ABSTRACT

Down syndrome (DS) is a common congenital disorder, caused by the presence of all or part of a third copy of chromosome 21, affecting 1/1000 live births, worldwide. The parents are genetically normal however, the extra chromosome in DS affected individuals occurs by chance. The DS affected individuals are at the high risk congenital heart defect, epilepsy, leukemia, thyroid diseases, mental disorders etc. Beside this, newborns and children with DS may also develop several hematological problems such neutrophilia, thrombocytopenia, polycythemia etc. The DS affected children are also at the high risk of benign and malignant abnormalities of the blood count and blood film, which may manifest at any age. DS affected children have 10-20 fold increased risk of leukemia.

Key words: Down Syndrome; Myeloid Leukemia; Hematological Manifestation; Neutrophilia; Polycythemia, Thrombocytopenia; Transient Myeloproliferative Disorder
INTRODUCTION

Down syndrome (DS) is a chromosomal abnormal condition caused by an extra copy of a whole or partial copy of chromosome 21 [1,2]. It is the most common chromosomal abnormalities found in live new born children affecting 1/1000, worldwide [3]. The patients with DS have several clinical features including mental retardation, characteristic faces, congenital heart defects, gastrointestinal abnormalities, hematologic abnormalities, weak muscle tone (hypotonia) in infancy, intellectual disability etc.

The hematological problems such as neutrophilia, thrombocytopenia, and polycythemia are very common. Neutrophilia is also known as neutrophil leucocytosis which shows a high number of neutrophil granulocytes in the blood. It is the most common hematological abnormality, with 80% of absolute neutrophil counts above the upper limit. The next most commonly detected abnormality is Thrombocytopenia. It refers to a condition for the relative decrease of thrombocytes, with 66% of platelet counts <150,000/µl, and with 6% of counts <50,000/µl. Another common hematological disorder is Polycythemia in which the level of circulating red blood cells in the bloodstream is increased, with 33% of hematocrit values above 65% or hemoglobin concentrations above 22 g/dl. Polycythemia is not related to cardiac defects and hypoxia which is frequently found in DS cases [4-6].

The children with DS are supposed to be at high risk of malignancy leading to major causes of death in DS affected new born. The population based studies, cancer registries and clinical trials have suggested that ~12-fold increased risk of acute leukemia in children with 5-30 years of DS. It may increase up to 40 fold in the children of age below 5 years and the up to 150 fold high risk of acute myeloid leukemia (AML) in the children younger than 5 years [3]. DS is associated with increased 150 fold increased risk of myeloid leukemia of DS (ML-DS) and 30 fold increased risk of acute lymphoid leukemia (ALL) [7,8]. As per report, ALL and AML incidence rate are found in 1 in every 100-200 children with new born [9-11]. In most of the cases ML-DS develops before the age of 5 years. The acute leukaemia is preceded by a clonal neonatal preleukaemic syndrome known as transient abnormal myelopoiesis (TAM) that is unique to Down syndrome [12,13]. The occurrence of TAM is around 10%-20% of DS newborns which further leads to ML-DS [14].

Both the TAM and ML-DS are caused by co-operation between trisomy 21, which itself perturbs fetal haematopoiesis and acquired mutations in the key haematopoietic transcription factor gene GATA1 [15].

The pathogenetic role of somatic mutations in the GATA1 gene has been suggested in uncontrolled proliferation of poorly differentiated megakaryocytic precursors. Mutations in exon 2 GATA binding protein 1 synthesizing gene, resulting in a premature stop codon within the N-terminal activation domain have been detected in almost all Transient myeloproliferative disorder (TMD) and DS AMKL cases [16-18]. Both GATA1s and GATA1 have similar DNA binding
abilities and interact with partner proteins, such as “Friend of GATA1” [19]. Expression of this mutated form potentially contributes to the uncontrolled proliferation of poorly differentiated megakaryocytic precursors [20].

TMD is a megakaryocytic type of leukemia, restricted to newborns with trisomy 21. The incidence of TMD is around 10% in newborns with DS [21]. It has been reported in non-Down syndrome cases who have acquired trisomy 21 to hematopoietic cell [22]. TMD can be defined as the morphologic detection of blasts in DS less than three months of age. Normally, TMD is detected in first week of newborn life and later on it is resolved in 3 months of the age [23]. The neonatal death caused by TMD is secondary to the death due to liver failure, heart failure, sepsis, hemorrhage etc [24-26]. The clinical features like congenital heart disease and gastrointestinal anomalies are secondary to DS but unrelated to TMD. In contrary to this, clinical findings like hepatosplenomegaly and effusions are secondary to TMD but unrelated to DS in the absence of TMD [23]. Moreover, some uncommon TMD can cause severe diffuse lobular liver fibrosis with high mortality rate [27].

Once the TMD is declared in the patients, AMKL was developed in approximately 13 to 29% of the patients after 6 months of age [24-26]. The AMKL occurrence is more common in TMDs cases if there is any cytogenetic abnormality beyond trisomy 21 at the initial stage [24]. TMD findings such as complete blood count, percentage of blasts, liver enzyme activities, age, and sex were not found to play ultimate role in AMKL [24].

![Figure 1: Cytology of the megakaryoblasts in TMD and AMKL.](image)

A. Large sized megakaryoblasts with irregular nuclei and moderate pale blue cytoplasm resembling myeloblasts.

B. Typical megakaryoblastic morphology with cytoplasmic projections and tiny azurophilic platelet granules.

Adopted from John et al., 2008 [23].
The blasts in TMD seem to be megakaryoblasts which can’t be differentiated from the blasts of AMKL. In general blast are medium to large sized with round to occasional bi-nucleation, fine to slightly condensed chromatin, numerous cytoplasmic blebbing, and occasional fine azurophilic granules with mark able presence of platelet granules [28,29] (Figure 1). The cytochemical stains visualizes the TMD blast as a megakaryoblasts. Acid-Schiff gives granular to block positive and strongly positive for acid phosphatase while negative for Sudan black B, myeloperoxidase, and chloroacetate esterase (Figure 2).
Figure 3: Blasts from the peripheral blood of 1-day-old patient with trisomy 21 and transient abnormal myelopoiesis.

Adopted from John et al., 2008 [23].

Clinically TAM is conventionally defined by combination of clinical features such as pericardial effusion, ascites, pulmonary edema, hepatosplenomegaly, hepatic fibrosis, liver failure, obstructive jaundice and hematological feature such as leukocytosis, persistence peripheral blood blast cell, abnormal platelet count are often reduced or raised but may be normal. Haemoglobin may be reduced, raised or normal.
Figure 4: Schematic representation of molecular, biological and clinical data, indicating that TAM and ML-DS are initiated before birth when fetal liver haematopoietic stem and progenitor cells (HSPC) trisomic for chromosome 21 demonstrate perturbed haematopoiesis with an expansion of megakaryocyte erythroid progenitors (MEP) and megakaryocytes. These cells subsequently acquire N-terminal truncating GATA1 mutations resulting in TAM in late fetal or early neonatal life. Although most cases of TAM spontaneously and permanently remit (~90%) by the age of 6 months, in ~10% of cases, additional genetic/epigenetic events lead to further clonal expansion resulting in ML-DS before the age of 5 years as shown in the figure 4.

Adopted from Neha et al., 2016 [3].

**DS-ASSOCIATED ACUTE LEUKEMIA**

The incidence of ALL and AML are high and associated with DS. The occurrence of DS-associated ALL (DS-ALL) was found in throughout childhood with a median age greater than 4 years [31] while DS-associated AML (DS-AML) occurs at a median age of 2 years [38], ranging from ages 6 months to 5 years [31]. DS-AMLS were found to have lower white blood cell count with increased preceding history of myelodysplastic syndrome as compared to non-DS counterparts [32]. The higher hemoglobin was reported in DS-ALLs as compared to non-DS counterparts [33]. The prognostic factors and outcome of DS-ALL patients treated in contemporary protocols are uncertain. Children with DS-ALL have an inferior outcome compared with non-DS patients because of both higher treatment-related mortality (TRM) and a higher relapse rate [34].
DS-ALL

DS-ALL is similar to non-DS associated ALL in aspirate and biopsy findings. DS-ALL are precursor B lymphoblastic leukemia in more than 90% while remaining being precursor T lymphoblastic leukemia [33,35-37]. About 50% of DS-ALLs have normal constitutive karyotype. DS-ALLs are also similar in terms of event free survival with non-DS-ALLs that do not have the favorable cytogenetic findings [38]. The chemotherapy induction causes more toxicity (mucositis, hyperglycemia, and infection) in children with DS-ALLs. The intense salvage therapy may result in decreased overall survival in DS-ALLs.

Adopted from Zipursky A 2003 [14].

Table 1: Collaborative studies adapted their standard AML protocol for ML-DS by reducing the dose of drugs.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>No of patients</th>
<th>EFS (%)</th>
<th>Relapse (%)</th>
<th>Death in CCR (%)</th>
<th>Cytarabine (g/m2)</th>
<th>Daunorubicin (mg/m2)</th>
<th>Mitoxantrone (mg/m2)</th>
<th>Etoposide (mg/m2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POG942</td>
<td>57</td>
<td>77 (5y)</td>
<td>7</td>
<td>14</td>
<td>20.7</td>
<td>135</td>
<td>80</td>
<td>1,000</td>
</tr>
<tr>
<td>CCG2891</td>
<td>161</td>
<td>77 (6y)</td>
<td>14</td>
<td>4</td>
<td>15.8</td>
<td>320</td>
<td>0</td>
<td>1,600</td>
</tr>
<tr>
<td>COG-A2971</td>
<td>132</td>
<td>79 (5y)</td>
<td>11</td>
<td>3</td>
<td>24.8</td>
<td>80</td>
<td>0</td>
<td>1,600</td>
</tr>
<tr>
<td>NOPHO-AML93</td>
<td>41</td>
<td>85 (5y)</td>
<td>7</td>
<td>5</td>
<td>49.6</td>
<td>150</td>
<td>30</td>
<td>1,600</td>
</tr>
<tr>
<td>AML-BFM98</td>
<td>67</td>
<td>89 (3y)</td>
<td>6</td>
<td>5</td>
<td>23-29</td>
<td>10</td>
<td>0-14</td>
<td>950</td>
</tr>
<tr>
<td>MRC-AML10/12</td>
<td>46</td>
<td>74 (5y)</td>
<td>3</td>
<td>15</td>
<td>7.8</td>
<td>300</td>
<td>50</td>
<td>1,500</td>
</tr>
<tr>
<td>AT-DS(Japan)</td>
<td>33</td>
<td>80 (5y)</td>
<td>6</td>
<td>9</td>
<td>4.2</td>
<td>100-400</td>
<td>35</td>
<td>2,700</td>
</tr>
<tr>
<td>AML99 DS</td>
<td>72</td>
<td>83 (4y)</td>
<td>12.5</td>
<td>1.4</td>
<td>3.5</td>
<td>THP 250</td>
<td>0</td>
<td>2,250</td>
</tr>
<tr>
<td>JCCLSG 9805DS</td>
<td>24</td>
<td>83 (5y)</td>
<td>0</td>
<td>13</td>
<td>12.6</td>
<td>THP 135</td>
<td>10</td>
<td>200</td>
</tr>
</tbody>
</table>

During the last decade, the large collaborative groups have develop standard AML-DS protocols, which leads to the reduction of chemotherapeutic agents dose or prolonging the interval between chemotherapy courses [39,40]. The lower incidence of induction failure and relapse compared with non-DS children with AML were the most valuable and useful findings. The recent reports suggested that the 5-year event-free survival (EFS) has exceeded 80%, largely because of the reduction in treatment-related deaths, with a fall from 30% to 40% in the early 1990s to 3% to 5% in recent studies [41-43]. Each drug was administered over a 1-hour infusion. Patients who achieved complete remission (CR) received four courses of intensification therapy of the same regimen. Prophylactic therapy for CNS leukemia was not included in the protocol.

In recent studies pirarubicin was used instead of the original daunorubicin under AML 99 DS protocol. The number of treatments courses was fixed to up to five. Pirarubicin were found to
be less cardiotoxic and more myelosuppressive than daunorubicin [44-46]. The cardiotoxicity of pirarubicin should be calculated as 0.8 compared with daunorubicin [46].

As per DS protocol pirarubicin was used as 25 mg/m2/d, on days 1 and 2, which was estimated to be equivalent as 25mg/m2/d of daunomycin (DNR), cytarabine (100 mg/m2/d on day 1 through 7), and etoposide (150 mg/m2/d on day 3 through 5). A total of 70 of the 72 patients (97.2%) achieved a CR. The 4-year EFS was 83.3% plus or minus 9.1% and the 4-year OS was 83.7% plus or minus 9.5%. The regimen related toxicities were relatively tolerable. Only one patient died as a result of pneumonia in the second course of intensification. The 3-year EFS in the five patients with monosomy 7 was significantly worse than in the 65 patients without monosomy 7 (40.0% plus or minus 26.3% vs 86.2% plus or minus 8.8%) [47].

References


