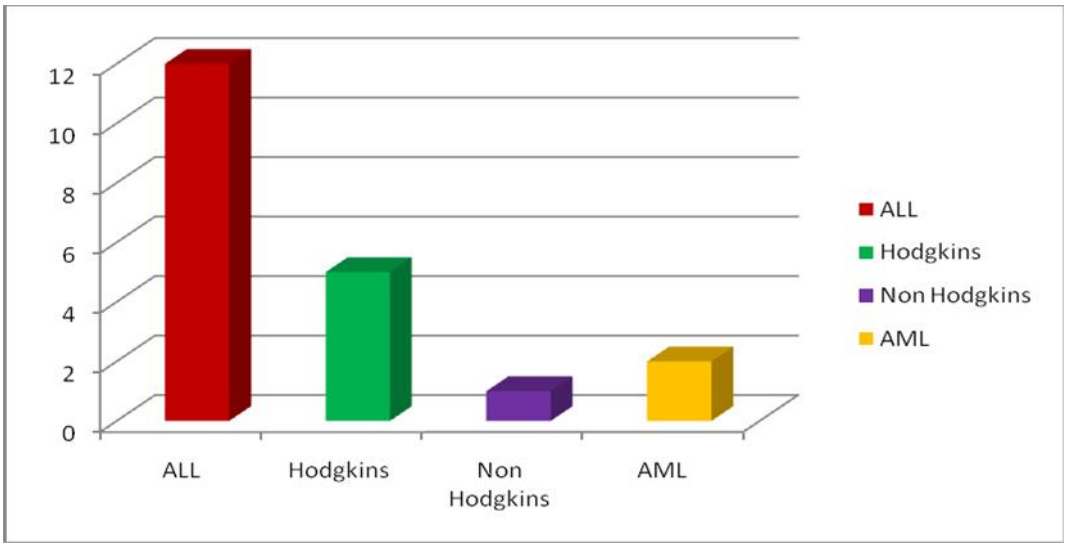

Table 8: Distribution of cases with Storage Disorders as etiology (8 Cases)

Storage Disorders	No. of cases	Percentage
Lipid Storage	2	25
Glycogen Storage	1	12.5
Mucopolysaccharidosis	1	12.5
Histiocytosis	2	25
Reyes syndrome	1	12.5
Wilson disease	1	12.5

In the present study lipid storage disorder and histiocytosis was the most common cause of storage disorder which constituted 25 % of cases with storage disorder.

Figure 13: Distribution of cases with Storage Disorders as etiology (8 Cases)

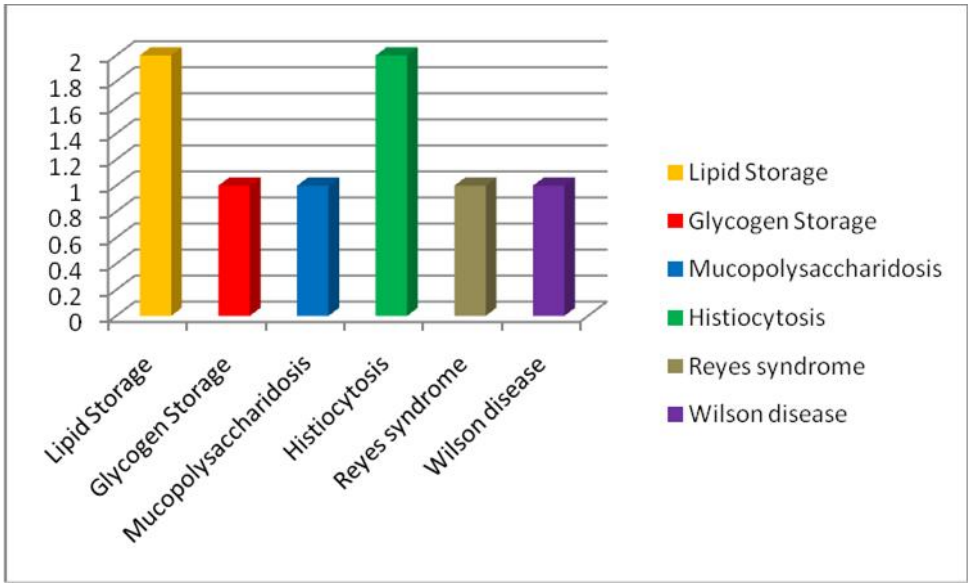

Table 9: Distribution of cases with Extramedullary Haematopoiesis as etiology

Extramedullary Hematopoesis	No. of cases	Percentage
Thalassemia Major	11	68.75
Sickle Cell Anaemia	2	12.5
Glucose 6-Phosphate Dehydrogenase Deficiency	1	6.25
Osteopetrosis	2	12.5

In the present study beta thalasemia major was the most common cause of hematopoesis, it constituted to 68.75% of all the cases with extramedullary hematopoesis.

Figure 14: Distribution of cases with Extramedullary Haematopoiesis as etiology

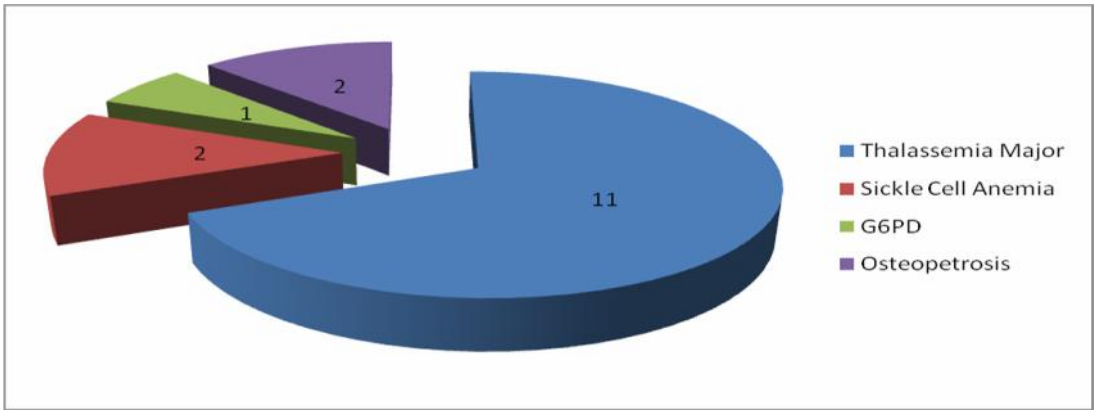

Table 10: Distribution ofcases with Congestive Etiology

Congestive Etiology	No. of Cases	Percentage
Portal Hypertension	2	33.3
Congestive Cardiac Failure with Infective Endocarditis	3	50
Non Cirrhotic Portal Fibrosis	1	16.67

In the present study Congestive Cardiac Failure with Infective Endocarditis was the most cause of congestive etiology with hepatomegaly seen in 50 % cases.

Figure 15: Distribution of cases with Congestive Etiology

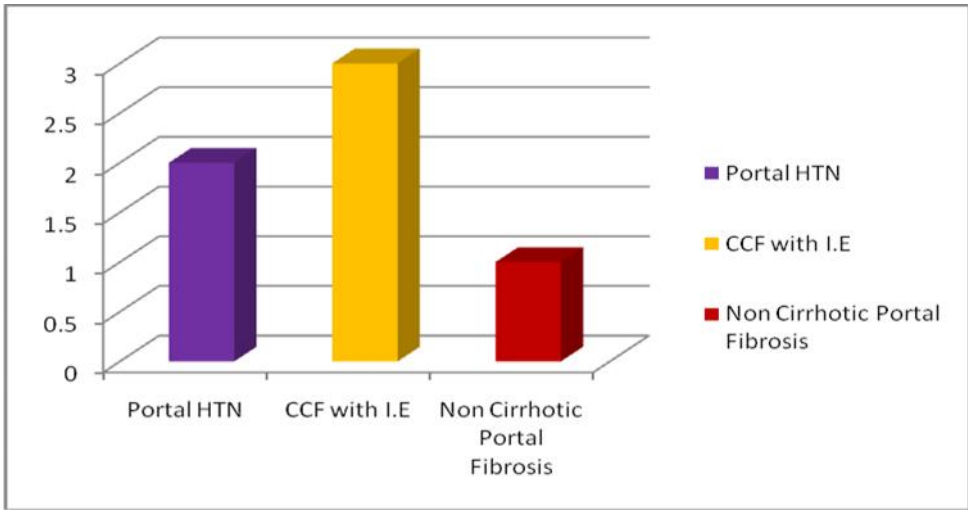

Table 11: Distribution of cases with Other Causes as etiology

Other Causes	No. of cases	Percentage
Biliary Atresia	3	30
Undiagnosed	3	30
Protein Energy Malnutrition	1	10
Systemic lupus Erythematosus	1	10
Hypersplenism	1	10
Megaloblastic anaemia	1	10

Biliary atresia was the most common cause of hepatosplenomegaly seen in 30 % cases among other causes as etiology

Figure 16: Distribution of cases with Other Causes as etiology

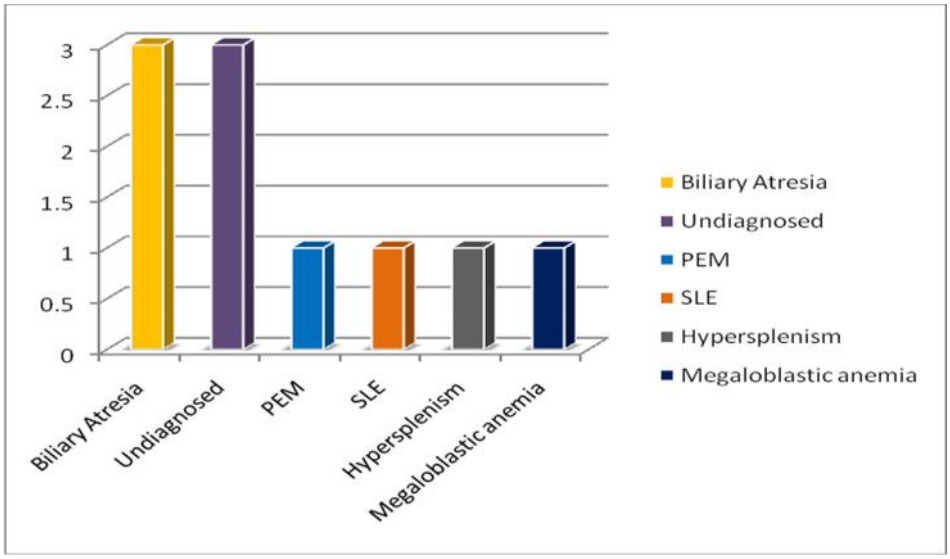

Table 12: DIAGNOSIS AND FEVER CROSSTABULATION :

Diagnosis	Fever present		Fever absent		Total	
	No.	%	No.	%	No.	%
Infections	33	94.3	2	5.7	35	100
Malignancy	18	90	2	10	20	100
Storage Disorder	4	50	4	50	8	100
Extramedullary haematopoiesis	13	81.3	3	18.8	16	100
Congestive	3	50	3	50	6	100
Others	3	30	7	70	10	100
Chi square	26.91			P value	<0.001	

In the present study it was observed that association of fever was significantly more in diagnosis such as infection, malignancy, extramedullary hematopoesis p <0.001.

Table 13: DIAGNOSIS AND ANAEMIACROSSTABULATION :

Diagnosis	Anaemia present		Anaemia absent		Total	
	No	%	No.	%	No.	%
Infections	21	60	14	40	35	100
Malignancy	19	95	1	5	20	100
Storage Disorder	3	37.5	5	62.5	8	100
Extramedullary haematopoiesis	16	100	0	0	16	100
Congestive	5	83.3	1	16.7	6	100
Others	7	70	3	30	10	100
Chisquare	20.0			P value	0.001	

In the present study it was observed that association of anaemia was significantly more in diagnosis such as infection, malignancy, extramedullary hematopoesis, congestive failure and other diagnosis, p <0.001.

Table 14: DIAGNOSIS AND JAUNDICECROSSTABULATION :

Diagnosis	Jaundice present		Jaundice absent		Total	
	No	%	No.	%	No.	%
Infections	11	31.4	24	68.6	35	100
Malignancy	0	0	20	100	20	100
Storage Disorder	2	25	6	75	8	100
Extramedullary haematopoiesis	1	6.3	15	93.8	16	100
Congestive	0	0	6	100	6	100
Others	3	30	7	70	10	100
Chi square	12.8			P value	0.026	

The association between the diagnosis and jaundice is significant as the pvalue is 0.026. Jaundice is commonly associated with infections and biliary atresia.

Table 15: DIAGNOSIS AND GENERALIZED LYMPHADENOPATHYCROSSTABULATION :

Diagnosis	Generalized Lymphadenopathy Present		Generalized Lymphadenopathyabsent		Total	
	No	%	No.	%	No.	%
Infections	7	20	28	80	35	100
Malignancy	11	55	9	45	20	100
Storage Disorder	2	25	6	75	8	100
Extramedullary haematopoiesis	1	6.3	15	93.8	16	100
Congestive	1	16.7	5	83.3	6	100
Others	0	0	10	100	10	100
Chi square	17.3			P value	0.004	

The association between diagnosis and generalized lymphadenopathy is significant as p=0.004. Generalized lymphadenopathy is commonly found in association with malignancy.

DISCUSSION:

A total of 95 patients were studied in this prospective study.

Age:

The maximum number of patients were below 6 years (70.5%). In Lucia F. Bricks et al [4]study 89 patients were studied and the maximum children are under 5 yrs (82.2%).

Sex:

There is slight male preponderance (55.8%) noticed in our study, correlating with Lucia F. Bricks et al [4]study where 52.8% males were found in the study. In Loredo Abdala et al study [5] of 57 cases patients are equally distributed by sex. In Sotelo Cruz N et al [6] study of 63 cases there was no difference in the number of males and female children.

Nutritional Status :

In our study 14.7% of patients showed short stature and 21% patients had weight below 3rd percentile, according to NCHS criteria, In Lucia. F Brick et al [4] Study reported 20% of children of short stature and 15% had weight below 3rd centile, according to NCHS criteria. In Sotelo-Cruz N et al [6] study nutritional status was normal in more than 80% of the patients. In Loredo Abdala A et al [5] study patients were not undernourished nor did they have low weight.

Symptoms :

The most common presenting features in our study are fever, pallor and anorexia, followed by loss of weight, abdominal distension. In Lucia F Bricks et al [4] study the most common presenting features are fever, pallor, weight loss and Jaundice. In LoredoAbdal a et al study [5] psychomotor retardation, Pallor, jaundice and bleeding were most common findings.

Fever is found to be most common presenting symptom in 74 cases (77.8%). It is intermittent in nature. It is most commonly seen in infectious and malignant causes. Pallor is the next most common symptom. It is predominantly seen in malignancy and infections.

Jaundice is commonly presenting feature of infectious causes like viral hepatitis, next common is biliary atresia. Abdominal distension is one of common symptom. Hepatomegaly and ascites contribute to distension and perhaps flatulence and congestion of gastrointestinal tract also important causes.
In sotelocruz N study [6] pallor, fever, adenomegalies are most common.

Investigations:
The minimum investigation done for all cases include complete blood picture and complete urine examination.

CBP :
Anaemia was present in 73.6% of patients correlating with Lucia F. Bricks et al [8] study where 78.7% of patients had anaemia.

Ultrasound :
Abdominal ultrasound is performed in all cases, where as in Lucia F Bricks et al study it is done in 74.2% cases. It not only confirms the presence of hepatomegaly and splenomegaly, it could detect other problems associated such as free fluid seen in 17cases (17.89%), mesenteric lymphadenitis in 3 cases (3.15%) etc.

Liver Function Test :
Liver Function Tests are performed in 38 cases (40%) where as in Lucia F Bricks et al study 66%.
Serum proteins : In mild to moderate cases, no change in serum proteins with normal albumin : Globulin ratio. In severe cases there was reversal of albumin, globulin ratio which was mostly due to rise in gamma globulin level.
Transaminases :
Elevation of transaminases was noticed in 17 cases which indicate hepatocellular damage.
Alkaline phosphatase :
Elevation of this enzyme is found in 22 cases.
Viral Markers : Were done in 26 cases, antibodies to Hepatitis A were found in 4 cases, HbsAg was positive in 1 cases, viral makers are normal in 21 cases.
Smear for Malaria parasite : Was performed in all cases of hepatosplenomegaly presented with fever and any suspicious case even without fever. It was performed in 90 cases, out of which 11 cases smear showed malarial parasites.
Reticulocyte count was done in all cases of anaemia with hepatosplenomegaly and all suspected case of hemolyticanaemia. It is elevated in 16 cases. Sickling test and Hb electrophoresis were done in all cases of elevated Reticulocyte count. Sickling test became positive in 2 cases. Hb electrophoresis showed beta thalassemia major in 11 cases.
Bone marrow aspiration was done in 24 cases (23.5%) where as in Lucia F. Bricks et al study [4] it is done in 9 cases. The various results of bone marrow aspiration are 12 cases of acute lymphoblastic leukaemia, 4 cases showed lymphoid infiltration, 2 cases of lipid storage disorder, 2 cases of acute myeloid leukaemia, 3 cases of normal study, 1 cases of megaloblastic anaemia

Biopsy :

15 cases had undergone histological examinations (15.78%) where as in the Lucia F. Bricks et al [4] study 9 cases (10.1%) cases have undergone histological examinations. Out of 15, 4 cases (4.2%) were undergone liver biopsies and 11 cases had undergone lymphnode biopsies.

The various diagnosis obtained through liver biopsy are 1 cases of glycogen storage disorder, 1 case s/o Reyes syndrome, 2 cases it is normal study.

The various diagnosis obtained through 11 cases (11.57%) of lymphnode biopsy are Hodgkins lymphoma in 4 cases, non Hodgkins lymphoma in1 case, caseous lesion in 4 cases, Histiocytosis in 2 cases.

Wilson Profile : was done in 4 cases, (4.21%) of which 1 caseshowed suggestive of Wilson's disease and remaining were normal.

Torch Profile : Was done in 6 cases (6.31%) it is positive in 3 cases. Normal in 3 cases.

Other examinations : which were done include opthalmoscopy, cranial ultrasound, chest roentgenogram, skeletal roentgenogram, widal test, C-reactive protein, 2 D echo, Renal function test, upper GI endoscopy, connective tissue profile, urine for metabolic profile, mantoux test, ESR, CT Scan brain etc.

Diagnosis :

The most common diagnosis obtained in the study are Infection 35 cases (36.8%) and Malignancy 20 cases (21%) followed by extramedullary hematopoiesis16 cases (16.8%). Metabolic and Storage in8 cases (8.6%). Congestive causes in6 cases (6.3%) and other 10 cases (10.5%) In Lucia F Bricks et al study [4] the distribution of diagnosis are anaemia 70 cases (78.56%), infection 42 cases (47.1%) followed by metabolic 7 cases (7.87%), malignancy 5 cases (5.6%). In Loredo Abdala et al [5] study infections, metabolic and neoplastic disorders are the usual cause of visceromegaly. In Sotelo-Cruz N et al [6] study infectious diseases, oncologic disease, metabolic disturbances are common etiologies.

Infections:

The most common diagnosis obtained in our study is infections 36.8%. Malaria is the most common infection obtained in our study, found in 11 cases (11.76%). Viral hepatitis is the next common infection found in the study.

Other less common infections found in study are enteric fever, TORCH infection, Septicaemia, Neonatal hepatitis, HIV, infectious mononucleosis.

Malignancy:

Are found in 20 cases, the most common among this is acute lymphoblastic leukaemia12 cases followed by Hodgkin's lymphoma. Other less common malignancies are Non-Hodgkin's lymphoma, acute myeloid leukaemia.

Storage disorders are found in 8 cases (8.4%) the most common among this is lipid storage disorders 2 cases followed by less common glycogens storage disorder, mucopolysaccharidosis, histiocytosis, Reyes syndrome. Metabolic disorder was found in 1 case that was Wilson's disease.

Thalassemiamajor: is the most common cause of extramedullary haematopoiesis found in the study followed by sickle cell anaemia, G6Pd deficiency, osteopetrosis.

Congestive causes: Associated with hepatosplenomegaly in the study are portal hypertension – 2 cases (2.10%) and congestive cardiac failure associated with infective endocarditis – 3 cases (3.15%).

The other significant diagnosis found in study is biliary atresia found in 3 cases

The mortality was maximum in malignancy.

Comparison of observed results with other studies:

Table no 16: Observed results compared with other studies

	Fever	Infectious	Anemia	Hepatitis	Hematologic	Congestive	Storage disorder	malignancy	Jaundice
Bricks LF[4]	44%	39%	79%	7%	-	-	8%	6%	16%
Ali N[7]	-	-	-	-	73%	-	9%	18%	-
Present study	77.8%	36.8%	73.7%	14.33%	16.8%	6.3 %	8.4%	21%	17.9%

CONCLUSIONS:

1. Hepatosplenomegaly is common pediatric problem.
2. Both sexes are affected equally with slight predominance of males.
3. It is highest in the below 6 years age group.
4. Fever, Pallor, Anorexia and Jaundice are the common presenting complaints.
5. Anemia, Jaundice, Fever, Stunting, Wasting and abdominal distension are the common examination findings.
6. The liver enlargement varied from 2.5cm to 14cm.
7. The spleen enlargement varied from 2cm to 15cm.
8. Infections and malignancy are the most common diagnosis found in the study.
9. Malaria is the most common infection detected in the study.
10. Acute lymhoblasticleukemia is the most common malignancy associated in the study.
11. Investigations required varies with the type of case presentation.
12. The progression of the disease varied in different conditions.
13. Retardation of growth was noticed in majority of storage disorders and malignancy.
14. Infections, malignancy and congestive disorders are found commonly between 4-9 years of age. Extramedullary hematopoietic disorders (hemolyticanemias, osteopetrosis) are commonly found between 1-6 years of age.
15. Hepatosplenomegaly with generalized lymphadenopathy is most commonly associated with malignancy in our study.

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