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A Small Cohort Review of Neonatal Transient Myeloproliferative Disease in Chinese Children

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Abstract

Background: Neonates with constitutional trisomy 21 are predisposed to develop transient myeloproliferative disease (TMD). TMD is characterised by a rapid accumulation of blast cells during the first few days of life followed by spontaneous resolution. Around 20% to 30% of them subsequently evolve into acute megakaryoblastic leukaemia (AMKL or FAB M7). ***Objective:*** To examine the natural history and biological characteristics of neonatal TMD, the clinical characteristic associated with subsequent AMKL, and the prognosis of AMKL with constitutional trisomy 21 in Chinese children. ***Methods:*** We retrospectively reviewed the charts of 4 neonates with trisomy 21 and TMD and compared them with that of the literature. ***Results:*** Trisomy 21 was the only cytogenetic abnormality identified in the blast cells of the 4 patients. In all of the neonates, peripheral blast cells cleared spontaneously, blood counts normalised and complete remission ensued without chemotherapy. Three of the 4 neonates developed AMKL at a mean age of 15 months of age and they were treated with chemotherapy. All achieved and maintained complete remission for a mean duration of 8 years (range 6.1-10.4 years). The remaining patient was found to have trisomy 21 only in the blast cells and he has normal phenotype without any Down's stigmata. ***Conclusion:*** Neonatal TMD is a unique clinical syndrome associated with spontaneous remission but with a high chance of developing AMKL subsequently. Interestingly, such AMKL are chemosensitive and can achieve long term remission with chemotherapy alone. Further research should focus on the role of genetic interactions of trisomy 21 in leukaemogenesis and on identifying specific therapeutic targets. Multicentre collaborative study has been conducting and risk stratification approach has been applied to minimise the therapy related toxicity currently.

Key words Acute megakaryoblastic leukaemia (AMKL); Down syndrome; Transient myeloproliferative disease; Trisomy 21

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Introduction

Transient myeloproliferative disease (TMD) is a unique syndrome that occurs almost exclusively in neonates with trisomy 21. It has been referred as transient abnormal myelopoiesis (TAM), or transient leukaemia (TL).[1] TMD has a high incidence of spontaneous remission. Many neonates with trisomy 21 are found to have blast cells in the peripheral blood at presentation associated with other congenital malformations, such as congenital heart diseases. TMD frequently resolves during the first 3 months of life,[2-4] but a significant percentage (20% to 30%) of patients develop Acute megakaryoblastic leukaemia (AMKL) within the next few years.[5,6] Unlike other types of childhood acute myeloid leukaemia, AMKL with trisomy 21 is very sensitive

to chemotherapy and has a better prognosis. Previous studies have obtained excellent results with intensity attenuated chemotherapy protocols, which produced long-term event-free survival (EFS) rates above 80%.[7,8] Here we reviewed our experience on four neonates with TMD and their long-term outcome.

Patients and Methods

Between January 1, 1998 and December 31, 2002, four neonates *with* morphologic evidence of blast cells in the peripheral blood or of more than 20% blast cells in aspirated bone marrow within the first three days of life were admitted to Queen Mary Hospital.

The clinical data including sex, gestational age, birth weight and Apgar score, congenital malformations, time of diagnosis of TMD, clinical signs and symptoms at diagnosis, presence of organomegly, complete blood count results, and percentage of blast cells observed in the peripheral blood or bone marrow (BM) were collected from the medical record and the hospital computer system.

Three were diagnosed with Down syndrome and one was found to have trisomy 21 only in the blast cells. He was phenotypically normal. Three patients had immunophenotyping done at diagnosis of TMD. All patients were confirmed to have trisomy 21 in their blast cells. All four patients did not receive chemotherapy for their TMD and achieve complete remission spontaneously, even though they had high WBC counts or signs of spontaneous tumour lysis syndrome.

All three patients with Down syndrome developed AMKL subsequently and it was confirmed by bone marrow biopsy and immunophenotyping, and they received chemotherapy according to the protocol of HKPHOSG AML 1996 but with dose modification. All four patients have been followed thereafter up to the current review period.

Results

Patient Characteristics

The 4 neonates (1 boy and 3 girls) were 1 day of age at diagnosis of TMD. The gestation age was 31-38 weeks (median 35 weeks). The birth weight was 1.8-2.9 kg (median 2.4 kg) (Table 1). All four patients showed signs of fetal distress but recovered after birth. Three patients showed signs of hepatomegaly and dysmorphic features of Down syndrome at birth. Two also had splenomegaly. Cardiac defects were diagnosed in all 4 patients. Three underwent surgical repair, while patent ductus arteriosus in one patient resolved without treatment. The three patients with Down syndrome stigmata had a variety of congenital malformations, including congenital hypothyroidism, anal atresia, and biliary tract malformation (Table 2).

Median (range) laboratory values at diagnosis were: WBC count 71.0×10^9/L ($43\sim109\times10^9$/L), platelet count 256×10^9/L($40\sim786\times10^9$/L), haemoglobin 153 g/L (97~210 g/L), and peripheral blast cell percentage 57% (47%~84%) (Table 1). Bone marrow cytogenetics showed trisomy 21 in all 4 patients at birth (Table 3). Blast cells from three patients expressed a unique immunophenotype that included the megakaryocytic antigens as CD41, CD42b, and/or CD61 (Table 3). No MLL arrangement or other translocations were detected. Approximately 12 days after exchange transfusion, patient 4's blast cells revealed the karyotype 47,XX,+21(16) while the constitutional karyotype was found as mosaic 47,XX,+21(4)/46,XX(14). At age 2 months, no evidence of trisomy 21 could be seen in cytogenetic analysis of 500 peripheral blood cells. The other three patients were confirmed to have Down syndrome with constitutional trisomy 21 after remission of TMD.

All four patients experienced spontaneous remission without chemotherapy. Peripheral blast cells were undetectable and blood parameters (haemoglobin, white cell count and platelets for age) were normal after a mean of 49 days (range, 19~90 days). TMD was managed with

Table 1 Patients characteristics at diagnosis of TMD

Patient	Gestational age (w)	Apgar score (1 min/5 min)	Sex	Birth weight (kg)	Age (d) diagnosis	Liver/ spleen (cm)	Down syndrome stigmata	CBC findings			
								WBC ($x10^9$/L)	Blast cells %	Hb (g/L)	Plt ($x10^9$/L)
1	37	6/8	F	2.99	1	0/0	Yes	58.7	49%	210	40
2	38	8/9	M	2.7	1	3/0	Yes	109	84%	150	64
3	35	8/9	F	2.2	1	5.5/2	Yes	43	49%	153	786
4	31	9/10	F	1.8	1	6/4	No	73.5	47%	97	135

Table 2 Abnormalities observed at diagnosis and their treatment

Patient	Abnormality	Treatment
1	Low type imperforated anus + duodenal atresia with malrotation + annular pancreas + anomalies of biliary communication	Surgery at 1 day
	ASD+VSD+CHF+PH	Surgery at age 2 years
	Bilateral VUR grade II	Follow-up
2	Tumour lysis syndrome	Exchange transfusion
	VSD+PDA	Surgery at age of 3 months
	Conjugated hyperbilirubinaemia	Conservative treatment
3	PDA+CHF	Surgery at age 20 days
	Umbilical hernia	Surgery at age 2 years
	Congenital hypothyroidism	Thyroxine therapy
	Tumour lysis syndrome	Hydration
4	Tumour lysis syndrome	Hydration + allopurinol
	Conjugated hyperbilirubinaemia	Exchange transfusion
	Gut perforation at age 3 days	Surgery at age 3 days
	PDA	Closed spontaneously
	Respiratory distress	Ventilation

ASD, atrial septal defect; CHF, congestive heart failure; PDA, patent ductus arteriosus; PH, pulmonary hypertension; VSD, ventricular septal defect; VUR, vesicoureteral reflux

Table 3 Characteristics of TMD and AMKL in the four patients

	TMD				Recurrent AMKL				
Patient	**Bone marrow morphology**	**Immuno-phenotype**	**Cytogenetics**	**Age at remission**	**Age at AMKL onset**	**Clinical symptoms and signs**	**Bone marrow morphology**	**Immuno-phenotype**	**Cytogenetics**
1	Not available		47,XX,+21	Day 60	13 mo	1 week of cutaneous peteachiae	Reduced megakaryocytes, many atypical	CD33; CD41	47,XY,+21
2	Not done	CD13; CD33; CD41; CD61 (peripheral blood)	47,XY,+21c	Day 19	12 mo	10 days of fever, pallor and petechiae	79% blasts with basophilic cytoplasm and prominent Golgi zone	CD7; CD13; CD33; CD41; CD42; CD61; Glycophorin A	47,XX,+21c
3	Heterogeneous blasts (35%); plentiful micro-megakaryocytes; No Auer rod	CD7; CD41; CD42b; CD45; CD61; CD117	47,XX,+21	Day 21	21 mo	1 month of thrombocy topenia	17% blasts similar to neonatal findings	CD33; CD42; CD41; Glycophorin A;	50-51,XX,+8, +10,+21,+21, +21(cp5)/ 47,XX,+21(15)
4	Increased in blasts and lymphoid cells	CD7; CD33; CD42b; CD61	Blast: 47,XX,+21(16); constitutional karyotype: mosaic 47,XX,+21(4)/ 46,XX(14)	Day 65		Cytogenetic re-examination after 2 months : No evidence of trisomy 21 among 500 cells			

supportive treatment, including hydratation, exchange transfusion, and other supportive care measures (packed red blood cells and platelets). All patients underwent surgery for repair of congenital abnormalities (Table 2).

Three patients developed subsequent FAB M7-AMKL at the ages of 12, 13 and 21 months (Table 3). All 3 patients' blast cells expressed the megakaryocytic antigens CD41 and myeloid antigen CD33. The transformed blast cells of patient 3 were found to be hyperdiploid: 50-51,XX,+8,+10, +21,+21,+21(cp5)/47,XX,+21(15). Chemotherapy was administered according to the HKPHOSG AML 1996 protocol (Table 4), with a 33% dose reduction for patient 2 and a 25% dose reduction for patient 3. All achieved complete remission after induction treatment and remained well during consolidation chemotherapy. None of them needed stem cell transplantation. All four patients have been followed up at our hospital on August 31, 2010. Mean follow-up time after the end of treatment was 8 years (range, 6.1~10.4 years).

Discussion

Trisomy 21 is the most common congenital chromosomal abnormality, occurring once in every 700 live births and it incidence increase with maternal age. Transient myeloproliferative disease (TMD) or previously known as transient abnormal myelopoiesis (TAM), transient leukaemia (TL) or leukaemoid reaction,[2,6,9] is characterised by a rapid but transient proliferation of abnormal blasts of megakaryocytic lineage. Although the exact incidence of the TMD has not been established, approximately 10% of the infants with trisomy 21 experience TMD. The megakaryocytic markers CD41, CD42b, and CD61 were expressed in our cases, although not uniformly. Other markers reported to be frequently expressed that were also identified in our cases were CD7, CD13, CD33, CD45, CD117, and Glycophorin A[2,3,10] suggesting the clonal proliferation of myeloid blast cells with megakaryoblastic or erythroblastic lineages.

All three patients with Down's stigmata were born with multiple congenital defects (Table 2) but no overt signs or symptoms of haematologic pathology initially. TMD was incidentally diagnosed by routine postnatal blood studies and they were diagnosed on the basis of leukocytosis (median 71.0×10^9/L, range $43\sim109\times10^9$/L) and a high percentage of circulating blast cells (median 57%, range 47%~84%).

Our patients sailed through the TMD with vigorous supportive care and prompt surgery and both interventions played an important role in their survival. Three recent large studies revealed that neonatal TMD is not really that benign and has a early death rate of 15% to 20%.[2-4] The risk factors for early death are preterm delivery (less than 37 weeks), ascites, leukocytosis $>100\times10^9$/L, and bleeding diatheses, while predictors of low risk were spontaneous remission and low-dose cytarabine treatment. Although all our patients had at least one of these risk factors, none of them received cytarabine.[2] That is because all these 4 cases were diagnosed before the publication of these reviews. In our latest practice, low dose cytarabine approach has already been adopted and we recently treated one Down's baby with TMD associated with pleural effusion, ascites and deranged liver function. After a week of low dose cytarabine, he responded rapidly without much side effect (data not included due to short follow up).

In contrast to previous reports that 20%~30% of patients with TMD and trisomy 21 develop non-transient leukaemia (typically AMKL, FAB AML-M7) within 3 years (median, 16~24 months) of birth,[11-13] all three of our cases with Down's stigmata developed AMKL within 15 months. This can be due to our small sample size leading to statistical bias. In addition, the bone marrow aspiration in case 3 (17% blasts) was within the diagnostic range of myelodysplastic syndrome RAEB-t, but as Zipursky et al reported,[6] the immunophenotype and cytogenetic results of this patient indicated Down syndrome with likely progression to overt AMKL. In addition, in the latest EWOG-Pediatric MDS classification, Down syndrome with either RAEB-t or AMKL are classified as one category and is considered as the different spectrum of a single disease. Case 3 showed a complex AML-cell karyotype 50-51,XX,+8,+10,+21,+21, +21(cp5)/47,XX,+21(15) that differed from that of the prior TMD blast cells and reflected evolution of the leukaemia cell clone. No information was available about *GATA1* mutations, which in cooperation with trisomy 21 play the key role in the leukaemogenesis in Down syndrome.[14-17]

All 3 patients who developed AMKL received chemotherapy according to HKPHOSG AML 1996 protocol (Table 4), with reduced doses for patients 2 and 3. All 3 patients attained complete remission after induction treatment and survived for 6 to 10 years after completion of therapy. The favourable outcome of these 3 cases is significantly better than that of AML in children without Down syndrome (DS),[8] suggesting that chemotherapy for DS patients with AMKL could be reduced further.

Case 4 was an unusual one, in which TMD was not accompanied by DS; approximately 16 similar cases have

Table 4 HKPHOSG AML 1996 protocol for low risk AML

Course	Drug	Dose	Route	Schedule
1	Daunorubicin	50 mg/m^2/day	IV over 6 hours	Day 1,3,5 (3 doses)
	Cytarabine	100 mg/m^2/12h	IV	Day 1-10 (20 doses)
	Etoposide	100 mg/m^2/day	IV over 4 hours	Day 1-5 (5 doses)
2	Daunorubicin	50 mg/m^2/day	IV over 6 hours	Day 1,3,5 (3 doses)
	Cytarabine	100 mg/m^2/12h	IV	Day 1-8 (16 doses)
	Etoposide	100 mg/m^2/day	IV over 4 hours	Day 1-5 (5 doses)
3	Amsacrine	100 mg/m^2/day	IV over 1 hour	Day 1-5 (5 doses)
	Cytarabine	200 mg/m^2/day	IV continuous	Day 1-5
	Etoposide	100 mg/m^2/day	IV over 4 hours	Day 1-5 (5 doses)
4	Mitoxantrone	10 mg/m^2/day	IV over 6 hours	Day 1-5 (5 doses)
	Cytarabine	1.0 g/m^2/12h	IV over 2 hours	Day 1-3 (6 doses)
Triple intrathecal therapy	Methotrexate	7.5 mg	IT	Day 1 of course 1,2,3
	Cytarabine	20 mg	IT	
	Hydrocortisone	7.5 mg	IT	

been reported.[18] The blasts in this case were positive for CD42b and CD61, markers of megakaryocytic differentiation, and had a 47,XX,+21(16) suggesting constitutional trisomy 21. After the blast cells became undetectable in peripheral blood, the constitutional karyotype was found to be normal, indicating trisomy 21 mosaicism. This patient had none of the typical DS features and has not developed leukaemia.

In conclusion, neonatal TMD is a unique clinical syndrome that often remits spontaneously. It predicts a high likelihood of subsequent AMKL that is sensitive to chemotherapy and has a satisfactory prognosis with appropriate treatment. Future research should focus on the effect of interaction between trisomy 21 and other genes in promoting leukaemogenesis and on potential therapeutic targets. Ongoing multicentre collaborative study could advance our knowledge on the risk stratification and optimal treatment for TMD and subsequent leukaemia.

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