Original Article

Clinical Course of Acute Leukemia among Children with Down Syndrome

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Abstract:

Objective: *To describe the clinical course of the hematologic abnormalities among children with Down syndrome, especially transient myeloproliferative disorders (TMD) and acute leukemia.* ***Methods:*** *A retrospective descriptive study was conducted. Demographic data including a chromosomal study, age of onset, clinical presentations, hematological profiles and outcome of the disease were reviewed among infants with Down syndrome diagnosed with TMD from 2005-2014.* ***Results:*** *Among 21 infants (M:13; F:8) diagnosed with TMD at median age 1 day (range from 2 hours-69 days), 19 (90.5%) patients had spontaneous regression at age of 36 days (12-231 days) with median follow-up time of 3 years (3.3 months-10.2 years), 2 (9.5%) patients died of severe pneumonia and cardiopulmonary failure. Six (28.6%) patients developed acute myeloid leukemia (AML) at median age of 1 year, 4 months (1.5-24.7 months). Three of 6 patients developing AML died. Clinical manifestations of TMD were asymptomatic (n = 11), hepatosplenomegaly (n = 7), and anemia (n = 3). Hematological profiles in TMD included thrombocytopenia and abnormal blasts with high white blood cell count. Flow cytometry analysis, performed among 3 patients, revealed positive results for CD33 compatible with AML, both TMD and acute leukemia.* ***Conclusion:*** *Infants with Down syndrome having TMD often had spontaneous regression. However, few patients could progress to acute myeloid leukemia with a mortality rate about 50%. Flow cytometry analysis might be helpful to predict the type of leukemia from TMD. Long term follow-up is warranted.*

Keywords : ● *Down syndrome* ● *Transient myeloproliferative disorder* ● *Transient leukemia* ● *Acute leukemia*

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นิพนธ์ต้นฉบับ

การดำเนินโรคของผู้ป่วยดาวน์ซินโดรมที่ได้รับการวินิจฉัยมะเร็งเม็ดเลือดขาว (AML)

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อรุณี เจตศรีสุภาพ และ กุณฑล วิชาจารย์
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บทคัดย่อ

วัตถุประสงค์ *เพื่อทราบการดำเนินโรคของผู้ป่วยดาวน์ซินโดรมที่ได้รับการวินิจฉัยมะเร็งเม็ดเลือดขาวที่โรงพยาบาลศรีนครินทร์*

วิธีการศึกษา *แบบย้อนหลัง เก็บข้อมูลตั้งแต่เริ่มวินิจฉัยภาวะมะเร็งเม็ดเลือดขาวชั่วคราวจนถึงเกิดมะเร็งเม็ดเลือดขาว ตั้งแต่ปี 2005-2014 โดยเก็บอายุที่เริ่มวินิจฉัย อาการและอาการแสดง ผลโครโมโซม ค่าความสมบูรณ์ของเลือดและผลการรักษา* ***ผลการศึกษา*** *ทารก 21 ราย เพศชาย 13 ราย เพศหญิง 8 ราย วินิจฉัยมะเร็งเม็ดเลือดขาวชั่วคราว(TMD) ค่าเฉลี่ยที่อายุ 1 วัน(ตั้งแต่อายุ 2 ชั่วโมง ถึงอายุ 69 วัน) ผู้ป่วย 19 ราย (90.5%) ที่ได้รับการติดตาม 3 ปี (3.3 เดือน ถึง 10.2 ปี) หายจากภาวะนี้ที่อายุ 36 วัน (12-231 วัน) 2 ราย (9.5%) เสียชีวิตจากภาวะติดเชื้อปอดและหัวใจล้มเหลว 6 รายเกิดมะเร็งเม็ดเลือดขาวชนิด myeloid เมื่ออายุ 1 ปี 4 เดือน (1.5 เดือน ถึง 24.7 เดือน) ผู้ป่วย 11 ราย ไม่มีอาการ 7 รายตับม้ามโต 3 รายซีด ความผิดปกติทางโลหิตใน TMD พบเกล็ดเลือดต่ำ ตัวอ่อนของเม็ดเลือดขาว และจำนวนเม็ดเลือดขาวสูง ผู้ป่วย 3 รายที่เกิด AML เสียชีวิตจากโรคมะเร็ง ผลการตรวจทาง flow cytometry ของผู้ป่วย 3 รายที่มี TMD และเกิด มะเร็งเม็ดเลือดขาวพบว่า CD33 มีผลบวกเข้าได้กับ AML* ***สรุป*** *ดาวน์ซินโดรมที่เกิด TMD ส่วนใหญ่หายได้เอง มีส่วนน้อยที่เกิดมะเร็งเม็ดเลือดขาวและผลการรักษามีโอกาสเสียชีวิตได้ร้อยละ 50 ผลของ flow cytometry อาจช่วยในการทำนายชนิดของมะเร็งเม็ดเลือดขาวในอนาคต ควรติดตามทารกดาวน์ซินโดรมที่เกิด TMD ในช่วง 2 ปีแรกอย่างใกล้ชิด*

คำสำคัญ : ● *Down syndrome* ● *Transient myeloproliferative disorder* ● *Transient leukemia* ● *Acute leukemia*
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Introduction

Down syndrome (constitutional trisomy 21) is the most common chromosomal abnormality among live born infants.[1] The incidence is approximately 1 in 733. Down syndrome is associated with congenital anomalies and characterized by dysmorphic features. Hematologic abnormalities are one of the clinical features of Down syndrome that can manifest from transient myeloproliferative disorder (TMD) to acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML).[2]

In all, 4% to 10% of infants with Down syndrome are born with TMD,[3-5] characterized by high leukocyte counts, blast cells in the peripheral blood, and associated anemia, thrombocytopenia and hepatosplenomegaly.[6] *GATA1* mutations in prenatal hematopoietic cells with trisomy 21 result in TMD, and are mostly resolved within the first three months of life. However, long term follow-up should be warranted because 20-30% of patients will develop leukemia, often acute megakaryoblastic leukemia (AMKL) by three years of life.[7]

Material and Method

The medical records of children with Down syndrome and TMD at Srinagarind Hospital, Khon Kaen University were retrospectively reviewed between January 2005 and December 2014. Twenty-one eligible patients were enrolled. Down syndrome was confirmed by chromosomal study. TMD is characterized as high leukocyte counts with blast cells in the peripheral blood or abnormal hematologic profiles with hepato-splenomegaly confirmed by a hematologist. The exclusion criteria comprised sepsis, thrombocytopenia other than TMD (immune thrombocytopenia), congenital infection and incomplete medical records.

The clinical course of hematological abnormalities of children with Down syndrome, especially TMD and acute leukemia was the main objective of the study described using diagnosis, laboratory data, treatment and outcome. Thus, the following data including baseline patient data, chromosomal study, age of onset, clinical presentation, hematological profiles (complete blood cell count, blasts in the peripheral blood), flow cytometry analysis, treatment and outcome in both TMD and leukemia, were obtained. *GATA1* gene analysis was unavailable in the institute.

This study was approved by the Human Ethics Committee of Khon Kaen University. Statistical analysis was performed. The results are shown as median (min-max) and percentage.

Results

Among the 21 infants with a diagnosis of Down syndrome with TMD at median age 1 day (range from 2 hours-69 days), 13 (62%) were male. Most were term; median gestational age was 37^{+5} weeks (range 35-39 weeks) with a median birth weight of 2,700 g (range 2,010-3,880 g). Eighteen patients had only trisomy 21. One patient had mos46XY, -21, +mar/46XY, +21,rob(21;21)(q10;q10) and two patients had rob(21;21)(q10;q10)

Among the 21 infants with TMD, 19 (90.5%) patients had spontaneous regression at median age of 36 days (12-231 days) with a median follow-up time of three years (3.3 months-10.2 years), two (9.5%) male patients became progressively worse and died. One died from hydrops fetalis with cardiopulmonary failure at day 5 of age and another developed AML with severe pneumonia at 2 months of age.

In the spontaneous regression group, 14/19 (73.7%) patients still had normal hematological profiles. Five patients developed abnormal hematological profiles and were subsequently diagnosed with AML at median age of 16.3 months (1.5-24.7 months) with median follow-up time at 3 years 17 days (3 months-10.2 years) as shown in Figure 1.

Clinical presentations

Most patients with TMD (52%) were asymptomatic whereas seven, three and two patients had hepatosplenomegaly, anemia and isolated splenomegaly, respectively. The most common presentation of AML was fever followed by anemia and petechiae. Clinical manifestations are shown in Table 1.

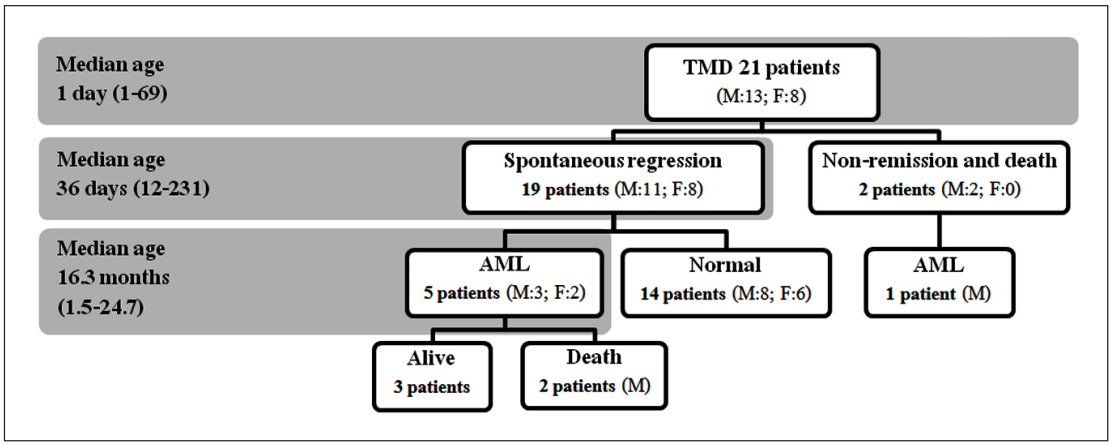

Figure 1 Clinical course of Down syndrome with transient myeloproliferative disorders (TMD) and acute myeloid leukemia (AML)

Table 1 Clinical presentations of TMD and AML

Clinical Presentations	TMD (N = 21)	AML (N = 6)
Asymptomatic	11	-
Hepatosplenomegaly	7	2
Anemia	3	4
Splenomegaly	2	-
Fever	-	5
Petechiae	-	4
Hepatomegaly	-	1

TMD, transient myeloproliferative disorders; AML, acute myeloid leukemia

Laboratory findings

Almost all infants with TMD showed normal red blood cell count: only two infants had anemia (Hb 6.5 and 7.1 g/dL). Median white blood cell count was 29.035 x 10^9/L (4.9-223.154 x 10^9/L). Thrombocytopenia was usually presented, while thrombocytosis (932-1,000 x 10^9/L) was less demonstrated. Blast cells presented from 0-86%.

All children developing AML were distinctly anemic and thrombocytopenic compared with infants with TMD. One patient had marked leukocytosis and thrombocytosis (WBC 148.70 x 10^9/L, platelets 455 x 10^9/L). Blast cells were presented in peripheral blood smear from 0-74%. One case with no blast cells seen in peripheral blood had an abnormal hematologic profile. The results are shown in Table 2.

Flow cytometry analysis

Immunofluorescent markers on the blast cell population were commonly expressed markers including CD7, CD33.

All three patients presenting TMD then developing AML were positive for CD33 compatible with the myeloid marker during TMD and AML. Other markers showed no correlation between the two groups. The results are shown in Table 3.

Treatment and outcome

Among nine patients with TMD receiving blood

Table 2 Complete blood count of patients with TMD and AML

Index	TMD (N =21)		AML (N = 6)	
	Median	Range	Median	Range
Hemoglobin (g/dL)	16.7	6.5-20.5	7.5	4-10.7
Hematocrit (%)	47.9	21.1-58.2	23.5	12.9-33.4
WBC (10^9/L)	29.035	4.9-223.154	10.21	1.8-148.7
Platelet (10^9/L)	86	14.7-1,000	28.5	6-455
Blast (%)	32	0-86	24.5	0-74

TMD, transient myeloproliferative disorders; AML, acute myeloid leukemia

Table 3 Flow cytometry analysis of 3 patients with TMD who developed AML (N = negative, ND = not done)

Index	Patient 1		Patient 2		Patient 3	
	TMD	AML	TMD	AML	TMD	AML
MPO	N	40.9%	70.7%	N	N	57.6%
HLA-DR	N	48%	47.0%	57.9%	N	31.0%
CD7	83.6%	N	76.4%	89.2%	36.8%	N
CD13	N	N	N	N	N	N
CD33	33.5%	25.3%	73.2%	44.9%	81.8%	40.5%
CD41	N	N	ND	50.1%	N	Out of test
CD61	N	N	ND	N	N	Out of test
Blast	74.6%	35.8%	17.7%	30.1%	90.5%	21.8%

TMD, transient myeloproliferative disorders; AML, acute myeloid leukemia

transfusion (leucocyte poor blood, platelet transfusions), only one had total exchange transfusion. Among six cases diagnosed with AML by morphology and flow cytometry analysis, two were AML-M7, two were AML -M2, one was AML-M1 and one was AML-M0. Five cases received antileukemic chemotherapy according to the Thai pediatric oncology group protocol consisting of cytarabine and doxorubicin but a cytarabine dose reduced by 50% (25-50%). Three of six patients were still alive with median follow-up time at 3 years 5 months (2.1–5.3 years), whereas one patient died from AML with severe pneumonia and two patients died from relapsed AML at median age 1 year 1 month (2 months to 2.5 years).

Discussion

Most infants with TMD were term, median gestational age 37^{+5} weeks and median birth weight was 2,700 g. Three of 21 infants had additional chromosomal abnormality other than trisomy 21 (mosaicism and Robertsonian translocation), two had TMD that resolved spontaneously but one died from relapsed AML. However, an additional chromosomal abnormality was not associated with early death (< 6 months of age) or with the subsequent development of AML.[12]

In the study, TMD was diagnosed at day 1 of life (range from 2 hours-69 days), which is earlier than a related study. Chotsampanchareon T, et al.[8] and other studies[9-11] reported diagnoses of TMD ranging from five days to two weeks. Having early diagnosis and giving appropriate treatment and counseling to parents are quite important regarding TMD. Almost all infants with TMD presented asymptomatic and spontaneous regression at 36 days (12-231 days). However, two patients became progressively worse and died, one case with AML died from severe pneumonia and the other with hydrops fetalis died from cardiopulmonary failure, similar to a related report[12] demonstrating the main courses of death involved organ failure, particularly cardiopulmonary and hepatic failure.

Patients with TMD developed AML at a median age of 16.3 months (1.5-24.7 months), while another study reported at 11-20 months.[8-10,12] Therefore, closely following up patients with Down syndrome having TMD over a period from 1-2 years of life is warranted regarding developing AML.

Patients with AML presented fever, anemia, and petechiae. Three of six (50%) with AML in the study died at 1 year, 1 month (2 months-2.5 years) from disease relapse; nevertheless, appropriate chemotherapy was commenced. The remaining patients were alive at a median follow-up time of 3 years, 5 months (2.1-5.3 years). Compared with a related study, 100% of patients with AML (N = 3) died from septicemia.[8]

Two patients had a diagnosis of AML-M7; one (50%) patient died from disease relapse, and the other was still alive.

Hematological profiles in TMD were as follows: thrombocytopenia, high white blood cell count but the AML showed distinctly as anemia and more severe thrombocytopenia (86 vs. 28.5 x 10^9/L). Both patients with TMD and AML had abnormal peripheral blasts. Compared with the previous study, all hematological profiles of TMD were mostly consistent in both quantity and variation.[9,10]

Flow cytometry analysis was performed among three patients. Immunofluorescent markers on the blast cells of the patients expressed CD7 and CD33, whereas the previous study showed the blast cells expressed CD7, CD33, CD45 and CD34 in more than 50% of the population.[9] Notably, all patients were positive for CD33 representing myeloid cells, both TMD and acute leukemia.

Even when 90.5% of patients with TMD had spontaneous regression without antileukemic chemotherapy, the outcome of TMD varied ranging from asymptomatic to severe complications that could be potentially fatal. The evolution of TMD is spontaneously favorable with complete remission within the first three months while early death has been reported in 15-20% of the cases.[5,9,12,13]

Approximately 28.5% of children with TMD developed AML (20% was reported in the general population).[7,14] These features are associated with high sensitivity to chemotherapy and favorable outcome, relating to the effect of the *GATA1* mutations and trisomy 21 on the levels of cytarabine metabolizing enzymes.[15] Considering chemotherapy related to toxicity, where the dose was reduced by 50%, we found a 50% mortality rate from infection and disease relapse. Therefore, the chemotherapy dose is the important factor for ensuring good outcome.

Due to limitations of the diagnostic method including flow cytometry analysis, only three patients with TMD who subsequently developed acute leukemia were provided flow cytometry analysis to correlate between TMD and the type of leukemia. Therefore, the results of flow cytometry analysis were uninformative. In addition, GATA*1* gene analysis is unavailable in our country. We recommend a further prospective study regarding morphology and flow cytometry analysis to predict the type of leukemia among infants with Down syndrome and TMD until acute leukemia develops.

Conclusion

Infants with Down syndrome having TMD often presented spontaneous regression. However, few patients could progress to acute myeloid leukemia due to the high mortality rate. Flow cytometry analysis might predict the type of leukemia from TMD leading to acute leukemia. Long term follow-up is warranted.

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