CLINICAL PATTERN AND DIAGNOSTIC TOOLS USED IN TUBERCULOUS MALNOURISHED CHILDREN IN KASSALA HOSPITALS

By

(MD in Paediatrics) Dr. Alam Eldin Musa Mustafa Musa

MBBS University of Khartoum

A thesis submitted in partial fulfillment for the requirement of the degree of clinical MD in Paediatrics and child health

Supervisor

Prof. Salah Ahmed Ibrahim
FRCPCH (UK), MD
Professor of Paediatrics
Department Of Paediatrics and Child Health
Faculty of Medicine of U of K

March, 2005
Dedication

To my parents
The 2 candles that lit my way
To my wife, kids and family hoping to repay
their great patience

To my teachers
The careful hands that guided my steps.
Acknowledgment

It is beyond my ability to express my great appreciations to the kind guidance and fruitful criticism of Prof. Salah Ahmed Ibrahim: Head Department of Pediatrics and Child Health, University of Khartoum, and to Dr. Yahia Shakir; Associate Professor Department of Pediatrics and Child Health, University of Khartoum.

I am greatly indebted to Dr. Eltayeb Ahemd El Sayed Director of EPI program Federal Ministry of Health for provision of mantoux and BCG and to DR. Abd Elmoneim Ali Elhag for the valuable advice and encouragement.

I would like to express thanks to the following:

Dr. Mahgoub Ali Adam and Dr. Mohammed Farouk Siddig, pediatricians in Kassala for their great support, Dr. Elwathig Ali, Dr Abd Ellah Osman and MR Mohammed Omer for reference provision, Dr Badr Eldin Ahmed and Dr. Ali Mohammed for their help in the study, the staff in Kassala teaching and Kwaiti pediatric hospitals, Mr Hassan Ali (statistician) and Miss Samia Gasm Elseed for typing the thesis.
Abstract

This is a hospital based cross sectional study done in Kassala Teaching Hospital and Kwaiti Pediatric Hospital during the period from January 2004 to December 2004. The objectives were to study the clinical pattern of tuberculosis and to evaluate the use of WHO clinical criteria and the accelerated BCG reaction in the diagnosis of tuberculosis in malnourished children below 5 years of age.

Data was collected through a questionnaire detailing full socio-demographic, nutritional and medical history, examination, anthropometric measurements and investigations of the children included in the study. This study has included 84 children of equal gender distribution. The mean(SD) age was 28.8(17.8) months. Almost all were of low socio economic class; 51 (60.7%) were BCG vaccinated. The mean duration of symptoms was 46 days.

The commonest symptoms were loss of weight in all patients, fever in 90.5% and cough in 79.8% of the study group. The cough had significant statistical relation to the pulmonary disease (P<0.042); 82.1% of the children had a weight/height percent ≤ 70%. Chest signs were seen in 66 (87.6%) patients. The mantoux test was positive in 18(21.7%) patients. The BCG test was accelerated in
51(60.7%) of the 66 tested children. Chest radiographic changes were present in 88% of the study group.

Pulmonary disease was diagnosed in 72.6% miliary in 8(9.5%) and meningitic TB in 4 (4.8%) of the children of the study group.

The WHO score was ≥ 7 in 65 (78.6%) of the study group and was statistically significantly related to the chest radiography (P< 0.027).

The following were recommended:

- Screening of children with adult TB contact.
- Sufficient nutritional rehabilitation of malnourished children prior to labeling them as tuberculous.
- The use of accelerated BCG test in mantoux negative patients in the diagnosis of TB in malnourished children.
ملخص الامروحة

Originally, the text appears to discuss a study conducted in 2004 to 2005 in education sectors in Kuwait, focusing on the assessment and evaluation of the performance of students. It seems to analyze the reasons behind the good performance of students in science and history and the decline in the performance of students in the second term. The study also seems to analyze the reasons behind this decline and seeks to improve the performance of students. The text contains various statistical data and analysis. It discusses the impact of various factors on the performance of students and seeks to improve the performance of students. The text is written in Arabic.
من توصيات الدراسة:

1. إجراء الأشخاص المبترين الأطفال الكلي علياً فحصами تكاثريًّا.

2. دقة مريض التغذية السيء للأطفال الكافي الغذائي الحراك المُركبين.

3. سيئة الأطفال في المتسارعة جيسي فهي ذلك استخدام في المنشأة غذائية لنزود وذل ذلك سبيل، انثى من التغذية لزيادة وذل ذلك سبيل، انثى من التغذية لنزود.
List of Tables

Table 1.1  Unvaccinated children 7-14 years old reactive to 1 tuberculin unit in North, central and East Sudan. 7

Table 1.2  Association of TB and HIV infection (1988-1996) 9

Table 1.3  Age groups and type of disease in 1987 9

Table 1.4  Cut off size of reactive area for a positive mantoux tuberculin reaction: 30

Table 1.5  WHO Pediatric TB Score Chart (TSC) 36

Table 1.6  The scoring criteria for the diagnosis of childhood TB adopted by the NTP of Sudan 40

Table 1.7  The essential anti TB drugs 43

Table 1  Age distribution of the study group (n= 84) 53

Table 2  Father occupation of the children in the study group (n= 84) 58

Table 3  History of contact with adult TB cases in the study group (n= 84) 62

Table 4  The pattern of fever in study group (n= 84) 66
Table 5  Comparison of pulmonary and non pulmonary TB with cough in the study group(n= 84) ...................... 67
Table 6  Comparison of severe TB disease with convulsions(n= 84) .................................................. 70
Table 7  The body temperature of the children in the study group (n= 84) .................................................. 74
Table 8.  The height centiles of the study group(n= 84) .......... 75
Table 9.  Weight/height percent of the study group(n= 84) ....... 76
Table 10.  The weight /height centiles in the study group ......... 77
Table 11.  The distribution of lymphadenopathy in the study group (n= 84) .................................................. 80
Table 12.  Distribution of abdominal mass in the study group(n= 84) .................................................. 83
Table 13.  Mantoux skin test size in the study group (n= 84) ...................................................................... 86
Table 14  Comparison between mantoux test size and PEM classification(n= 84) ....................................... 87
Table 15.  Comparison between diagnostic BCG reaction and age in months (n=84) ................................. 89
Table 16.  The chest X-ray picture in the study group(n= 84) 93
Table 17  Pattern of tuberculous pulmonary disease in the study group (n=84)………………………….. 96

Table 18.  The WHO tuberculosis score chart (TSC) in the study group(n=84)………………………. 98

Table 19. 19. Comparison of WHO score and chest x-ray findings in the study group(n= 84)………………. 99

Table 20. 20. Comparison of IUATLD score and cough in study group(n= 84)…………………………….. 101
# List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The residence of children in the study group (n= 84)</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Tribal distribution of children of the study group (n= 84)</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>Gender distribution of the study group (n= 84)</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>Size of families of the study group (n= 84)</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>The number of individuals per one room (n= 84)</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>The duration of symptoms in the study group (n= 84)</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>The main presenting symptoms in the study group (n= 84)</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>Pattern of weight loss in the study group (n= 84)</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>The distribution of the BCG vaccination in the study group (n= 84)</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>Distribution of oedema in the children of the study group (n= 84)</td>
<td>79</td>
</tr>
<tr>
<td>11</td>
<td>The chest signs seen in the children of the study group (n= 84)</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>The Welcome's classification of malnutrition in the study group (n= 84)</td>
<td>84</td>
</tr>
</tbody>
</table>
Figure 13  The accelerated BCG reaction in the study group (n=84)…………………………………………………………………………………………… 88

Figure 14  ESR Distribution of the study group (n=84)………………… 91

Figure 15  The number of lesion per chest x-ray in the study group (n=84)………………………………………………………………………………… 92

Figure 16  The pattern of tuberculous disease in the study group (n=84)…………………………………………………………………………………………… 95
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB</td>
<td>Acid fast bacilli</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>ARI</td>
<td>Annual risk of infection</td>
</tr>
<tr>
<td>BC</td>
<td>Before Christmas</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacille- Calmette- Guerin</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT scan</td>
<td>Computed tomographic scan</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxy ribo nucleic acid</td>
</tr>
<tr>
<td>DOTS</td>
<td>Directly observed treatment short course</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme Linked immuno- sorbent assay</td>
</tr>
<tr>
<td>EST</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immuno deficiency virus</td>
</tr>
<tr>
<td>ICT</td>
<td>Immuno chromatographic test</td>
</tr>
<tr>
<td>IUATLD</td>
<td>International Union against tuberculosis and lung disease</td>
</tr>
<tr>
<td>LJ medium</td>
<td>Lowenstien- Jensen medium</td>
</tr>
<tr>
<td>MDR</td>
<td>Multidrug resistant</td>
</tr>
<tr>
<td>NTP</td>
<td>National tuberculosis programme</td>
</tr>
<tr>
<td>PCM</td>
<td>Protein calorie malnutrition</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PEM</td>
<td>Protein energy malnutrition</td>
</tr>
<tr>
<td>PPD</td>
<td>Purified protein derivative</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribo nucleic acid</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TSC</td>
<td>Tuberculosis score chart</td>
</tr>
<tr>
<td>TST</td>
<td>Tuberculin skin test</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
List of contents

<table>
<thead>
<tr>
<th>Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dedication</td>
<td>I</td>
</tr>
<tr>
<td>Acknowledgement</td>
<td>II</td>
</tr>
<tr>
<td>Abstract in English</td>
<td>III</td>
</tr>
<tr>
<td>Abstract in Arabic</td>
<td>V</td>
</tr>
<tr>
<td>List of tables</td>
<td>VII</td>
</tr>
<tr>
<td>List of figures</td>
<td>IX</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>XI</td>
</tr>
</tbody>
</table>

Chapter One

1. Introduction and literature review ....................... 1
   1.1. Global history and epidemiology of tuberculosis..... 1
   1.2. History and epidemiology of tuberculosis in the Sudan 4
   1.3. Bacteriology and immunology of tuberculosis......... 10
   1.4. Tuberculosis and malnutrition.......................... 15
   1.5. The Baacille calmette Guerin (BCG).................... 19
   1.6. Clinical aspects of TB in children................... 20
   1.7. Diagnostic test used in childhood tuberculosis..... 26
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8. Clinical diagnostic criteria in childhood tuberculosis</td>
<td>35</td>
</tr>
<tr>
<td>1.9. Treatment and control</td>
<td>41</td>
</tr>
<tr>
<td>1.10 Justification</td>
<td>44</td>
</tr>
<tr>
<td>1.11 Objectives</td>
<td>45</td>
</tr>
</tbody>
</table>
# Chapter Two

2. Material and methods ........................................ 46
   2.1. Study design.............................................. 46
   2.2. Study area ................................................ 46
   2.3. Study period ............................................ 46
   2.4. Sample size ............................................. 46
   2.5. Inclusion criteria......................................... 47
   2.6. Exclusion criteria......................................... 47
   2.7. Research tools and techniques............................. 47
   2.8. Ethical consideration....................................... 49
   2.9. Methodology ............................................. 50
   2.10. Research team ........................................... 50
   2.11. Data entry and statistics ................................ 51
Chapter three

3. Results ........................................................................ 52
  3.1. History ................................................................. 52
  3.2. Clinical examination .............................................. 73
  3.3. Investigations ....................................................... 85
  3.4. The pattern of the TB disease................................. 94
  3.5. The clinical diagnostic scores............................... 97

Chapter four

4. Discussion.................................................................... 102
  4.1. Socio-demographic characteristics......................... 102
  4.2. Clinical findings ................................................... 105
  4.3. Examination ........................................................ 109
  4.4. Investigations ....................................................... 109
  4.5. Pattern of the disease ............................................ 114
  4.6. The use of the diagnostic criteria......................... 115
    • Conclusion .......................................................... 117
    • Recommendation............................................... 118

References ...................................................................... 120

Appendix : Questionnaire
Chapter One

1. INTRODUCTION AND LITERATURE REVIEW

1.1. Global History and epidemiology of tuberculosis:

1.1.1. Global History:

Biologic and genetic data suggest that the pathogen Mycobacterium tuberculosis evolved from Mycobacterium bovis after the domestication of cattle approximately 15000 years ago. The disease crossed over to humans. Historians believe that the disease appeared in the Middle East area. It has been mentioned in the Babylonian codes of Hamorabi 2000 years B.C. The disease was recognized in skeletons from stone ages and mummified bodies of ancient Egyptians. Homers mentioned TB in his work. Hippocrates and Aristotle in the 5th century B.C. described the disease and named it phthisis from a Greek word meaning to (dry up) or consumption. The Arabic physician Rhazes (AL razi) 850-623 and the Arab prince of
physicians Avicenna (Ibn sina) 980-1037 described TB in some detail\textsuperscript{(2,3)}.

The earliest recorded TB epidemic in Europe began at least 400 years ago. Sylvius (1614-1672) recognized the characteristic nodule (the tubercle). Bunyan emphasized the prevalence of TB in England when he said “The captain of all these men of death, was consumption”. By the late 17\textsuperscript{th} century TB was a major killer in Europe\textsuperscript{(4,6)}.
Schonlein in 1830 first used the term tuberculosis. Anton Ghon described in details the primary focus. On March 24th, 1882, Robert Koch reported the discovery of the tubercle bacillus. (Mycobacterium TB). Pirquet introduced tuberculin test in 1907. This was more developed by Mantoux, Mandel and Moro 1907-1910. The BCG vaccination was introduced in 1921 by Calmette and Guerin in France. Pyrazinamide and rifampicin were introduced in 1952 and 1967 respectively\(^{(5,6)}\). Death rate among European children with TB fell sharply after the introduction of streptomycin in 1947\(^{(6)}\).

1.1.2. Global epidemiology of the disease:

One third of the world population (about 1.7 billion people) are thought to harbor the infection with TB with 30 million cases of active TB and 8 to 10 million new cases annually, 3 million people die of TB each year and TB probably causes 6% of all deaths world wide \(^{(7,8)}\). The 1990s has been notable for the global reawakening of the disease, the number of incident cases was estimated at 7.5 million in
In 1993 the WHO declared TB a global emergency. In 1997 a panel of 86 TB experts and epidemiologists from more than 40 countries chosen by the WHO estimated the new cases at 7.92 million with 44% of these cases of infections smear positive pulmonary disease and the global case fatality rate was 23% but exceeded 50% in some of the African countries with high HIV rate. 8% of incident TB cases have HIV infection \(^{(1,8,9)}\). 14% of the annual TB deaths predicted for the year 2000 by the WHO are attributable to HIV co-infection \(^{(1)}\).

95% of cases and 98% of TB deaths occur in the developing countries where 0.2 to 1% of the total population are infectious. The estimated incidence in Africa is 272 cases per 100,000 population \(^{(10)}\). In developing countries as many as 40% of TB notifications may be in children. TB may
be responsible for 10% or more childhood hospital admission and 10% or more of hospital deaths. Furthermore with the annual risk of infection of 2-3% close to 40% of population may be infected by the age of 15 year \(^{(8,11)}\). In children it is estimated that 1.3 million cases are infected annually and 450,000 annual deaths due to TB occur\(^{(12)}\). TB is spread from person to person through air by droplet nuclei particles measuring 1-5 mm in diameter treating the infectious patient is the most effective way to reduce the number of bacilli released into air\(^{(13)}\). On the basis of WHO criterion no single country in the world has succeeded to reach the point of control i.e less than 1 percent tuberculin positivity among children in the age group 0-14 years \(^{(8,14)}\).

1.2. History and epidemiology of tuberculosis in the Sudan.

1.2.1. History of TB in the Sudan.
Early in the past century (1908-1911) pioneer published work was carried by Commins. He studied TB in the Egyptian army and noticed that incidence of TB among Sudanese soldiers was 3.7/1000 while it was 1.5/1000 among Egyptian soldiers. Balfour and Archibald related this to the fact that Sudanese people live in ill ventilated dwellings in order to exclude the powerful sunrays \(^{(3,15,17)}\).

The first tuberculin test survey was conducted in 1925 on 700 school boys, soldiers and hospital patients in Blue Nile province, positive results ranged from 7-27% in different groups.

The age distribution of positive tests ranged from 8 to 35 years. By late 1920s there was evidence that the disease was gaining grounds in the northern and central parts of the Sudan counterbalanced by better nutrition and disease control. In the south the isolated rural population had little chance of acquiring immunity \(^{(3,17)}\). The tuberculin surveys
done among southern tribes in 1928-1930 showed that the prevalence rate was 0.2/1000.

A survey carried out on two groups of urban and rural school children in Khartoum province in 1932 showed slightly higher positive rate in rural (40%) than urban (37%). Up to 1939 the rate of hospital admission with TB was constant (About 1%)\(^{(16,17)}\).

In 1950 health services were oriented towards improved TB control by establishing a pilot TB service training specialized personnel and WHO advisor visits for initiation of Mantoux testing and BCG vaccination. The pilot project in that year in Khartoum showed that nearly 50% of population under 25 years were Mantoux negative. Therefore requiring BCG vaccination \(^{(16,19)}\). The WHO prevalence survey \(^{(16,20)}\) in 1954 used PPD. RT 19, 20 and 2,156,702 people were tested country wide. 16% were positive in age group 0-6 years and 43.2% positive in age
group 7-14%. A representative sample of all ages from this population showed 47% negative reaction. These were considered nonimmune and given BCG vaccination and followed for 28 weeks with no serious post vaccination effects\(^{(16,18)}\). In 1957-1958 a mass campaign with Mantoux testing and BCG vaccination was carried out in the southern Sudan and by 1960 about 622,000 had been tested and 250,000 vaccinated. Freeze dry BCG vaccine was introduced in 1965 since the late sixties of the last century (1968-1969). In 1966 Mahdi M.E. used PPD TR23 to examine 431,553 people in North Gezeira and found: 4.57% positive in age group 0-6 years 26.67% positive in age group 7-14 years. He also examined 14,132 school children in Khartoum area and found that 21.6% were positive in age groups 5-14 years. A tuberculin survey was carried out in 1976 and 1986 in children 0 to 17 years old in Khartoum, central, Northern,
Eastern and in Kordofan regions and the ARI was calculated according to standard methods to be 1.9% and 1.8% respectively. (Table 1.1)

Table 1.1. Unvaccinated children 7-14 years old reactive to 1 tuberculin unit in North, central and East Sudan.

<table>
<thead>
<tr>
<th>Years</th>
<th>Subjects tested no</th>
<th>Diameter 8mm</th>
<th>ARI %</th>
<th>Approximately in 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>3407</td>
<td>686(20.1)</td>
<td>1.9</td>
<td>95</td>
</tr>
<tr>
<td>1986</td>
<td>39.9</td>
<td>716(18.2)</td>
<td>1.8</td>
<td>90</td>
</tr>
</tbody>
</table>


In May 1995, the Federal MOH prepared a draft NTP development plan for 1996 and 1997 with implementation of revised NTP policies in step wise approach (18).

1.2.2. Epidemiology of TB in the Sudan:
Tuberculosis is one of the most important public health problems in Sudan. In 1995 according to the Federal MOH TB is:

1. A leading cause of health service utilization in the ambulatory services ranking the 4th.

2. The most frequent reason for hospital admission constituting 11.6% of all cases admitted to hospital.

3. The 4th most frequent cause of hospital deaths constituting 16% of all patients who died in hospital (19).

The best indicator for the problem of TB in Sudan is the average annual risk of infection which is the proportion of population that is likely to be newly infected over a period of one year, it is derived from studies of tuberculin positively. The estimated annual risk of infection (ARI). In Sudan is 1.8% which gives an Incidence of 90 smear positive cases per 100,000 population. This puts Sudan among the high
prevalence countries for TB in the East Mediterranean region.

The estimated average incidence of all forms of TB is twice the incidence of smear positive cases i.e: 180 per 100,000 population. In the population of 27,899,000 in 1998 therefore, the estimated new cases was 50,218 with a detection rate coverage of 43.6% in that year (18,19,21). In 1999 reported cases of TB were 25,713. The infection prevalence was estimated at 38%. Deaths per 100,000 cases were 60 cases (23).

Table 1.2 below shows, the association of TB and HIV infection (From the global AIDS programme/ Sudan MOH, half annual report 1998(19).

Table 1.2: Association of TB and HIV infection (1988-1996)
Table 1.3 below shows age groups and type of disease in 1987(19).

Table 1.3: Age groups of TB patients in (1987)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Pulmonary TB</th>
<th>Extra pulmonary TB</th>
<th>All forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 years</td>
<td>3.471</td>
<td>120</td>
<td>3.591</td>
</tr>
<tr>
<td>≥15 years</td>
<td>12.774</td>
<td>287</td>
<td>13.061</td>
</tr>
<tr>
<td>All ages</td>
<td>16.245</td>
<td>407</td>
<td>16.652</td>
</tr>
</tbody>
</table>

TB in Sudan constitute 9% of new cases in North Africa and the Middle East region making the country the 3rd after Pakistan (42%) and Afghanistan (12%).\(^{(22)}\) By June 2000 DOTS coverage was 75% all over the country with a cure rate of more than 87% \(^{(23)}\).

1.3: **Bacteriology and Immunology of Tuberculosis:**

1.3.1: **Bacteriology of tuberculosis:**

*Mycobacterium tuberculosis,* the tubercle bacillus is one of more than 30 well characterized and many unclassified members of the genus *mycobacterium,* most *mycobacteria* are not pathogenic to humans. There are 5 closely related *mycobacteria* grouped in the *mycobacterium tuberculosis* (MTB) complex: *M. tuberculosis,* *M. bovis,* *M. africanum,* *M. Microti* and *M. canetti* \(^{(7,24)}\). *M. tuberculosis* is a nonsporing, non capsulated, straight or slightly curved slender rod measuring 1-4 MmX 0.2 to 0.6 Mm. Although it
does not Gram stain well due to its waxy surface, the organism has a Gram positive cell wall.\(^{(23,27)}\)

1.3.2: **Staining and culture of the mycobacteria:**

When stained with the ZN technique MTB is an acid fast and stains red. This is due to mycolic acids (fatty acids) in the cell wall which form a complex with the carbol fuchscin (an arylmethane dye) and can not be removed by the acid in the decolorizing reagent. The ZN stain is carbol fuchsin combined with phenol.\(^{(25,28)}\)

Auramine phenol fluorochrome is a staining technique used to detect MTB in sputum, CSF and other specimens it enables more rapid smear examination and the X40 objective can be used. When the dye is removed from the back- ground with acid alcohol, the smear is then washed with a weak pottassium permanganate to darken the background and the bacilli fluoresce white yellow against a dark back ground\(^{(25)}\).
Culture of the mycobacteria is used for detecting, identifying and antibiotic sensitivity tests of the organism. Culture is considerably more sensitive than microscopy detecting 10-100 viable organisms/ml of sputum. The organism is strictly aerobic, need carbon e.g: CO₂ for growth and energy and need ammonia and amino-acids as source of nitrogen.

1.3.3. Types of media used:

- Simple synthetic media:

  Containing abundant mineral supply, Ammonia, glucose or glycerin. Albumin and activated charcoal aid the growth here.

- Oleic acid albumin media:
Here mycobacteria grow in clumps with tweens (commercial name of water soluable esters of fatty acids) used to permit its dispersed growth.

- **Complex organic media:**

  Contain organic substances e.g: egg yolk, animal serum or tissue extract. Examples are

  1. Lowenstein- Jensen medium: It contains egg yolk, mineral salts/glycerol asparagine, malachite green and antibiotic e.g: penicillin (a selective medium).

  2. Fluid medium of Dubos and Middle brook: contains asparagines/ glycerol, salts of Mg/Cu/Zn and fe.

Bactec rapid radio metric culture system, developed by Becton Dickinson is an automated early detection system. Growth here can be detected within 12 days. (25,27) of the new tests used in detecting mycobacteria in specimens are:
1. Nucleic acid probes and nucleic acid amplification tests using polymerase enzymes to amplify specific DNA or RNA sequences extracted from mycobacterial cells.

2. Bacteriophage based test to detect MTB. In sputum: Sensitivity of the test is similar to culture detecting as 100 bacilli/ml.

3. Mycodot antibody test: Most common serology used in diagnosis of TB are enzyme linked immuno-sorbent assay (ELISA). It is a 20 minutes immunoassay using purified lipo-arabino-mannan as antigen (25,27).

1.3.4. Immunology of tuberculosis:

Mycobacterium TB initially infects macrophages. The bacillus lipid rich outer capsule protects it from the toxic radicals and hydrolytic enzymes and generally the infection is not eliminated entirely. A delayed hypersensitivity response with granuloma formation then occurs. Macrophages activation by CD4 T lymphocytes enable them
to destroy the bacilli within the tubercle. CD4 T cells are primarily T helper cells which secrete inter-leukins and of 2 subsets TH1 and TH2. TH1 cells produce interferon gamma (IFN-g) and interleukin-2 (IL-2) important in activation of antimycobacterial activities and essential for the delayed hypersensitivity response. IFN-g specifically activate the macrophages which in turn secrete several cytokines in addition to IFN-g and IL-2 and include tumor necrosis factor alpha (TNF-a). Characteristics of activated macrophages include increased hexose monophosphate shunt activity, augmented surface adhesiveness, expression of characteristic membrane structures and increased mycobacteriocidal activity. There is induction of rapid phagosome-lysosome fusion generating reactive oxygen and nitrogen intermediates which are toxic to the mycobacteria. TGFB1 a cytokine produced by activated macrophages is acritical
immuno-modulator that facilitates macrophage migration into inflammatory sites and also is an chemotactic factor for CD4 and CD8 T cells\(^{(7,29--32)}\).

CD8 T lymphocytes also contribute to macrophage activation by producing IFN-\(\gamma\). These cells also may have cytolytic functions. Gamma/delta T cells are a minor subpopulation that might have a role in initial innate immune response to TB infection. Natural killer (NK) cells are capable of lysing host cells infected with the mycobacterial pathogens. TB is associated with both qualitative and quantitative defects in the cell immune response. In children with TB the total number and percentages of CD3 and CD4 cells are reduced suggesting this is directly related to tuberculosis\(^{(34)}\).

1.4. **Tuberculosis and Malnutrition:**

There is strong link between malnutrition and increased susceptibility to and/or severity of TB. The nutrients that
have been implicated in the immune response to tubercle bacilli include protein, Zinc and vitamin D. Other elements deficiency including vitamin A, vitamin C and iron can also cause profound impairment of cellular immunity and TB resistance. On the other hand, increased protein breakdown in TB leads to muscle wasting and as a response to infection there is profound impact on micro nutrient status of the child affecting vitamins A,E,B6,C,D and folate. Also there is decrease of serum levels of iron, zinc and selenium during the infection. (35,37)

Malnutrition exerts detrimental effects on many aspects of host immune responses against mycobacterial infection. (35,36) Dietary protein malnutrition down-size the immune system to spare limited nutrients for use and maintainace of the more vital organs such as the brain and heart. The thymus shows profound atrophy and involution with marked decrease in the number of cortical lymphocytes and thymic
hormones including thymulin, thymopoitin and thymosin with resultant loss of differentiation and maturation functions of thymic micro-environment. The peripheral lymphoid tissue including spleen, lymph nodes, Tonsils, peyer’s patches and appendix also show significant atrophy with marked depletion of T. lymphocytes mainly CD4 subsets. Also there is significant CD8 T cells drop and reduction of the CD4:CD8 ratio.

Dietary protein deficiency also causes intrinsic functional defects of T lymphocytes and consistently results in mitogen and antigen induced lymphoproliferation and decreased mobilization and trafficking of reactive lymphocytes which are then trapped or sequestered in broncho- tracheal lymph nodes.\(^{(36,38,39)}\). Zinc is required for optimal immune response especially for thymus dependant immune functions. Chronic dietary zinc deficiency result in thymic atrophy. Zinc deficient guinea pigs failed to develop
PPD induced delayed hypersensitivity reaction. It is clear that calcitriol is capable of acting synergistically with cytokines such as IFN-g to contain intra cellular replication of M. tuberculosis and M. avium within cultured human monocytes. It has been reported also that vitamin D deficiency altered macrophage functions in mice. The dermal tuberculin and PPD induced T cell proliferation was reduced in vitamin D deficient guinea pigs. In a study on 22 children aged 1-12 years with TB (Barnes et al). The percentage of CD3 and CD4 cells was significantly lower in the 10 malnourished patients (weight for age <75%) compared to the 12 patients who were not malnourished. Studies on animal models subjected to TB infection were carried to provide more supportive information that PEM debete the immunity against TB these include studies done by McMurray et al and Chan et al. There is good evidence that malnutrition increases the frequency of occurrence and exacerbate the clinical manifestations of TB.
in a bidirectional relationship. Studies in south Africa indicate that TB can be found in 12-30% of children presenting with different forms of malnutrition. It is evident that 66% of tuberculous children fail to gain weight or show weight loss prior to diagnosis \(^{(37,44)}\).

Our knowledge on how PCM affects the clinical presentation of pulmonary TB is limited. In one study (Madebo et al) the clinical and radiological features of pulmonary TB in 239 adults positive for acid fast bacilli 78% of patients were malnourished (body mass index (BMI) < 18.5). and 43% were severely malnourished (BMI <16) 20% were HIV positive. HIV negative severely malnourished patients presents more often with dyspnea, diarrhea and night sweats and less often with hemoptysis and cavitation. The size of the mantoux test was associated with malnutrition. Both HIV status and malnutrition were associated with the atypical presentation of pulmonary
TB. In a study on 203 patients hospitalized with culture positive TB at BJC hospital between 1988-1996 to define the factors associated with mortality of tuberculosis malnutrition was found to be one of the important markers. Nutritional status measured by serum albumin concentration and hemoglobin was an important predictor of survival among patients with respiratory failure due to non-miliary TB. The study suggests that specific intervention on potentially reversible factors such as malnutrition may improve the patient outcome.

Nutritional assessment was conducted in 30 patients with chronic intractable pulmonary TB. The grade of malnutrition was significantly associated with reduction in delayed type hyper sensitivity response. The Study suggested that nutritional support should be taken in consideration combined with chemotherapy in treating chronic pulmonary TB.
1.5: The Bacille Calmette Guerin (BCG):

The vaccine BCG is the most widely used vaccine in the world; however, its efficacy in protecting against TB remains controversial. Average results pooled from a range of studies indicate an overall reduction of TB risk by 50% with individual studies showing a range of efficacy from zero% to 80%.

Fewer than one in 1000 people vaccinated with BCG develop significant local reactions and serious disseminated disease develop in fewer than one in million. Wallgren (1960) has stated that both miliary TB and meningitis can be prevented by vaccination. Literature review of 97 published articles indicates that there is little relationship between BCG vaccination and PPD. BCG vaccination status should not be considered in the interpretation of a positive PPD. DNA vaccines are promising alternatives that would provide an easily produced and stable vaccine.
In recent years several articles have been published about BCG tests in the diagnosis of TB particularly in children. The test is reportedly more sensitive and more specific than the tuberculin test (PPD). In one of the Turkish studies authors evaluated the results of simultaneous application of PPD and BCG test in order to assess efficiency in adults and adolescents with TB. BCG test and PPD were applied concurrently in 35 healthy and 41 tuberculous cases presented to research hospital İnönü university and Malatya TB dispensary with clinical and radiological findings. The subjects also have sputum examined for presence of acid fast bacilli by direct microscopy, culture on LJ medium and PCR. The conclusion was that BCG test is more sensitive and specific than PPD in diagnosis of TB in adults and adolescents.


1.6.1. General consideration:
Natural history of TB in children includes 3 stage exposure, infection and disease. Exposure implies a recent and substantial contact with an adult or adolescent with suspected or confirmed pulmonary TB. Children especially infants are less likely to contain infection. Studies show that with no specific treatment infection will progress to disease in 43% of infants less than one years, 24% of those from 1-5 years of age and 16% of those 11-15 years old compared to only 5-10% of immunologically competent adults. In 25 to 35% of children TB is extra pulmonary. Clinical presentation varies with age. A history of contact is found in about 50% of cases. Sensitivity and specificity of clinical symptoms and signs are extremely low and can lead both to over or under diagnosis in absence of further evidence\(^\text{55,56}\).

1.6.2. Pathogenesis:

Surviving initial host defenses, the bacillus grow slowly within alveolar macrophages dividing every 25-32 hours. In
patients with intact cell mediated immunity a brisk granulomatous response usually stops the progression of infection. The Ghon complex of initial nodal and peripheral lung parenchymal lesions may undergo healing. When infective inocula are high and nutritional status or other host factors less favorable failure of complete healing occur. Famine and intercurrent diseases adversely affect healing.(8,57)

1.6.3. Primary TB:

Usually asymptomatic or presents with signs and symptoms of upper respiratory infection. In a 16 years study in Belloevue hospital out of 964 children with primary TB only 14 (less than 1%) have extrapulmonary primary sites including tonsils, small intestine and also skin, conjunctivae and subscutaneous tissue (6,58).
1.6.4. Pulmonary TB:

The most common form onset is usually insidious, 60% of children die within 2.5 year in absence of specific treatment. Central necrosis with caseation of pulmonary lesions leads to loss of pulmonary volume and architecture. Laryngeal and endobronchial forms are associated with pulmonary TB. Pleurisy due to hypersensitivity reaction usually goes unnoticed. Empyema is rare and is associated with a broncho-pleural fistula \(^{(6,7,58)}\).

1.6.5 Tuberculous lymphadenitis:

Usually a group of nodes is affected those most commonly involved are the cervical constituting 35% of tuberculous adenitis. Scrofula is chronic cervical adenitis in children below 5 years old, of the frequent causes of it are M.scrofulaceum and M.intracellulare.

In early stages the nodes are discrete and non tender with normal over lying skin. Pathologically there is lymphoid
hyperplasia then a granuloma followed by caseation which may break in through a sinus tract and the nodes become matted together and adherent to skin. A study by Jones et al showed that in children with untreated bronchitis, bronchiectasis was the sequela in one third of patients and similar results were obtained in the Bellevue hospital study\(^{(6,7,58)}\).

1.6.6. **Disseminated and miliary tuberculosis:**

Occurs due to inadequacy of host defenses to contain TB infection. There is multiorgan involvement. The lesions are in form of yellowish nodules 1-2mm in diameter and histologically are granulomas. In the lungs they produce the miliary radiographic pattern. Symptoms are nonspecific and dominated by systemic effects particularly fever, anorexia, wasting, night sweats, hepatomegaly, pulmonary findings, lymphadenopathy and splenomegaly in descending order.

Choriodal tubercles strongly suggest disseminated TB \(^{(59)}\).
This generalized hematogenous TB spread in children by 3 hemic types of bacilli seeding.

Occult hematogenous spread. 1.

Acute massive miliary spread. 2.

Repeated blood stream injection (protracted type). 3.

Grieco and Chemel reported that only 14 out of 28 patients with disseminated TB (50%) had a miliary chest radiograph pattern. Munt et al reported that 90% of their 69 patients had this pattern \(^{(6,60)}\).

1.6.7. **Tuberculous meningitis:**

Although treatable in 90% of cases, this is the most serious form of childhood TB. The bacilli lodged in cerebral cortex may form a caseous focus discharging in the cerebrospinal fluid leading to meningoencephalitis. The lesion may become encapsulated forming a tuberculoma. TB meningitis always involves **meninges** around brain stem.
with cranial nerves involvement due to oedema or exudate. Clinically apathy is the most striking symptom. The course has 3 stages.

Initial: with general symptoms for 1-2 weeks. 1.

Second: neurological involvement with drowsiness, 2. neck stiffness, tremors, encephalitic signs, positive Kernig's and Brudzinski signs.

Third: Unresponsiveness and decelerated rigidity. In 3. most series more than 50% patients with meningitis have abnormal chest rays.

In Bellevue hospital study TB meningitis occurred within 4 months of estimated date of infections in 40% of children. Apathy occurred in more than 50% of those patients. 10% had upper respiratory infection at onset and 89% of those 241 children had abnormal chest X-rays \(^{(6)}\).

**Skeletal TB:** 1.6.8.
Due to hematogenous spread. Dactylitis with painless bone thickening is more common in infants and spondylitis in older children. Infection begin in metaphyseal portions of the epiphyses. Granulation and caseation develop. Cold abscess and synovitis may occur. Spine is the most common site affected followed by hip then knee. Bone involvement is found in approximately 1% of young children with TB. Multiple bony lesions occur in disseminated forms. \(^\text{(6,7)}\).

**Abdominal TB: 1.6.9.**

_Sites involved are:

1. The lymphnodes as initial complex or more commonly as hematogenous spread seen as adherent nodes to visceral peritoneum which may cause partial or complete intestinal obstruction._
2. Peritoneum: Omental adhesions with partial intestinal obstruction and exudative ascites may develop.

3. Intestinal disease: Ileitis with chronic diarrhea and rarely fistula formation\(^{(6,7)}\) the most common sites are the terminal ileum and the cecum.

1.6.10. Rare extra pulmonary forms: Include tuberculous pericarditis, cutaneous TB, ocular TB, Genitourinary and adrenal TB.

**Diagnostic Tests Used in Childhood Tuberculosis 1.7.**

1.7.1. **Mycobacterial culture:**

Diagnosis of TB in children is mainly epidemiologic and relies on clinical signs and symptoms, tuberculin skin testing and chest radiographs. From 1985 to 1988 in United States 90% of adult TB was bacteriologically confirmed compared to 28% in children. Culture sensitivity is from 80-85% and specificity is approximately 98%.
Growth detection on automated culture systems such as the BACTEC 460 using radio or calorimetric methods is within 1-3 weeks compared to 3-8 weeks on solid media. Genotyping of mycobacteria widely replaced phage typing \(^{(61)}\).

For most children with pulmonary TB culture confirmation is not needed. The best specimen for culture is the early morning gastric aspirate obtained in hospital using a nasogastric tube before the child arises. The yield is only 30% to 50% and gastric aspiration is inconvenient, expensive and uncomfortable\(^{58}\).

Other specimens for mycobacterial culture and antibiotic sensitivity include sputum in older child, urine, csf, pleural fluid, bronchial washing and bone marrow biopsy specimen. Procedure is very costly and needed time. 3 single specimens of sputum are needed preferably on different days using a 50ml plastic centrifuge tube. Aerosol
inhalation of sterile hypertonic saline 3-15% may induce sputum production\(^{(58)}\).

**Staining and microscopy:** 1.7.2.

The easiest, least expensive and most rapid procedure for preliminary information is the examination of acid fast stained smears from clinical specimens. It is positive in fewer than 20% of tuberculous children compared to up to 75% in adults. The newer fluorochrome stains such as rhodamine and auramine are superior to classic carbol fuchsin stains \(^{(62)}\). Concentration
Methods increase the test sensitivity. Negative results do not preclude TB disease\(^{(58)}\).

**Mantoux tuberculin skin testing:** 1.7.3.

Uses 5 tuberculin units of purified protein derivative (PPD) and is the standard method for detecting infection by *M. tuberculosis*. Host factors including young age, H.I.V. infection, overwhelming TB disease Co-existing viral infections including varicella, and influenza and poor technique used all these diminish area of in duration. False positive TST is recognized in infection by non-tuberculous mycobacteria and as a booster effect of serial TST (lower in children). The test is a delayed hypersensitivity reaction. The PPD is prepared by heating bacilli in culture filtrate and isolated by protein precipitation using ammonium sulphate or trichloroacetic acid. A patch of PPD produced by Siebert and Glenn in 1939 called PPD-S has continued to serve as
the international standard. The 5 tuberculin units dose of PPD-S is the amount of activity contained in 0.1mg/0.1ml of PPD-S. **Tween** 80 detergent 0.0005% is added to the diluents to reduce its adsorption to glass or plastic syringe.

A disposable plastic tuberculin syringe with a ½ inch long no 26 or 27 gauge needle is used. Best site of injection is the central part of volar aspect of forearm. Intradermal injection of 0.1ml to produce a wheal of 6-10mm in diameter is performed. Test should be read within 48-72 hours. The induration should be measured through its maximum transverse diameter with a millimeter ruler. Margins of induration (not the erytherma) delineated by gentle palpation or by ballpoint pen method of Sokal \(^{(6,55,58)}\).
Table 1.4:  Cut off size of reactive area for a positive mantoux tuberculin reaction:

<table>
<thead>
<tr>
<th></th>
<th>≥5mm</th>
<th>≥10mm</th>
<th>≥15mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of contact in low risk area.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants. Persons with no risk factors.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV infected and immuno suppressed other medical risk factors e.g.:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>children.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons with malnutrition.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons with abnormal chest radiographs or clinical features of TB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children in high risk area with history of contact.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


1.7.4. Radiology:
Radiology is the first diagnostic tool that should be used after a positive TST reaction. Radiological evidence of pulmonary TB varies but usually shows enlarged hilar, mediastinal or subcarinal lymph nodes and lung parenchymal changes most of these changes are caused by a combination of lung disease and mechanical effect produced by partial or complete airway obstruction due to enlarged intrathoracic nodes.

Most common findings are segmental hyperinflation then atelectasis, alveolar consolidation, interstitial densities, pleural effusion and rarely a focal mass. Cavitation is rare in young children. CT scan has no current role in evaluation of asymptomatic TB infected child\(^{(55)}\)

**Bronchoscopy and transbronchial biopsy:** 1.7.5.

Role of bronchoscopy is controversial. In a recent study of 36 children with pulmonary TB bronchoscopy showed endobronchial involvement in 42% of them\(^{(55)}\).
Tissue biopsy and body fluid examination: 1.7.6

Use of histopathology of skeletal system, pleura and superficial lymphnodes and specimens for staining, microscopy and culture are important TB diagnostic tools. Specimens include:

1.7.6.1. Pleural, peritoneal and pericardial fluids:

A high protein, lymphocytosis and low glucose are usually found. Adenosine deaminase may be elevated in these fluids. Pleural fluid culture is positive in less than 25% of cases and pleural biopsy shows a granulomatous inflammation in up to 60% of patients

1.7.6.2. Tissue biopsy:

These invasive procedures to obtain specimens from lymphnodes, bones, joints, lungs bowels and pericardium should be considered only in difficult cases. Closed techniques such as percutaneous needle or aspiration biopsy may only be needed.
1.7.6.3. **Urine:**

First morning voided mid stream sample is preferred, multiple specimens are needed but usually negative\(^{(58)}\).

1.7.6.4. **CSF:**

Should be analysed for protein, glucose, white blood cells count and differential count. High protein >50% of serum protein, lymphocytosis and low glucose are typical of tuberculous meningitis. A minimum of 5ml of CSF is needed. AFB smear is usually negative but culture may be positive\(^{(58)}\).

1.7.7. **Polymerase chain reaction:**

A technique of DNA amplification that uses specific target sequences as markers for the organism detected through use of nucleic acid probe. The most used sequence
is the mycobacterial inserion element IS 6110. Positive results can be obtained if specimen contains as few as 10 bacilli in research laboratories. Sensitivity is approximately 95% and specificity 98% in AFB positive specimens.

They do not replace the need for routine AFB or culture. Many studies on the use of PCR in diagnosis of TB in children were conducted worldwide. Studies done by Pirre et al, Deltacourt, Jantana et al and Montenegro et al. found positive results ranging from 25% to 100% of their study groups. (64-67).

1.7.8. Serology and antigen detection:

Despite dozens of studies, serology has found little place in routine diagnosis of TB. ELISA assay was extensively studied recently. Berrera et al found a sensitivity of 51% for culture positive children but only 28% for clinical cases. Hussey et al found a 62% sensitivity and 98% specificity
using autoclaved suspension of mycobacteria to detect antibodies in serum from 132 children with clinical TB. No co-relation with the TST, BCG vaccination and nutritional status was found\(^{(56)}\).

Deltacourt et al used ELISA to detect IgG and IgM antibodies against A 60 antigen in children with TB at the specificity of 98% IgG was detected in 86% and IgM in only 19% of children with clinical disease\(^{(67)}\) A commercial ICT kit for TB of a nitrocellulose strip containing 5 fixed mycobacterial antigens including the 38-Kd was used in 243 patients with clinical pulmonary TB results were compared to microscopy and culture. The method was simple and rapid specificity was 85.2% conclusion was that multiantigenic serologic tests may be as sensitive as microscopy\(^{(63)}\).

1.7.9. Diagnostic BCG:

In non tuberculous child BCG reaction takes 2-3 weeks to start as a papule, then a nodule and then a scar in about 3
months. In tuberculous child the reaction is accelerated a papule appears within 1-2 days, a pustule by 5-7 days and scab by 2 weeks. This accelerated reaction is of particular importance in diagnosis of TB in malnourished children, in early TB stages in miliary and in meningitic tuberculous disease \(^{(50.54)}\).

One study in Turkey showed that the BCG accelerated test was positive in 100% of patients with pulmonary TB while the mantoux was positive in 44.5% of patients. The BCG was positive in 82% of malnourished children while the mantoux in only 18% of these patients. The conclusion was that the BCG is more reliable and sensitive than the tuberculin test in the diagnosis of TB especially in developing countries where the disease is a major health problem with lack of sophisticated diagnostic methods \(^{(68)}\). A study in India showed that the mantoux was 50% and BCG 100% positive in patients with bacteriologically proved pulmonary TB \(^{(69)}\).
Clinical Diagnostic Criteria in Childhood

Tuberculosis:

The pediatric TB score chart (TSC) was developed and adopted by the WHO first developed in Papua New Guinea it is as follows:

Table 1.5: WHO Pediatric TB Score Chart (TSC):

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>1. Duration of illness</td>
<td>&lt;2wks</td>
</tr>
<tr>
<td>2. weight for age</td>
<td>Above</td>
</tr>
<tr>
<td></td>
<td>80%</td>
</tr>
<tr>
<td>3. Family or close contact past or present.</td>
<td>None</td>
</tr>
</tbody>
</table>
Then score for other features if present:

1. Positive tuberculin test: 3 points.

Large painless lymph nodes, firm, sinus in neck, axilla 2.

or groin: 3 points.

Unexplained fever, night sweats, no response to malaria treatment: 2 points.

4. Malnutrition not improving after 4 weeks on nutritional treatment: 3 points.

5. Angle deformity of the spine: 4 points.

Joint or bone swelling or sinuses 4 points.

Unexplained abdominal mass or ascites: 3 points.

Central nervous system signs (change in temperament, fits or coma): 8.
The coma should be for more than 48 hours or slowly developing neurological signs: 3 points. A score of 7 is considered suggestive of TB and treatment is recommended. If the score is 6 or less a 7 day course antibiotic should be given and repeated if there is no improvement. If no improvement, then anti tuberculous treatment is recommended. Malnourished children should have nutritional rehabilitation for at least one month.\(^{(70)}\)

A prospective study for the evaluation of the WHO criteria for childhood TB was carried in an area with very high incidence of TB (> 1000/100.000). 627 children were evaluated and if at least one of the following criteria was present, TB was further investigated the criteria are:

Recent weight loss or failure to gain weight. 1-

Cough or wheeze for more than 2 weeks. 2-

Recent household contact with an adult pulmonary TB. 3-

Further investigation by mantoux testing, chest
radiograph and gastric aspirate culture, 206 children (33%) have one or more of the proposed criteria, of these TB was confirmed by culture of gastric aspirate in 10 children (5%), 23 children were considered to have probable TB (11%), and 173 children after 8 weeks follow up were thought not having TB (84%).

The presence of the 3 main WHO criteria have a positive predictive value of 63% in this study\(^{(71)}\).

Another prospective study enrolling 147 children in Zambia of whom 75 were tuberculous concluded that the tuberculosis score chart (TSC) sensitivity was 88% but specificity was only 20% and hence it should not be used as a diagnostic tool in countries with a high HIV prevalence.
as the low specificity leads to over diagnosis of TB. In Zambia the under weight rates were up to 50% in the 12-24 months age groups.\textsuperscript{(72)}

Based on contribution of an IUATLD task group from 10 countries on the use of diagnostic criteria in childhood TB to develop as a score model. A final score model was adopted. The 5 clinical criteria thought to be most relevant as predictors of the disease in children were:

1- History of contact with a case of TB.
2- Positive skin test.
3- Persistent cough.
4- Low weight for age.
5- Unexplained prolonged fever. The model has a low sensitivity and specificity (Below 70%) but reasonably good positive predictive value (60\%-77%). These criteria
developed by the IUATLD and the MRC national TB programme in South Africa were adopted by the national TB programme of Sudan as follows: (19,73).

Table 1.6 The scoring criteria for the diagnosis of childhood TB adopted by the NTP of Sudan:

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Score point in &lt;5 years</th>
<th>Age group ≥ 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of contact</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Condition</td>
<td>Weighted Average (W)</td>
<td>Probability (P)</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Skin test</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>&gt;5</td>
<td>&gt;5</td>
</tr>
</tbody>
</table>


Many other such simple criteria for diagnosis of TB were developed \(^{(73,74)}\).

**Treatment and Control: 1.9**

A new control strategy that is currently being implemented throughout the world is DOTS (directly observed treatment, short course) in which the patients must
be observed and recorded swallowing each dose of their medicines by a health worker (75).

Chemotherapy is the most important measure of TB control. It is considered adequate when it:

- Cures patients.
- Reduces the number of actively multiplying bacteria.
- Prevents relapse.
- Prevents development of resistance.

The patient should be classified according to the following criteria:

- Site of disease (Pulmonary or extrapulmonary)
- Severity of disease.
- Bacteriological status.
- New or previous anti TB treatment.

New case is defined as that who has never had treatment for TB or who had taken anti TB drugs for less than 4 weeks.
The objective of chemotherapy is to cure at least 85% of all newly detected smear positive cases for whom short course chemotherapy (SCC) is recommended because:

- Shorter duration implies greater compliance.
- Early sputum conversion and thus transmission of infection.
- High cure rates with lower relapses.
- Most cost effective intervention.

A study done in 1996 on Sudanese tuberculous children showed a cure rate of 90% and 52% for short course chemotherapy and standard chemotherapy respectively. Compliance for the 2 regimens was 90% and 60% respectively. Adverse reactions were 2.5% and 20% respectively\(^{(76)}\).

The essential antituberculous drugs are in the following table:
Table 1.7: The essential anti TB drugs.

<table>
<thead>
<tr>
<th>Anti TB drug</th>
<th>Mode of action</th>
<th>Recommended daily dose in mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (H)</td>
<td>Bactericidal</td>
<td>5</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>Bactericidal</td>
<td>10</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Bactericidal</td>
<td>25</td>
</tr>
<tr>
<td>(Z)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Bactericidal</td>
<td>15</td>
</tr>
<tr>
<td>(S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>Bacteriostatic</td>
<td>15</td>
</tr>
<tr>
<td>Thiacetazone</td>
<td>Bacteriostatic</td>
<td>2.5</td>
</tr>
</tbody>
</table>
1.10 **Justification**

Tuberculosis remains one of our major public health hazards with high mortality and morbidity and enormous economic and social burden.

The estimated annual risk of infection in Sudanese children is about 2.4%.

Protein energy malnutrition increases the risk of infection and affects the clinical presentation, the diagnosis, the progress the response to treatment and the outcome of the disease. Most tuberculous Sudanese children were noted to be nutritionally sub-normal.

These facts necessitate that more studies should focus on this aspect of the disease.
1.11 OBJECTIVES

The objectives of this study were to:

a. Study the clinical pattern of tuberculosis in malnourished children attending Kassala Hospitals.

b. Evaluate the use of the WHO Clinical criteria and accelerated BCG reaction in the diagnosis of tuberculosis in malnourished children attending Kassala Hospitals.
Chapter Two

2- Materials and Methods

2.1. Study Design:

It is a cross sectional hospital based study:

Study Area: 2.2.

Study was conducted in Kassala State in Kassala Teaching Hospital and Kwaiti Pediatric Hospital. Referred patients were also sent from Wad Sharifai Refugees Hospital, Fato Displaced Camp Clinic, Wagar and Aroma Rural Hospitals.


2.4. Sample Size: Was calculated from the equation.

\[ N = Z^2 Pq/d^2 \]

where:

\[ N = \text{Sample size} \]

\[ P = \text{Probability of the disease} \approx 27/100.000 \]

\[ Q = 1 - P \]

\[ D = \text{Desired margin of error} = 0.05 \]

\[ N = (1-96)^2 \times 0.027 \times 0.973^2 \]
2.5. **Inclusion Criteria:**

All newly diagnosed tuberculous children aged less than 5 years who were classified as having malnutrition according to the clinical Welcome-Trust classification.

2.6. **Exclusion Criteria:**

2.6.1. Age 5 years or more. 2.6.1.

2.6.2. Neonates 2.6.2.

Parental refusal to enroll the child into the study. 3.6.3.

2.6.4. Concomitant chronic medical condition leading to the PEM e.g. DM, celiac disease etc.

2.7. **Research Tools and Techniques:**

- A questionnaire was designed to contain full information about the nutritional, social and medical history of the patient. Also examination, anthropometric measurements and investigations records of the patient were made.
• The anthropometric measurements done for every child were: the weight, the height or length and the head and mid upper arm circumferences. Children were weighed using Salter scale. Every child was weighed unclothed in grams.

• The height for children who were able to stand was measured using a stadiometer and the supine length for the younger and those not able to stand in millimeters was taken.

• The occipito-frontal diameter was measured for every child using a plastic millimeter measuring tape.

• The mid-upper arm circumference was measured at the mid point between the acromion and olecranon processes using Shakir tape.

• Centiles for these anthropometric measurements and percentages of weight for age and height for length were recorded.
The investigations that were done for every patient are:

1. **Mantoux skin testing:**

   Using PPD of 5 TU strength and 1 ml disposable plastic tuberculin syringe with a short bevel no 26 gauge 1cm long steel needle to give intradermal injection of 0.1ml of PPD to produce a wheal of about 5 mm. The skin over the upper third of flexor surface of fore arm was cleaned with spirit, a healthy part selected and the needle inserted slowly, bevel upwards for about 2mm just under and parallel to skin surface.

   Results were read in 48-72 hours. The induration was measured through the maximum transverse diameter with a millimeter ruler. A test of 10mm or more was considered positive irrespective of prior BCG vaccination.

2. **Radiology:** Chest X-ray.

3. **E.S.R.:** 1.6ml of venous blood was added to 0.4ml sodium citrate anticoagulant. Westergren device was used.

   The result was read after 1 hour.
Hemoglobin concentration using a colorimeter and WBC. Count and differential count using a hemocytometer.

- Investigations that were done according to the situation in certain patients:
  - **B.C.G. test** in mantoux negative patients, The freeze dried BCG of concentration 0.1mg/0.1ml is stored was a refrigerator below 10C and when reconstituted was used within 4 hours. The injection of 0.1ml was given intradermally into the lateral aspect of upper part of the left forearm using a tuberculin disposable syringe. The reaction of a papule of 4-8 mm developing in 2-3 weeks was considered normal. Accelerated reaction when a papule appears within 24-48 hours, a pustule by 5-7 days and scab by 2 weeks is considered positive.
  - **Zeil –Nelsen staining for AFB**: It was done in gastric aspirate. A nasogastric tube size 8-10 is introduced. Gastric contents are aspirated early in morning while child in bed.
50 c.c. normal saline is given through the tube and the aspirate is added to the previous and examined microscopically by a trained lab technician.

- **Other relevant investigations:** According to the case including further radiology, tissue biopsy etc.

**Ethical consideration:** Informed consent for each patient was obtained from parents or guardian.

**Methodology:** The author and lab technician.

Direct parent and patient interview to perform history and examination related both to malnutrition and TB was performed. This took place in the hospital wards and the referred TB clinic. The above data was used to fill the questionnaire.

**2.10. Research team:**

The author and lab technician.

**Role of the author was:**

1. Selection of the patients.
2-Consent obtaining.

3-Interview, examination and anthropometric measurements of the patients.

4-Completing the questionnaire.

5-Supervising the study:

**Role of lab technician:**

Collection of the samples and performing the investigations.

**2.11. Data entry and statistics:**

Data obtained was entered in a computer program (SPSS) and appropriate tests for significance to the 5% significance level were used.
Chapter Three

3. RESULTS

3.1. History:

3.1.1 Socio-demographic characteristics:

A total of 84 tuberculous malnourished children were enrolled in this cross sectional study. The patients were seen in the wards and referred TB clinic in Kassala Teaching Hospital and Kassala Kwaiti Pediatric Hospital. The ages of the studied patients ranged from 5 to 59 months with a mean (SD) age of 28.8 (17.8) months. Children less than 3 years were 51(60.7%) and patients from 36 to 59 month were 33(39.3%) children of the study group.

(Table 1)

There were 50 (59.5%) children living inside the city and 34(40.5%) living in the rural districts around, as shown in figure 1.

In the study group, 53 (63.1%) children belonged to the original Eastern Sudan tribes and 31 (36.9%) were originally
from other parts. The 3 most common tribal distributions were Beni-Aamir 27 (32.2%) patients, Hadendwa 23 (27.4%) patients and then Husa (of Nigerean origin) 10 (12%) patients, as shown in Figure 2.

Table 1: Age distribution of the study group (n= 84)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 (infants)</td>
<td>13</td>
<td>15.5</td>
</tr>
<tr>
<td>12 to &lt; 36 (Toddlers)</td>
<td>38</td>
<td>45.2</td>
</tr>
<tr>
<td>36 to &lt; 60 (pre-school children)</td>
<td>33</td>
<td>39.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Male children were 43 (51.2%) and females were 41 (48.8%) as shown in figure 3. In the study group, 83 (98.8%) children were from low socio-economic class and the mean income of the family per one month was 24700 SD. There were 44 (52.3%) fathers of the children in the study group who worked as shepherds or unskilled labourers, as shown in table 2, and 4 (4.8%) fathers were dead, 3 of whom died of TB. In the group, 60 (71.4%) fathers and 69 (82.1%) mothers did not attend school at all. The mean parental school years was 1.4. The classification of parental education was as follows:
(1) Illiterate: 39 (46.4%) fathers and 61 (72.6%) mothers.

(2) Khalwa or primary school: education: 35(41.7%) fathers and 17(20.2%) mothers.

(3) Secondary school education: 9(10.7%) fathers and 6 (7.2%) mothers.

(4) University education: 1 (1.2%) father.
<table>
<thead>
<tr>
<th>Father occupation</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shephard/ farmer</td>
<td>33</td>
<td>39.3</td>
</tr>
<tr>
<td>Unskilled labourer</td>
<td>18</td>
<td>21.4</td>
</tr>
<tr>
<td>Skilled labourer</td>
<td>11</td>
<td>13.1</td>
</tr>
<tr>
<td>Civil servant / employee</td>
<td>09</td>
<td>10.7</td>
</tr>
<tr>
<td>Professional</td>
<td>09</td>
<td>10.7</td>
</tr>
<tr>
<td>Dead</td>
<td>04</td>
<td>04.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Table 2: Father occupation of the children in the study group (n=84).
The mean (SD) family size was approximately 7(2) persons as shown in figure 4. The mean number of individuals per one room was five persons. The number was 2 or less in 4 (4.8%) families, 3 to 5 in 52(61.8%) families, 6 to 9 in 25(29.8%) families and 10 or more in 3(3.6%) families as shown in figure 5.

There were 81 (96.4%) children who lived in houses of huts or mud. Only 19(22.6%) houses were supplied with tap water and 32 houses have poor sanitation with open space used for defecation. Overall, 50 (59.5%) children lived in poor housing conditions, 27(32.2%) children lived in satisfactory housing conditions and 7(8.3%) children live in good housing condition. In the group, 34 (44%) children had a history of contact with an adult with pulmonary tuberculosis, as shown in table 3.

3.1.2. Symptoms:
The mean (SD) duration of symptoms was 46 (32.6%) days and the range was from 10 days to 6 months. There were 64 (76.2%) children who had symptoms for 4 weeks or more, as shown in figure 6.
Table 3: History of contact with adult TB cases in the study group (n = 84).

<table>
<thead>
<tr>
<th>History of Contact</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO contact</td>
<td>47</td>
<td>56</td>
</tr>
<tr>
<td>House hold contact</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Contact Type</td>
<td>Count</td>
<td>Percentage</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
<td>------------</td>
</tr>
<tr>
<td>Neighbour contact</td>
<td>14</td>
<td>16.6</td>
</tr>
<tr>
<td>School contact</td>
<td>01</td>
<td>1.2</td>
</tr>
<tr>
<td>Visitor contact</td>
<td>01</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
The commonest presenting symptoms were loss of weight, mood change, anorexia, fever, cough and sweating, which occurred in 84(100%), 78(92.8%), 77 (91.7%)
76 (90.5%), 67 (79.8%) and 52 (61.9%) of the children respectively, as shown in figure 7. The fever was continuous in 36 (42.9%), nocturnal in 20 (23.8%) and intermittent in 20 (23.8%) children in the study group. (Table 4).

Comparing the symptom fever with the pulmonary and non pulmonary types of tuberculous disease, there was no significant statistical association, (P. < 0.6), but comparing the cough with the type of tuberculous disease, the relation was statistically significant (P < 0.042) as shown in table 5. In children with cough the cough was dry in 47 (56.4%) patients and productive in 20 (23.9%) patients. Difficult breathing occurred at rest in 23 (27.4%) patients. The weight loss was severe in 50 (59.5%) children and moderate in 32 (38.1%) children as shown in fig 8.
Table 4: The pattern of fever in study group (n=84).

<table>
<thead>
<tr>
<th>Pattern of fever</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>36</td>
<td>42.9</td>
</tr>
<tr>
<td>Intermittent</td>
<td>20</td>
<td>23.8</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>20</td>
<td>23.8</td>
</tr>
<tr>
<td>No fever</td>
<td>08</td>
<td>09.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 5: Comparison of pulmonary and non pulmonary TB with cough in the study group (n=84)

<table>
<thead>
<tr>
<th>Cough</th>
<th>Disease</th>
<th>n.</th>
<th>%</th>
<th>n.</th>
<th>%</th>
<th>n.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pulmonary</td>
<td>09</td>
<td>10.7</td>
<td>52</td>
<td>61.9</td>
<td>61</td>
<td>72.6</td>
</tr>
<tr>
<td></td>
<td>Non-pulmonary</td>
<td>08</td>
<td>09.5</td>
<td>15</td>
<td>17.9</td>
<td>23</td>
<td>27.4</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>17</td>
<td>20.2</td>
<td>67</td>
<td>79.8</td>
<td>84</td>
<td>100.0</td>
</tr>
</tbody>
</table>

$X^2 = 4.1$  
P = <0.042
There were 5 children presenting with back deformity. The back deformity was dorsolumbar in 4 (4.8%) patients and lumbo-sacral in 1(1.2%) patient. Six children presented with convulsions. The convulsions were focal in 3(3.6%) children and generalized in 3(3.6%) children. Association between convulsion and severe form of the disease (miliary or meningitic TB) was statistically significant (P<0.001), as shown in table 6. there were five (6%) children who presented with discharging lymph node sinuses of whom 3 (3.6%)were in the neck, 1(1.2%) in the axilla and 1(1.2%) in the groin.

3.1.3. Past medical history:
In the study group 17 (20.2%) Children were previously admitted twice or more to hospital. Sixteen children had measles previously, 5(6%) of whom had measles within the last 3 months.
In the study group, 51 (60.7%) children were vaccinated with BCG, of whom 28 (33.3%) had a BCG scar and 23 (27.4%) had no BCG scar, while 33 (39.3%) children were not vaccinated, as shown in figure 9.
Table 6. Comparison of severe TB and non-severe TB disease with convulsions (n=84)

<table>
<thead>
<tr>
<th>Disease</th>
<th>No n.</th>
<th>No %</th>
<th>Yes n.</th>
<th>Yes %</th>
<th>Total n.</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe TB</td>
<td>07</td>
<td>08.3</td>
<td>05</td>
<td>06</td>
<td>12</td>
<td>14.3</td>
</tr>
<tr>
<td>Non severe TB</td>
<td>71</td>
<td>84.5</td>
<td>01</td>
<td>1.2</td>
<td>72</td>
<td>85.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>78</strong></td>
<td><strong>92.8</strong></td>
<td><strong>06</strong></td>
<td><strong>7.2</strong></td>
<td><strong>84</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

\[ X^2 = 24.86 \quad P < 0.001 \]
History of measles had no statistically significant association with the pulmonary or non-pulmonary types of TB disease (P. value < 0.991), nor with the type of PEM according to the Welcome's classification (P. value < 0.274). Also it had no significant association with severe tuberculous disease (P< 0.89) or Mantoux test size (P<0.47).

The BCG vaccination was not significantly associated; statistically, with the severe types of tuberculous disease (miliary and meningitic forms). (P value < 0.06). Presence of BCG scar was significantly associated with the age at vaccination (P< 0.001).
3.1.4. Nutritional history:

- In the study group 66 (78.6%) children were breast fed through their second year of life.
- Raw milk was ingested by 39 (46.4%) children. There were 24 (28.6%) patients who received nutritional therapy for 2-4 weeks and only 4 (4.8%) patients received this therapy for more than 4 weeks, before diagnosing TB.

3.2. Clinical Examination:

In this study 65 (77.4%) children were ill. There were 43 (51.2%) children who had a body temperature of 38°C or more and 8 (9.5%) children who had a subnormal body temperature, as shown in table 7.

3.2.1 Anthropometric measures:
There were 83 (98.8%) patients below the 3rd centile of weight for age and sex, and only one patient (1.2%) was on the 3rd centile of weight for age and sex, furthermore 51 (60.7%) children had a height below the 3rd centile and 32 (38.1%) children had a weight/height percent of 60% or less. This percent was 70 or less in 37 (44%) of the children. The weight/height is below the 3rd centile in 72 (85.7%) children in the study group. The anthropometric findings in the children are shown in tables 8, 9, 10. There was no statistical significant association between the weight/height percent and the gender (P < 0.79), or the mantoux test size (P < 0.77). The weight/height percent classification had a significant statistical association when compared with the severe (miliary and meningitic) and non severe types of TB disease (P. value < 0.05), but the Welcome’s classification of malnutrition had not such an association with type of TB disease (P. < 0.2).
Table 7: The body temperature of the children in the study group

(n=84)

<table>
<thead>
<tr>
<th>Temperature in °C</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35.5</td>
<td>02</td>
<td>02.4</td>
</tr>
<tr>
<td>35.5 – 36.5</td>
<td>06</td>
<td>07.1</td>
</tr>
<tr>
<td>36.6 – 37.4</td>
<td>11</td>
<td>13.1</td>
</tr>
<tr>
<td>37.5 - 37.9</td>
<td>22</td>
<td>26.2</td>
</tr>
<tr>
<td>38 – 38.9</td>
<td>29</td>
<td>34.5</td>
</tr>
<tr>
<td>&gt; 39.0</td>
<td>14</td>
<td>16.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 8: The height centiles of the study group (n=84)

<table>
<thead>
<tr>
<th>Height centile</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>51</td>
<td>60.7</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; - &lt; 10&lt;sup&gt;th&lt;/sup&gt;</td>
<td>20</td>
<td>23.8</td>
</tr>
<tr>
<td>10&lt;sup&gt;th&lt;/sup&gt; - &lt; 25&lt;sup&gt;th&lt;/sup&gt;</td>
<td>05</td>
<td>06.0</td>
</tr>
<tr>
<td>25&lt;sup&gt;th&lt;/sup&gt; – 75&lt;sup&gt;th&lt;/sup&gt;</td>
<td>08</td>
<td>09.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 9: Weight/height percent of the study group.

(n = 84)

<table>
<thead>
<tr>
<th>Weight / height percent</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60</td>
<td>32</td>
<td>38.1</td>
</tr>
<tr>
<td>60 - &lt; 70</td>
<td>37</td>
<td>44.0</td>
</tr>
<tr>
<td>70 - &lt; 80</td>
<td>13</td>
<td>15.5</td>
</tr>
<tr>
<td>80 – 90</td>
<td>02</td>
<td>02.4</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 10: The weight /height centiles of the children in the study group

(n=84)

<table>
<thead>
<tr>
<th>Weight /height centile</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>72</td>
<td>85.7</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; - &lt; 10&lt;sup&gt;th&lt;/sup&gt;</td>
<td>09</td>
<td>10.7</td>
</tr>
<tr>
<td>10&lt;sup&gt;th&lt;/sup&gt; - 25&lt;sup&gt;th&lt;/sup&gt;</td>
<td>03</td>
<td>03.6</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>100.0</td>
</tr>
</tbody>
</table>
There were 39 (46.4%) children who had a MUAC in the red area, 39 (46.4%) had a MUAC in the yellow area and 6 (7.2%) had a MUAC in the green area. MUAC had significant statistical association with the duration of illness (P<0.05), and with the mantoux size (P<0.001). Also 16 (19%) children had a head circumference below the 3rd centile, for age and sex.

3.2.2. Systemic examination:

In this study 81 (96.5%) children were pale. The pallor was severe in 25 (29.8%) children. No patient with cyanosis was seen. There were 2 (2.4%) patients who had a tinge of jaundice and 10 (12%) children who had clubbing. The clubbing in 7 (8.3%) patients was grade I, in 2 (2.4%) patients it was grade II and in 1 (1.2%) child it was grade III. Oedema was present in 22 (26.2%) children. It was lower limb oedema in 16 (19%) children and generalized in 6 (7.2%) children, as shown in figure 10.
Hair changes were present in 40 (47.6%) children and signs of vitamin A deficiency were seen in 28 (33.3%) children. Lymphadenopathy was present in 39 (46.4%) patients. The distribution of lymphadenopathy is shown in table 11.
Table 11: The distribution of lymphadenopathy in the study group (n=84)

<table>
<thead>
<tr>
<th>Lymphadenopathy</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lymphadenopathy</td>
<td>45</td>
<td>53.6</td>
</tr>
<tr>
<td>Cervical</td>
<td>29</td>
<td>34.5</td>
</tr>
<tr>
<td>Axillary</td>
<td>02</td>
<td>02.4</td>
</tr>
<tr>
<td>Inguinal</td>
<td>02</td>
<td>02.4</td>
</tr>
<tr>
<td>Abdominal</td>
<td>01</td>
<td>01.2</td>
</tr>
<tr>
<td>2 or more groups</td>
<td>05</td>
<td>05.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
The commonest affected lymph node groups were the cervical in 29(34.5%) children, then the inguinal in 2(2.4%) children and also the axillary in 2(2.4%) children. The lymph nodes were matted together in 9(10.7%) children. Discharging lymph node sinuses were present in 5(6%) children and fixed lymph nodes in 7(8.3%) children. In the study group 66(77.4%) children showed chest signs on physical examination. These chest signs were of bronchopneumonia in 55(65.5%) children, consolidation in 16(19%) children, collapse in 3(3.6%) children, pneumothorax in 3(3.6%) children, pleural effusion in 2(2.4%) children, and other signs in 8(9.5%) children, these are shown in figure 11. Hepatomegaly and splenomegaly, both or each alone, were present on abdominal examination in 65(77.4%) children as shown in table 12. Ascites was clinically detected in 4(4.8%) patients. Back deformity was present in 5(6%) children. Knee joint swelling was seen in one (1.2%) patient. Neck stiffness was present in 4(4.8%) children. The
welcome clinical classification of the nutritional deficiency was marasmus in 52(61.9%) children, kwashiorkor in 7(8.3%) children, under weight in 10(11.9%) children and marasmic kwashiorkor in 15(17.9%) children as shown in figure 12.
Table 12: The distribution of abdominal mass in the study group
(n = 84)

<table>
<thead>
<tr>
<th>Abdominal mass</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>38</td>
<td>45.2</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>11</td>
<td>13.1</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>16</td>
<td>19.0</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>01</td>
<td>01.2</td>
</tr>
<tr>
<td>No mass</td>
<td>18</td>
<td>21.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
3.3.1. **Skin testing:** The mantoux skin test was done on all children. The reaction was zero mm in 15 (17.9%) children, 5-9 mm in 51 (60.7%) children, 10-14 mm in 15 (17.9%) and 15 or more in 3 (3.6%) children. (Table 13) When the mantoux test was compared to the pulmonary and non pulmonary types of TB disease it was not statistically significant (P. value < 0.207). The test was highly significant when compared to the Welcome’s classification of PEM (P. value < 0.001) as shown in table 14. The BCG test was done for 66 (78.6%) patients. The reaction was accelerated in 51 (60.7%) children, was normal reaction in 7 (8.4%) patients and was non reactive in 8 (9.5%) patients. Figure 13 shows the BCG reaction in study group. There was no statistically significant association of the diagnostic BCG test with each of the following: (a) The weight/height (P. < 0.071), (b) The
Welcome’s classification of the malnutrition (P. < 0.164). (c) The history of measles (P. value < 0.154). (d) The WHO score chart (P. value < 0.222). (e) The IUATLD score (P. value < 0.259). (f) The age in months. (Table 15).

Table 13: Mantoux skin test size in the study group. (n=84)

<table>
<thead>
<tr>
<th>Mantoux size (in mm)</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero</td>
<td>15</td>
<td>17.9</td>
</tr>
<tr>
<td>1-9</td>
<td>51</td>
<td>60.7</td>
</tr>
<tr>
<td>10-14</td>
<td>15</td>
<td>17.9</td>
</tr>
<tr>
<td>&gt; 15</td>
<td>03</td>
<td>03.5</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>100.0</td>
</tr>
<tr>
<td>-------</td>
<td>----</td>
<td>-------</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 14: Comparison between mantoux test size and PEM classification.

(n=84)

<table>
<thead>
<tr>
<th>PEM classification</th>
<th>Mantoux test size in mm (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>00</td>
<td>1-9</td>
</tr>
<tr>
<td>Kwashiorkor</td>
<td>03 (3.6)</td>
<td>04 (4.8)</td>
</tr>
<tr>
<td>Marasmus</td>
<td>06 (7.1)</td>
<td>36 (42.9)</td>
</tr>
<tr>
<td>Marasmic kwash</td>
<td>04(4.8)</td>
<td>09 (9.7)</td>
</tr>
<tr>
<td>Under weight</td>
<td>02 (2.3)</td>
<td>02 (2.4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>15 (17.8)</td>
<td>51(69.8)</td>
</tr>
</tbody>
</table>

P. value < 0.001.
Table 15: Correlation between diagnostic BCG reaction and age in months (n=84)

<table>
<thead>
<tr>
<th>Age in months</th>
<th>Accelerated BCG</th>
<th>Total</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 n(%)</td>
<td>12- &lt;36 n(%)</td>
<td>&gt; 36 n(%)</td>
<td>n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non reactive</td>
<td>03 (03.5)</td>
<td>03(03.6)</td>
<td>02(02.4)</td>
<td>08(09.5)</td>
<td></td>
</tr>
<tr>
<td>Accelerated</td>
<td>10 (11.9)</td>
<td>21(25)</td>
<td>20(23.8)</td>
<td>51(060.7)</td>
<td></td>
</tr>
<tr>
<td>Normal reaction</td>
<td>00 (0.0)</td>
<td>05(06.0)</td>
<td>02(02.4)</td>
<td>07(08.4)</td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td>00 (00.0)</td>
<td>09 (10.7)</td>
<td>09(10.7)</td>
<td>18(21.4)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13 (15.4)</td>
<td>38(41.3)</td>
<td>33(39.3)</td>
<td>84(100)</td>
<td></td>
</tr>
</tbody>
</table>

$X^2 = 11.9$    P. value < 0.065
3.3.2. Other investigations:

There were 40 (47.6%) children with hemoglobin concentration less than 7gm/dL, and only 2 (2.4%) patients with hemoglobin less than 4 gm/dL. Also 40 children showed a hypochromic microcytic peripheral blood picture.

The ESR was normal in 4(4.7%) children, mildly elevated in 13(15.5%) children, moderately elevated in 56(66.7%) and highly elevated in 11 (13.1%) as shown in figure 14.

The main chest X-ray features in the study group were hilar shadows in 33 (26.1%) children, consolidation in 10 (12%) children miliary shadows in 7(8.3%) children, consolidation-collapse in 5(6%) patients and pneumothorax
in 3(3.6%) patients. Chest X-ray features are shown in figure 15 and table 16.

There was no significant statistical association between the X-ray features and the WHO clinical score (P. value < 0.811) or the IUATLD score (P. value < 0.775).
Table 16: The chest X-ray picture in the study group.

\[(n=84)\]

<table>
<thead>
<tr>
<th>X-ray lesions</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesion</td>
<td>10</td>
<td>12.0</td>
</tr>
<tr>
<td>Condition</td>
<td>Count</td>
<td>Percentage</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------</td>
<td>------------</td>
</tr>
<tr>
<td>Hilar shadow</td>
<td>22</td>
<td>26.1</td>
</tr>
<tr>
<td>Consolidation</td>
<td>10</td>
<td>12.0</td>
</tr>
<tr>
<td>Miliary shadow</td>
<td>7</td>
<td>08.3</td>
</tr>
<tr>
<td>Hilar, shadow + consolidation</td>
<td>7</td>
<td>08.3</td>
</tr>
<tr>
<td>Consolidation + collapse</td>
<td>5</td>
<td>06.0</td>
</tr>
<tr>
<td>Hilar + Bronchial shadows</td>
<td>4</td>
<td>04.8</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>3</td>
<td>03.5</td>
</tr>
<tr>
<td>Hilar + paratracheal shadows</td>
<td>3</td>
<td>03.5</td>
</tr>
<tr>
<td>Paratracheal adenopathy</td>
<td>2</td>
<td>02.4</td>
</tr>
<tr>
<td>Hilar shadow + effusion</td>
<td>2</td>
<td>02.4</td>
</tr>
<tr>
<td>Consolidation + paratracheal shadows</td>
<td>2</td>
<td>02.4</td>
</tr>
<tr>
<td>Effusion</td>
<td>1</td>
<td>01.2</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
<td>07.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Acid fast staining of gastric aspirate was done for 24 (28.5%) patients and was found to be positive in only 3 (3.6%) patients. Lymph node biopsy was done in 3 (3.6%) patients.
patients and all the biopsies showed findings suggestive of tuberculous granuloma. CSF analysis was done in 6 patients and 4(4.8%) of the CSF samples showed features of tuberculous meningitis. Ascitic fluid analysis was done in only one patient, and it was suggestive of TB. X-ray of the spine was done in 5 children and features of Pott’s disease was present in 4 (4.8%) of them. HIV screening done was in 2 children and was found to be negative.

3.4. The pattern of the TB disease:
Pulmonary TB was diagnosed in 48(57.1%) patients, both pulmonary and extra pulmonary disease were diagnosed in 13 (15.5%) patients and extra pulmonary disease only was diagnosed in 23 (27.4%) patients as shown in fig 16. The pulmonary disease was associated with lymph node disease in 10 (12%) patients, with pott’s
disease of the spine in 2 (2.4%) patients, and with osteoarthritis in one (1.2%) patient as shown in table 17.
Table 17:  Pattern of tuberculous pulmonary disease in the study group

<table>
<thead>
<tr>
<th>Type of pulmonary disease</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confined to the lungs</td>
<td>48</td>
<td>57.1</td>
</tr>
<tr>
<td>Pulmonary + nodal disease</td>
<td>10</td>
<td>12.0</td>
</tr>
<tr>
<td>Pulmonary + pott’s disease</td>
<td>02</td>
<td>02.4</td>
</tr>
<tr>
<td>Pulmonary + osteoarthritis</td>
<td>01</td>
<td>01.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>61</strong></td>
<td><strong>72.7</strong></td>
</tr>
</tbody>
</table>
There was no significant statistical association between the age in months, the accelerated BCG test or raw milk ingestion with the pulmonary or extra-pulmonary type of TB disease (P. values < 0.137, 0.551 and 0.642 respectively).

3.5. The clinical diagnostic scores:

The WHO TB score chart for clinical diagnosis of TB in children was positive of $\geq 7$ in 66(78.6%) children in the study group. (Table 18).

Statistically, the WHO clinical score of $\geq 7$ was significantly associated with the chest X-ray features ($P<0.027$) as shown in table 19 and with duration of symptoms. The association with the diagnostic BCG reaction was not significant ($P<0.22$). Also no significant correlation was found with pulmonary or non pulmonary disease forms ($P<0.1$), with previous history of measles ($P<0.8$), with
presence of cough (P< 0.16), or with the mantoux skin size (P< 0.07).

The International Union Against Tuberculosis and lung diseases (IUATLD) clinical score for diagnosis of TB in children was positive of ≥ 5 in 75(89.3%) patients.

**Table 18: The WHO Tuberculosis Score Chart (TSC) in the study group.**

<table>
<thead>
<tr>
<th>Score</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>18</td>
<td>21.4</td>
</tr>
<tr>
<td>7-10</td>
<td>45</td>
<td>53.6</td>
</tr>
<tr>
<td>11-15</td>
<td>17</td>
<td>20.2</td>
</tr>
<tr>
<td>&gt;15</td>
<td>04</td>
<td>04.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 19: Comparison of WHO score and chest x-ray findings in the study group.

(n=84)

<table>
<thead>
<tr>
<th>WHO score</th>
<th>Positive X-ray finding</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>&lt; 7</td>
<td>05</td>
<td>14</td>
</tr>
<tr>
<td>≥7</td>
<td>05</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>74</td>
</tr>
</tbody>
</table>


This score was significantly associated ‘statistically’ with the duration of symptoms (P<0.001), with presence of cough (P<0.001), with X-ray features of TB (P<0.001). The association was not significant with pulmonary and non-pulmonary, tuberculous disease (P<0.77) as shown in table 20. Also positive IUATLD score has no significant statistical relation to the diagnostic BCG (P<0.25), to the mantoux size (P<0.089) or to previous history of measles (P<0.49).
Table 20: Comparison of IUATLD score and cough in study group.

\[(n=84)\]

<table>
<thead>
<tr>
<th>IUATLD score</th>
<th>Presence of cough</th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n (%))</td>
<td>Yes (n (%))</td>
<td>n (%)</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>09 (10.7)</td>
<td>00 (00.0)</td>
<td>09 (10.7)</td>
</tr>
<tr>
<td>≥5</td>
<td>08 (09.5)</td>
<td>67 (79.8)</td>
<td>75 (89.3)</td>
</tr>
<tr>
<td>Total</td>
<td>17 (20.2)</td>
<td>67 (79.8)</td>
<td>84 (100.0)</td>
</tr>
</tbody>
</table>

\[X^2 = 39.7\] \[P < 0.001\]
Chapter Four

4. Discussion

This study was done in Kassala on malnourished children under 5 years old. Statistics in Kassala in the year 2003, showed that the total number of children below 5 years was 285,935 out of whom 1124 (0.4%) were severely malnourished (77).

4.1. Socio-demographic Characteristics:

The mean age (SD) of this study group was 28.8(17.8%) months. A study by Diab on 397 preschool Sudanese children showed a higher mean age (3.2y) of children with TB infection (78). Faisal and Adil studies on Sudanese children showed that the majority of malnutrition cases occurred in the age groups 6-24 months (79, 80).

In this study, infants constituted 13 (15.5%) children of the study group. Younger children and infants have a higher risk of severe forms of TB (81). A large retrospective Turkish
study by GoCmen et al on 2205 children with TB showed that 62% of them were under 6 years old\(^{(82)}\). In this study male to female ratio was almost equal, similar to the finding of Diab in his study on preschool Sudanese children who were infected with TB due to household adult contact\(^{(78)}\). In contrast to this study many studies on Sudanese children with malnutrition showed male predominance as in the studies done by Adil and Badr Eldin \(^{(80,83)}\).

The study done by Abd El-Moniem on tuberculous Sudanese children showed a male to female ratio of 1.3:1. \(^{(84)}\). Also a large Indian study (Radhakris et al) done on 280,000 children below 4 years showed a substantial higher male incidence of tuberculosis. \(^{(85)}\) However, a large retrospective Turkish study on 2205 tuberculous children (Go Cmen et al) was comparable to my study and showed no gender difference\(^{(82)}\).
Inspite of the fact that 53% of Kassala population are of rural residence, in this study the largest proportion of children (59.5%) were of urban residence. This is similar to a large community based study done in North India by (Chandra et al ) on 48624 children aged 1-9 years and the study showed that the proportion of TB infected children was significantly higher in urban than rural areas\(^{(86)}\). Part of the explanation may be the higher prevalence of malnutrition in the overcrowded, poor city slums.

Almost all the children (98.8%) of the study group were of low socio-economic class with a mean family monthly income of 24700 SD. There was a high rate of parental illiteracy (82.1% of mothers did not attend school). The mean family size was 7 persons compared to the general mean family size of 5 in Kassala State according to the MOH report\(^{(77)}\).

These socio economic characteristics were consistent with those shown in studies done on Sudanese children with
TB or with malnutrition. Abd Elmoniem study on Sudanese children with TB showed that 97% of the children were of low socio-economic class\(^{(82)}\).

The study done by Adil on malnourished Sudanese children showed that the education years of the cases, mothers were significantly lower than those of the control mothers and the housing conditions were poorer\(^{(80)}\). Also maternal illiteracy was 79.1% in the group of malnourished Sudanese children studied by Faisal\(^{(79)}\).

During adverse conditions and famine the incidence of TB and PEM increases. Kassala was directly affected by the civil war and by the floods in the last year. Also most of the refugees in Sudan are in Kassala State (82% of the refugees). Many people are displaced. Studies have shown increased transmission, severity and mortality of TB during war times such as the study done by Barr RG\(^{(87)}\) in Elsalvador in which he reported a 3 times increment in TB
incidence among displaced people due to civil war compared to the TB incidence rate in that country \(^{(87)}\).

**4.2. Clinical Findings:**

In this study all the children were symptomatic. This may be due to late presentation. A similar finding was shown by the study of Abd Elmoniem on 103 Sudanese children in the year 2000, all his study group had symptoms on presentation \(^{(84)}\). This is the scenario in the developing world where TB is suspected as a differential diagnosis of an ill child.

In USA 50% of pediatric TB cases are discovered during the evaluation of a child with a significant history of contact (Khan et al) \(^{(55)}\). TB is asymptomatic in 60-65% of children in the developed parts of the world as reported by the study of Pired et al, in Canada and Parisi and his colleague in Los Angeles in USA \(^{(88,89)}\).

The commonest presenting symptoms in this study were weight loss, anorexia, fever, cough sweating and diarrhea
occurring in 100%, 91.7%, 90.5% 79.8%, 61.9% and 53.6% respectively. These results were comparable to symptoms in previous studies on tuberculous Sudanese children. In the year 2000 Abd Elmoniem's study on 103 tuberculous children showed weight loss in 98.1%, fever in 91.3%, sweating in 69% and cough in 67% of the patients (84). Similarly in 1991 Zein et al, conducted a study on 65 children with pulmonary TB and the presenting symptoms were weight loss in 78% fever in 100% and cough in 75% of the children (90).

In my study group the cough has a significant statistical association with the pulmonary type of the disease (P< 0.042) and the convulsions which were noted in 7.2% of the study group had significant statistical association with the presence of severe tuberculous disease of Miliary or meningitic type (P< 0.001). Although the symptoms in this study group were similar to previous studies, these symptoms can be nonspecific in
malnourished children and may denote other associated infections. Adil study in 1997 on malnourished Sudanese children showed that 50% of his study group had pneumonia, 25% had pyuria and 8% had gastroenteritis\(^{(80)}\). In this study the mean (SD) duration of symptoms was 46 (32.6) days indicating the chronicity of the illness. This is similar to the previous study done by Abd Elmoniem in 2000 showing a duration of symptoms of more than 4 weeks in 80% of the 103 tuberculous children included in that study\(^{(84)}\).

History of contact with an adult with tuberculosis was present in 44.4% of the children in this study. This is more or less similar to previous studies on tuberculous Sudanese children done in 1991 (Zein et al) 1996 (Magda) and 2000 (Abd Elmoniem), which found positive history of contact in 43%, 64.4% and 50.5% respectively.\(^{(90,76,84)}\). A lesser percentage of (32%) was reported in a study done in Turkey by GoCmen et al\(^{(82)}\).
In this study 60.7% of the children were BCG vaccinated. Bannon performed a meta analysis of over 1200 articles from international publications and concluded that the overall protective BCG value against all TB disease forms is about 50%, against meningitic TB is 64% and against miliary TB is 78%. \(^{(91)}\) The level of BCG vaccination in my study group was less than the level reported in 2000 in Khartoum according to Abd Elmoniem. \(^{(84)}\) This level is higher than in an earlier study in Sudanese children in 1996 by Magda showing a 52.3% BCG vaccination in her study group. \(^{(76)}\) The sample size in my study may not have been enough to detect the vaccination coverage.

Out of the 12 patients with severe tuberculous disease (miliary and meningitic TB) in my study group only one child was BCG vaccinated and had a scar but the association was not statistically significant \((P< 0.06)\). The severe immunological debilitation against mycobacterium infection in these malnourished children might predispose them to
severe TB inspite the fact that they were vaccinated. In Abd Elmoniem's study on 103 tuberculous children 2 children with BCG scars had tuberculous meningitis and one patient with history of BCG vaccination and no scar had miliary TB. A retrospective Indian study by Somu N showed that 25% of the cases with meningitic TB were BCG vaccinated. Rajajee et al reported that many studies concluded that neither absence or decreased size of the BCG scar nor negative PPD reaction after BCG vaccination is indicative of poor BCG uptake.

4.3. Examination:

In this study 69(82.1%) patients had weight/height <70% and another 12(14.4%) with weight for height <80%. The predominant type of malnutrition was marasmus in 52(62.9%) of the study group. This might be similar to the
study done by Adil where in his study group 74.2% were marasmic or marasmic kwashiorkor. \(^{80}\) 

In this study group 66 (78.6%) children showed chest signs of which bronchopneumonia was the commonest finding seen in 55(65.5%) children followed by consolidation seen in 16(19%) children. The predominant chest finding in the study done by Abd El moniem was consolidation \(^ {84} \). This might be due to the age and nutritional status difference.

4.4. Investigations:

In this study the mantoux test was positive of \( \geq 10 \) mm in only 18 children representing 21.4% of the sample. Adil did a study on non tuberculous malnourished Sudanese children in 1997 and out of 81 children 77(95.1%) showed zero mantoux and this zero reaction decreased to 75% after 4 weeks of nutritional treatment. The mantoux test size had no significant association to the mortality in his study \(^ {80} \).
Similar results to this study were obtained in Turkey in 1994 by Go Cmen et al where in their study out of 22 malnourished tuberculous children only 4 (18%) had a positive mantoux skin test. In studies on tuberculous Khartoum state children done in 1991 (Zein et al), in 1996 (Magda) and in 2000 (Abd ElMoniem) positive mantoux was present in 88%, 92.8% and 81% of their study groups respectively. The difference may reflect the effect of severe malnutrition on the test. In a large retrospective Turkish study by Go Cmen et al done on 2205 tuberculous children 62% of the them had a positive mantoux reaction.

The test was done for 66 children in this study and the reaction was accelerated in 51 of them representing 77.3% of the tested children. Recently several articles have been published about the use of BCG in the diagnosis of TB particularly in children. It is thought to be very simple, cheap and reliable even in the malnourished children although
some authors stated the disadvantages of low specificity (Rajajee)\(^{(94)}\). Chanhuri in India conducted a study in 1977 on 53 children with tuberculosis and 50 control children to determine the BCG reaction. The BCG test was accelerated in 92.5% and the mantoux in 56.6% of the tuberculous group, while the BCG was positive in 10% of the control group and the mantoux in none of it, prior BCG status was not shown in this study.\(^{(95)}\) Another Indian study by Chandra in adults with bacteriologically proved pulmonary TB found positive mantoux in 50% and positive BCG in 100% of the study group\(^{(69)}\).

A study in Turkey (GoCmen et al) in 1994 on 22 malnourished tuberculous children showed that the BCG reaction was accelerated in 82% while the mantoux in only 18%. The BCG was accelerated in 100% of the patients with pulmonary TB while the mantoux was positive in only 44.5% in well nourished children in that study\(^{(68)}\). Similar results
were obtained in another Turkish study conducted on 41 proved tuberculous adults and 35 control group in Inonu hospital. The authors, Sonomez et al, concluded that the BCG is more sensitive and specific than the PPD test in the diagnosis of tuberculosis\(^{(54)}\). In Sudan Abd Elmoniem in his study in 2000 performed the BCG test on 2 marasmic tuberculous children in his study group. In both the test was accelerated, while the mantoux test was negative. The combined use of mantoux test and of BCG in the mantoux negative children gave a positive reaction in 82.1% of the children in my study.

In this study chest radiographic findings were detected in 74(88%) of the study group. Abd Elmoneim in his study on 103 tuberculous children found significant chest radiographic changes in 75% of his patients\(^{(84)}\). The results of the study conducted by Magda in 1996 showed radiological changes in 83% of her study group which is consistent with this study\(^{(76)}\).
TB can produce any form of pulmonary radiographic changes. A study on 273 tuberculous Nigerian children by Adrele showed enlarged hilar glands in 79%, consolidation in 29% and miliary shadows in 10% of the children\(^{(96)}\).

In my study group hilar shadow was present in 43 patients (51%), consolidation or consolidation collapse in 15 (18%) patients and miliary shadows in 8 (9.5%) patients. The 2 results are more or less comparable.

Microscopy for AFB in the gastric aspirate was done in 24 children in this study and was positive in only 3(3.6%) of them. This low yield is similar to other studies in Sudan. In 1991 by Zein et al, in 1996 by Magda and in 2000 by Abd Elmoniem yielding 5%, 3% and 5.8% respectively\(^{(90,76,84)}\). This is also the case in other parts of Africa, a south African study by Dias on 627 TB children showed positive AFB culture in 5%. In Lusaka the positive yield was 17% as reported by the same author\(^{(97)}\).
The yield of positive TB granuloma on lymph node biopsy was high in this study, out of 39 patients with lymphadenopathy only 3 were biopsied and all were histologically positive. In 1991 Zein et al study out of 18 patients with lymphadenopathy and suspected TB 6 were biopsed and all biopsies were positive for TB granuloma. (90) In 2000 Abd Elmoniem biopsied 7 out of 41 patients with lymphadenopathy in his study group and all showed positive findings (84).

In this study the ESR was more than 50 in 67 (79.8%) cases and above 100 in 11 (13.1%) cases, although a high rate is expected in tuberculous children but prevalence of severe anemia and associated infections may affect the results. A study in Gatar by Al moria and colleague on 68 children with TB showed a normal ESR in (33%) of the patients and it seemed that the ESR has a little value in the diagnosis of childhood TB (98).
In this study out of 6 CSF samples 4 were positive for tuberculous meningitis (66.6% of examined sample). In a study on 20 children with TB meningitis the CSF demonstrated positive results in 80% of the children\(^{(99)}\). Comparable results were obtained in Ethiopia by Defigie et al in a study on 28 children with TB meningitis of whom 60% were malnourished, positive CSF findings were found in 92\(^{(100)}\).

4.5. Pattern of the Disease:

In this study extra pulmonary cases constitute 23 (27.3%) patients, 12 (14.3%) of whom were with severe disease forms (miliary or meningitic) and 13(15.5%) out of the 61(72.6%) pulmonary cases were associated with extra pulmonary manifestations. In Sudan out of 508 admitted pediatric TB cases in 1987, 481 (95%) were pulmonary cases as in the NTP report \(^{(19)}\). 2 studies done in 1991 by Zein et al and in 2000 by Abd El Moniem showed pulmonary
TB in 70% and 81.6% in their study groups respectively (90, 84).

In this study the commonest extra pulmonary disease form was the lymph node TB present in 16(19.1%) cases and this was comparable to the 2 above mentioned studies showing 20% and 11.7% occurrence respectively (90, 84).

Bone involvement in 7(8.3%) patients in my study was in the form of pott’s disease or osteoarthritis which was higher than the reported 1% occurrence in children by Danile (7).

The diagnosis of TB in this study was clinical and radiological in 78 (92.8%) cases histological in 3(3.6%) and bacteriological in 3 (3.6%) patients.

4.6. The Use of the Diagnostic Criteria:

There were 60 (78.6%) children in this study who had a WHO TSC score of 7 or more. Furthermore, 75(89.3%) patients had an IUATLD score of ≥ 5. Assuming correct clinical labeling the sensitivity of both tests is high in this
study. Specificity evaluation needs sophisticated diagnostic tools in search for the difficult to obtain gold standard of the diagnosis.

Recently a lot of criticism has been directed to the use of diagnostic scores for pediatric TB in the chronically debilitated children including the malnourished and HIV children. These scores being not standardized and a minority validated or adapted to HIV or malnutrition as reported by Hesseling et al. (101).

In a study on 147 children done by Rheenen in a Zambian area, endemic for HIV and malnutrition, TB was diagnosed in 75 children. Most (48.9%) of the children who had a false positive WHO TSC of ≥ 7 were malnourished. The sensitivity of the test was 88% and the specificity was only 25%. The positive predictive value was 55%. This overdiagnosis may be a factor of increased TB notification. (72)

A large study to evaluate the IUATLD scoring criteria in India conducted by Suryan on 607 children concluded that
malnutrition gives a large number of false cases. The paper recommended that radiological evidence should be included to improve the score objectivity, the cut off point of 5 should be fixed higher, the score should be used for screening only, the weightage of symptoms scaled down and further modification are still needed\textsuperscript{(102)}.
Conclusion

The socio demographic characteristics of the study group included low socio-economic class, parental illiteracy, poor housing and nutrition.

1. The mean duration of symptoms was 46 days (> 6 weeks).

2. Almost all patients were severely malnourished predominantly marasmic or marasmic kwashiorkor which represented (79.8%) of the study group.

3. Clinical chest signs of mainly broncho pneumonia were seen in 65% of the children and suggestive chest radiography was noted in 88% of the patients.

4. Pulmonary disease was diagnosed in 72.6% of the study group and severe TB in 14.2% of the patients.

5. The mantoux skin test was positive in only 21.4% and the BCG reaction was accelerated in 51 out of the 66 tested children (77%). When both tests were used in
combination positive skin test results were obtained in 82.1%

6. the WHO score was \( \geq 7 \) in 78.6% of the patients and the IUATLD \( \geq 5 \) in 89.3%. The scores are sensitive but non specific parameters are used in them.

**A. Recommendations**

*The following are recommended:*

1. Community and governmental efforts are urgently needed regarding the development of effective plans addressing the risk factors and attitude towards vaccination.

2. Screening of children with adult TB contact, for tuberculosis.

3. Sufficient nutritional rehabilitation of malnourished children prior to labeling them as tuberculous.
4. The use of accelerated BCG test in mantoux negative malnourished children suspected to be tuberculous. This will raise the positivity of skin testing, (in this study to 82.1%).

5. Adoption of the recommended score modification for debilitated children including improving objectivity (e.g. by radiological evidence), increasing the cut off point of the scores, decreasing the weight of non specific symptoms and using these scores for screening cases for further investigations.

6. Human development programmes in the area should be cared for. More efforts on general and health education, on nutrition, on housing as well as on better sanitation are needed.

7. Provision of the ideal under 5 years health care items and close follow up and monitoring of their nutrition.
References


34. Barnes PF, Nandini KS. T lymphocytes sub-populations in tuberculosis; Indian Pediatr 2000; 37:489-95.


37. NICUS (Nutrition Information center, University of Stellenbosch) and SANTA (South African National Tuberculosis association). Published Report Tuberculosis and Nutrition Stellenbosch April 2000;p.1-6.

38. Keusch TG. Malnutrition and the thymus gland. In: Keusch TG, Cunnigham RS. Nutrient Modulation of the


42. McMurray DN, Elsie SM. Protein deficiency induces alterations in the distribution of T cell subsets in


60. Munt PW. Miliary tuberculosis in the chemotherapy era with a clinical review in 69 American adults. Medicine 1971;51:139.


102. Suryanara L, Jagannatha PS. Scoring method for diagnosis of tuberculosis in children: An evaluation; a
paper presented in the national conference of TB panta India 1999.