INTRODUCTION

Neonates with Down’s syndrome develop an enigmatic myeloproliferative disorder clinically and morphologically indistinguishable from leukaemia. That is why it is called by a variety of terms, including transient leukaemia (TL), transient abnormal myelopoiesis (TAM), transient congenital leukaemia or ineffective regulation of myelopoiesis.1-3 Signs and symptoms of TMS are growth retardation, hepatosplenomegaly, anaemia and leukocytosis present at birth or shortly thereafter. This intriguing syndrome is diagnosed in 10% of Down syndrome (DS) neonates.1,4 The age of onset of TMS in DS patients varies from 30 weeks gestation in utero to 180 days of postnatal life.2 It is reported that approximately one in 5 fetuses with Down syndrome may appear healthy. Zipursky et al.1 have reported that approximately 25% of new born who recover from TMS may develop Acute Megakaryoblastic Leukaemia [AMKL (FAB M7)] in first 04 years of life.1 It is not known whether this is recurrence of original disease or appearance of new disease, but prior to onset of AML, there is often a prodromal period of several months characterized by thrombocytopenia and bone marrow myelofibrosis with dysplastic megakaryocytes.4 It is important to point out that the response rate of DS infants having TMS or AML to chemotherapy is very high over several years of follow-up.1,6,7 However, TMS is self-limiting disease, regressing spontaneously by the age of 2 or 3 months.1,4,6 Diagnosis of TMS needs strict follow-up for at least 4 years after the diagnosis as this benign condition may go into malignant one where management strategy entirely gets changed. TMS should be differentially diagnosed from leukaemoid reactions, erythroblastosis fetalis, congenital infections and congenital leukaemia.

Neoplasm noted at birth or during the first 6 weeks of life is strictly defined as congenital.3 Congenital leukaemia

ABSTRACT

Objective: The objectives of the study were to determine the spectrum of the clinical and pathological findings, the management and prognosis of patients of transient myeloproliferative syndrome (TMS) and congenital leukaemia.

Study Design: Case series.

Place and Duration of Study: The study was conducted over a period of 8 years, from January 2000 to December 2007, at the Children’s Hospital and the Institute of Child Health, Lahore.

Methodology: Suspected patients presenting with fever, pallor, bruises and hepatosplenomegaly and diagnosed as either transient myeloproliferative disorder or congenital leukaemia were studied. The complete blood count, reticulocyte count, leukocyte alkaline phosphatase score, liver function tests, karyotyping studies and bone marrow aspiration biopsy were performed in all of those patients. Management and out come was noted. Results were described as frequency percentages.

Results: Out of 10,000 patients presenting during this period, 24 patients were diagnosed as either of transient myeloproliferative syndrome or congenital leukaemia. Fifteen of these were diagnosed as patients of TMS and 9 as patients of congenital leukaemia. Down syndrome (DS) was diagnosed in 75% of these patients. TMS patients were put on supportive treatment and recovered spontaneously. One DS patient with congenital leukaemia went into spontaneous remission and 2 of DS patients with congenital leukaemia responded to chemotherapy while rest of them either died or lost to follow-up.

Conclusion: TMS and congenital leukaemia were not very uncommon in the studied population. Majority had Down syndrome. It is important to differentiate their clinical and pathological presentations for proper management. TMS may resolve with supportive treatment while congenital leukaemia is a fatal condition requiring chemotherapy.

Key words: Transient myeloproliferative syndrome (TMS). Congenital leukaemia (CL). Down syndrome (DS).
is rare in infants, 175 to 200 reports of this disorder have appeared in literature so far.8 Neonatal leukaemia occurs at the rate of 1 per 5 million births.3 It is characterized by non-specific symptomatology requiring high index of suspicion for referral and diagnosis with peculiar biological features. Most of congenital leukaemia cases reported have acute non-lymphocytic leukaemia (ALL) found in the older children.9 Certain chromosomal anomalies, syndromes and malformations are found in association with leukaemia. Congenital or neonatal leukaemia is ten times more frequent in new born with Down syndrome.1 Chromosome 11q23 translocations t(9, 11), t(4, 11) are found in about half of neonates with either AML or ALL.10

The objectives of the present study were to determine clinical and pathological findings in patients of TMS and congenital leukaemia diagnosed at the Children’s Hospital, Lahore, and to describe their management and prognosis.

**METHODODOLOGY**

Neonates and children upto 6 years of age referred to Haematology Department at The Children’s Hospital, Lahore, during the period of 8 years from January 2000 to December 2007 with presenting complaints of pallor, bruises, fever and hepatosplenomegaly were included in present study. Patients who were already diagnosed as cases of leukaemia or infants born with TORCH infections were excluded.

Complete physical examination of each patient was done. All patients underwent complete blood count (CBC) using haematology analyzer (Sysmex SF 3000), peripheral smear examination stained with Giemsa stain, reticulocyte count stained with brilliant cresyl blue, leukocyte alkaline phosphatase score (LAP) and liver function tests (LFTs). Peripheral blood chromosomal analysis was done on patients with suspicion of dysmorphic features to confirm diagnosis of Down syndrome. Bone marrow aspiration biopsy performed using Jamshedi needle in all children and special stains were used to differentiate the type of leukaemia, if required.

TMS patients were managed on supportive treatment while patients with congenital leukaemia were either observed for spontaneous remission or offered appropriate chemotherapy. The patients were followed-up for a period of 04 years after diagnosis and their clinical and laboratory parameters were assessed every 2 months.

The data were entered and analyzed using SPSS 16 (Statistical Package for Social Sciences). Mean ± S.D was given for quantitative variables like age and laboratory parameters. Frequencies and percentages were given for qualitative variables like gender and clinical symptoms and signs.

**RESULTS**

During the study period 10,000 children presented with fever, pallor, bruises and hepatosplenomegaly. Of those, 24 patients were diagnosed as having either TMS or congenital leukaemia.

TMS was diagnosed in 15 patients with male to female ratio (M:F) of 3:2. All presented in infancy from 1/2 months to 04 years of age with complaints of pallor and failure to thrive. All cases revealed pallor and hepatosplenomegaly, bruises were observed in 9 of these patients and element of dysmorphism i.e. low set ear, close set eyes, microcephaly, flat face, upward and slanted palpebral fissure, varying degree of growth retardation were found in 9 patients (Table I). Laboratory investigations revealed Hb (g/dl) in range of 5.3 – 13.4 (mean 8.253) with nucleated RBC/100 WBC in range of 02 – 26/100 WBC. Their white blood cell (WBC) count (x 10³/L) ranged from 2.9 – 80 (mean 25.253) and differential revealed blast cell count from 04 – 30% (mean 17.400) with high percentage of immature myelocytes and neutrophil. Platelets (x 10³/L) count ranged from 42 – 180 (mean 110.733). Reticulocyte percentage ranged from 0.2 – 4% (mean 1.420). LFTs were normal in all of these patients. LAP score was also normal in all patients, ruling out infections. Blood samples of all the TMS patients were karyotyped for chromosomal defects. Trisomy 21 was detected in 12 patients (80%) and they were confirmed as suffering from Down's syndrome (Table II). Bone marrow aspiration confirmed diagnosis of transient myeloproliferative syndrome (TMS) with blast cells in range of 8 – 13% (mean 10.5%).

**Table I:** Clinical characteristics of patients presented with transient myeloproliferative syndrome (TMS) and congenital leukaemia (CL).

<table>
<thead>
<tr>
<th></th>
<th>TMS 15 cases</th>
<th>CL 9 cases</th>
<th>Total 24 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (mean)</td>
<td>8.046 months</td>
<td>1.34 months</td>
<td>-</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>9:6 (3:2)</td>
<td>7:2 (3:5:1)</td>
<td>16:8 (2:1)</td>
</tr>
<tr>
<td>Pallor</td>
<td>15 (100%)</td>
<td>9 (100%)</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>Bruises</td>
<td>9 (60%)</td>
<td>7 (78%)</td>
<td>16 (67%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>0 (0%)</td>
<td>3 (33%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Nodular mass</td>
<td>0 (0%)</td>
<td>5 (56%)</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>Liver palpable</td>
<td>15 (100%)</td>
<td>9 (100%)</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>Spleen palpable</td>
<td>15 (100%)</td>
<td>9 (100%)</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>Dysmorphism</td>
<td>9 (60%)</td>
<td>6 (67%)</td>
<td>15 (63%)</td>
</tr>
</tbody>
</table>

Congenital leukaemia was diagnosed in 9 patients with male to female ratio (M:F) of 3.5:1. All presented within 8 weeks of their birth. Their clinical presentation was pallor, rash, fever abdominal distension, jaundice and bruises. Element of dysmorphism i.e. Down facies were found in 6 of these patients. On examination hepatosplenomegaly was found in all cases and nodular masses over the abdomen were observed in 5 of these patients (Table I). Laboratory investigation revealed Hb
Liver Function Test.

Table II: Laboratory evaluation of patients with transient myeloproliferative syndrome (TMS) and congenital leukaemia (CL).

<table>
<thead>
<tr>
<th>Disease</th>
<th>TMS (15)</th>
<th>CL (9)</th>
<th>Normal 15 (100%)</th>
<th>Total 24 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>8.243</td>
<td>9.955</td>
<td>3.277</td>
<td>2.512</td>
</tr>
<tr>
<td>NRBC/100WBC</td>
<td>5.06</td>
<td>10.333</td>
<td>6.670</td>
<td>10.535</td>
</tr>
<tr>
<td>WBC x10^9</td>
<td>25.253</td>
<td>53.966</td>
<td>21.356</td>
<td>26.729</td>
</tr>
<tr>
<td>Blast (%)</td>
<td>17.400</td>
<td>21.888</td>
<td>8.525</td>
<td>22.513</td>
</tr>
<tr>
<td>Retic (%)</td>
<td>1.420</td>
<td>110.733</td>
<td>1.272</td>
<td>45.037</td>
</tr>
<tr>
<td>LAP score</td>
<td>1.244</td>
<td>72.000</td>
<td>0.524</td>
<td>43.657</td>
</tr>
<tr>
<td>LFT</td>
<td>15 (100%)</td>
<td>18 (70%)</td>
<td>0.328</td>
<td></td>
</tr>
<tr>
<td>Karyotyping (Trisomy 21)</td>
<td>15 (100%)</td>
<td>6 (66%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| NRBC - Nucleated Red Blood Cells; WBC - White Blood Cell Count; Pit - Platelet; LAP - Lecocyte Alkaline Phosphatase; LFT - Liver Function Test.

DISCUSSION

In the present study 15 cases of TMS and 9 cases of congenital leukaemia out of 10,000 are reported. Both of these diseases are extremely rare and their diagnosis during the period of study suggest that they may not be very uncommon in the local population.

Neonates with Down’s syndrome have various haematological disorders i.e. neutrophilia, thrombocytopenia and leukaemia being the most common. All of TMS patients presented with anaemia, leukocytosis, hepatosplenomegaly falling into the category of this intriguing syndrome and 12 out of those 15 patients confirmed trisomy 21, strongly favours this chromosomal anomaly presentation as transient myeloproliferative syndrome.

The mechanism by which trisomy 21 predisposes the carrier to development of TMS is thought to involve increased expression of a gene or genes on chromosome 21 that stimulate abnormal proliferation of haematopoietic stem cells in infancy with frequent induction of TMS. It is frequently difficult to distinguish the disorder from true congenital leukaemia. Unlike leukaemia, TMS generally resolves within weeks to months. As all of the cases in which younger ages, higher haemoglobin concentrations, platelet counts, and white blood cell counts of TMS patients provided a clinical contrast with frankly leukemic cases. The peripheral white cell count is relatively low in most cases of TMS, profound cytopenia are rare and often the percentage of blast in peripheral blood is higher than in marrow. Almost all the cases showed significant ratio of blast cell in peripheral film. But congenital leukaemia often presents in the neonatal period with cutaneous infiltration, high white blood cell (WBC) count and is usually of myelomonocytic morphology. The literature supports the present findings as AML (M4) and (M5) account for over half of reported cases of neonatal leukaemia.

The clinical findings of neonatal leukaemia are variable from typical findings in infants over 06 months of age and older children with AML. Nodular cutaneous infiltrate (leukaemia cutis, “blue berry muffin” baby) and hepatosplenomegaly are characteristic features of

(g/dl) in range of 5.6 – 13.8 (mean 9.955) with nucleated RBC/100 WBC in range of 02 – 30%. The WBC count (x 10^9/L) ranged from 10 – 85 (mean 53.966) and differential revealed blood cell count 04 – 76% (mean 21.88%) with high percentage of immature myelocytes. Platelet count (x10^9/L) ranged from 12 – 150 (mean 72.00). Reticulocyte count ranged from 0.4 – 2% (mean 1.244). LFTs were deranged in three of these cases. Karyotyping revealed trisomy 21 in six out of 9 patients making 67% of these cases as having Down syndrome (Table II). Bone marrow aspiration confirmed diagnosis of congenital leukaemia, five were diagnosed to have AML (M5, FAB) and on cytochemical stain, monocytic component stained strongly with non-specific esterases (ANBE, alphanaphthyl butyrate esterase) and few promonocytes showed some scattered myeloperoxidase (MPO) positivity. Two cases were of AML (M4, FAB). One case was of AML (M2, FAB) which was positive for Sudan Black B (SBB) and myeloperoxidase (MPO). Only one case among these 9 congenital leukaemia was ALL which was positive for periodic acid schiff (PAS) and negative for SBB. Bone marrow blast cell count ranged from 30 – 95% (mean 62.5%).

Patients diagnosed with TMS were put on supportive treatment and all recovered spontaneously. One of DS
neonatal leukaemia, especially AML (M4, M5),16 and more than half of congenital leukaemia in this series presented in this manner. Often the disease is characterized by a rapid downhill course, but it may be unpredictable. Some neonates show signs of leukaemia at birth and die shortly thereafter, while others appear normal following delivery but develop clinical and haematologic problems later. In a third group, leukaemia is not discovered until the third to sixth week of life, with a history suggestive of haematologic abnormalities dating back a few weeks earlier.17 Congenital leukaemia must be differentiated from leukaemoid reactions observed in response to infection, hemolytic disease or hypoxia and severe hemolytic disease of newborn.

The biological mechanism of spontaneous resolution in TMS is unclear. Holt et al.18 have recently demonstrated that telomerase activity was diminished in this benign form of TMS and suggested that this deficiency may explain the spontaneous regression. Although TMS is by definition transient but it has many clinical and laboratory features of malignancy. Light microscopy, cytochemistry, immunophenotyping and electron microscopy indicate that these are dysplastic megakaryoblast.2,13,14 In fact the relationship between TMS and AMKL in DS is controversial. Whereas the clinical course of TMS is that of spontaneous resolution, around 25% of these patients will relapse later as AMKL, usually within 3 years.19 Leukemic blasts cells in TMS and AMKL shared same immunophenotype. Taken together, these clinical observations raise the possibility that the neoplastic clone in TMS and AMKL is related and that the acquisition of additional genetic events may be responsible for subsequent relapse of TMS clone manifesting as AMKL.

Another investigation was liver function tests (LFTs) and all of the patients showed normal LFTs. If there is rising conjugated bilirubin then it indicates serious liver disease in infants with TMS. TMS is sometimes complicated by hepatic fibrosis which is life threatening and often fatal.20,21 The frequency of hepatic fibrosis is not known.

Karyotyping studies are very useful diagnostic tool for diagnosis of both TMS and congenital leukaemia. As mentioned earlier this syndrome is diagnosed in 10% DS neonates with at least 20 fold increased incidence of congenital leukaemia compared with cytogenetically normal individuals.22

In the presently reported cases of TMS, blood culture for karyotyping did not yield trisomy, 21 but these patients were subjected to clinical assessment for DS extensively and got differentiated from leukaemoid reaction. The 6 cases of congenital leukaemia revealed trisomy 21. So this is a common feature among two differently behaving diseases as TMS is benign disorder but congenital leukaemia is highly fatal disorder without treatment, though management discussion is not the scope of this paper.

The haematologic picture in TMS cases returned to normal after 04 months with only supportive care, while the course of congenital leukaemia is one of rapid deterioration and death.2 The congenital leukaemia has unexplained natural tendency to undergo spontaneous remission lasting in months or years.23 This was the case in one of the 9 patients who went into spontaneous remission, 2 congenital leukaemia with DS responded to treatment while all others either died or lost to follow-up.

Leukaemia with trisomy 21 mosaicism has a good prognosis.3 Down syndrome myeloblasts show 10-fold more sensitivity to arabinoside C than non-Down syndrome myeloblast. The current management strategy in infants is “do less” in AML and “do more” in ALL from treatment point of view.2 The low dose cytosine arabinoside is curative in AML. In case of ALL, the vincristine and methotrexate is given according to standard protocols.

Findings regarding the age of onset, presence or otherwise jaundice and nodular mass in present study is consistent with already established demarcating features between the two diseases.

Although a case series has been reported from Pakistan on congenital leukaemia by the same group,24 but no study on TMS and congenital leukaemia in DS patients has been published from Pakistan so far. Our findings and diagnosis are well supported by Homans et al. who reviewed 95 cases of TMS in DS.25 Similar study on 69 neonates with DS who presented with TMS was done by Isaacs.3 The overall mortality was almost double that of the series by Homans et al.25

**CONCLUSION**

This study concludes that TMS and congenital leukaemia are two different entities both clinically and pathologically. Both of these disorders are common in children in Down's syndrome. Congenital leukaemia is lethal disease while TMS undergoes self remittance.

Since these are two different diseases with different presentation and outcome and in both diseases, immunologic, cytogenetic and molecular studies need to be conducted for better understanding and subsequent management of these diseases.

**Disclosure:** The same groups of authors have already published a case series on congenital leukaemia from the same institute and during the same study period.

**REFERENCES**


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