A Review of Transient Abnormal Myelopoiesis (TAM) in Neonates with Down syndrome

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Abstract: Occurring exclusively in patients with Down syndrome, transient abnormal myelopoiesis manifests during the neonatal period. It is marked by abnormal, immature blood-forming cells in the blood and bone marrow (especially the cells involved in making platelets). In most cases it resolves spontaneously by 3 to 6 months of age, but for some the disease can be fatal leading to transient myeloproliferative disease (TMD) later on in life. The condition almost always occurs before 5 years of age. Transient abnormal myelopoiesis is caused by mutations (changes) in a gene called GATA1. Somatic GATA mutations have proven to be a marker of clonal identity in its evolution to megakaryoblastic leukemia. It is characterized by involvement of multiple organ systems leading to cardiac, kidney, and liver failure. It predisposes to infection, bleeding diathesis and abnormal build-up of fluid in the tissues that cover the organs in the body. Here we review the clinical manifestations, natural history, laboratory features, molecular genetics, and postulated disease pathogenesis of this disorder.

Keywords: Down syndrome, trisomy 21, transient abnormal myelopoiesis, TAM, Transient myeloproliferative disorder.

1. INTRODUCTION

Incidence of Down syndrome (DS) (trisomy 21) is 1 in 700 births, most common among all human chromosomal abnormalities1. Studies have shown that children with Down syndrome are more at risk of developing acute leukemia versus children without Down syndrome2. Greater than 95% of cases are secondary to chromosomal nondisjunction. Rarely, Robertsonian translocation or mosaicism may occur3. Typical physical traits include small stature, decreased muscle tone, flat nasal bridge, up slanting palpebral fissures, epicanthal folds and a single central deep palmar crease. Varying degrees of developmental delay are present and multiple other medical problems can occur, particularly congenital heart defects like endocardial cushion defects. In Down syndrome increased risk of acute megakaryoblastic leukemia (AMKL) is seen in one to five years of age4. Children with Down syndrome have a 10- to 20-fold increased risk of developing acute leukemia in late childhood5, but lymphoblastic leukemia then becomes more common. There are preleukemic and leukemic phases of the disease during infancy and early childhood. The “preleukemic” phase manifests at, or soon after, birth with circulating megakaryoblasts that are clonal in origin. Typically spontaneous resolution occurs; hence, this phase is now referred to as transient abnormal myelopoiesis. The blasts enter a seemingly latent/quiescent phase, but are believed to acquire additional mutations through the process of clonal evolution with subsequent progression to Acute megakaryoblastic leukemia (AMKL).

2. TRANSIENT ABNORMAL MYELOPOIESIS CLINICAL AND LABORATORY MANIFESTATIONS

Seen exclusively in Down Syndrome, transient abnormal myelopoiesis affects approximately 4% to 10% of neonates6,7. The median age of presentation is 3 to 7 days, though patients may be diagnosed at up to sixty days of life8. The most common clinical manifestations include hepatomegaly (60%), splenomegaly (35%–40%), jaundice(15%), pericardial effusion.
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(15%), pleural effusion (10%–15%), ascites (10%), respiratory distress (10%), and bleeding diathesis (10%). Characteristic blood findings include leukocytosis, thrombocytopenia and increased circulating blasts⁸. Some cases are asymptomatic and are found incidentally. On peripheral smear, blasts typically exhibit round to ovoid nuclei, dispersed chromatin, small nucleoli, and deeply basophilic cytoplasm with cytoplasmic blebbing (figure 1).

**Figure 1.** Blasts commonly express stem cell (variable CD34, CD117), myeloid (CD13, CD33), nonlineage (CD4, CD7, CD56), and megakaryoblastic/megakaryocytic (CD61, CD41, CD42) antigens.

**3. Natural History**

Most neonates with TAM (>80%) undergo spontaneous resolution in 3 months after birth with a 5-year overall survival of ~80% and event-free survival of ~60%. The overall mortality is reported to be ~20%, however, only half of the deaths are directly attributable to TAM usually due to hepatic failure secondary to fibrosis and blast cell infiltration⁹. Approximately 20% of patients with TAM develop AMKL within the first 4 years of life and this may be preceded by a myelodysplastic-like syndrome¹⁰. The World Health Organization 2008 classification system introduces the category “myeloid leukemia associated with DS” (herein referred to as DS-AMKL) to encompass both myelodysplastic and leukemic manifestations regardless of blast percentage, as there is neither prognostic nor therapeutic significance to finer discrimination¹⁰. Typical manifestations include leukopenia cytopenia, progressive marrow fibrosis, organomegaly¹¹-¹³. Blasts in DS-AMKL are morphologically and immunophenotypically similar to those seen in TAM¹⁴. Patients with DS-AMKL have a favorable prognosis with 80% 3-year overall survival². This response rate is attributed to enhanced chemosensitivity of megakaryoblasts to cytarabine due to increased drug efficacy¹⁵.

Figure 2 shows natural history of TAM and myeloid leukemia of Down syndrome (ML-DS) with appropriate indices of those affected. Both trisomy 21 and somatic GATA mutations are required for progression to TAM. (Figure adapted from Mateos et al., 2015).
4. GATA MUTATIONS AND PATHOGENESIS OF DISEASE

Somatic GATA1 mutations seem to be pivotal in the development of TAM and are a marker of clonal identity in its evolution to DS-AMKL. GATA1 mutations were first detected in blasts from patients with DS-AMKL, but not in healthy controls, non-DS-AMKL and in patients with DS who had other subtypes of acute leukemia suggesting they were specific to trisomy 21. Subsequently, GATA1 mutations were detected in the blasts of patients who have DS and TAM. In sequential longitudinal samples from a single patient, megakaryoblasts detected first during TAM and subsequently during DS-AMKL were both found to harbor an identical GATA1 mutation. These findings and other corroborative reports indicate that TAM and DS-AMKL are indeed clonally related.

The GATA1 gene encodes a zinc finger transcription factor that is essential for normal erythropoiesis and megakaryopoiesis. Various acquired mutations in exon 2, or less commonly exon 3, ultimately yield a mutant N-terminally truncated GATA1 protein (designated GATA1s) that has been detected exclusively in patients with DS.

Transient abnormal myelopoiesis may arise in utero within the fetal liver with “spontaneous resolution” reflecting the natural process of hepatic hematopoietic down-regulation. In support of this hypothesis, trisomy 21, in the absence of GATA1 mutation, has been shown to alter normal second-trimester hematopoiesis in fetal liver but not in fetal bone marrow. Liver parenchyma from postmortem examination of fetuses with DS (21 and 23 weeks of gestation) also contain GATA1 mutations but were not detected in concurrent bone marrow that supports the theory of GATA1 mutation acquisition during fetal liver hematopoiesis. Lastly, TAM cannot be evoked in GATA mutation in nonhematopoietic tissues.

A multistep process postulated by Bombery et al. states that trisomy 21 represents the “initiating” event in disease pathogenesis. In utero trisomy 21 creates an environment in which hematopoietic progenitor cells within fetal liver are primed for acquisition of either single or multiple somatic GATA1 mutations that reflect a “secondary hit” and promote hematopoietic dysregulation and emergence of TAM. Hematopoiesis naturally transitions from fetal liver to bone marrow with birth and the GATA1 megakaryoblastic clone becomes quiescent. However, this clone persists over time and undergoes other yet-to-be-defined genetic and/or epigenetic events that ultimately lead to the impaired megakaryocytic differentiation and uncontrolled proliferation characteristic of DS-AMKL.

5. CONCLUSION

Children with Down syndrome have a markedly increased risk of developing acute myeloid leukemia (ML-DS) compared with children without Down syndrome which is preceded by clonal neonatal preleukaemic disorder, known as TAM, which maybe clinically overt or silent. TAM and ML-DS have unique biological, cytogenetic and molecular characteristics. ML-DS has three distinct steps in pathogenesis. While the majority of cases of TAM resolve without sequelae as the GATA1 mutation is lost, ~10% of children harbor residual GATA1-mutant cells which then lead to ML-DS. Uncovering the mechanisms which underlie these events remains an a challenge and is important to offer better prospects in treatment. Down syndrome–AMKL has a favorable prognosis with enhanced chemotherapeutic responsiveness to cytarabine. New agents need to be investigated for improved survival and less toxicity.

REFERENCES

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