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Transient leukaemia of Down syndrome (TL-DS) in neonate with tri-somy 21: A case report

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Abstract

Transient Leukaemia of Down Syndrome (TL-DS) is a pre-leukaemia syndrome which occurs exclusively in patients with Down syndrome. Approximately 10% of neonates with Down Syndrome develop features consistent with TL-DS. It manifests in the neonatal period, and is characterised by varied degrees of multi-system organ involvement. While majority of neonates with TL-DS have spontaneous remission by 3 to 6 months; 10-20% of cases progress to acute leukaemia within first 5 years of life which can be fatal.

Somatic GATA1 mutations together with a peripheral blood blast percentage >10% is believed to be pivotal in the diagnosis of TL-DS. We describe a case report of Transient Leukaemia of Down Syndrome for its rarity and absence of blast cells in peripheral smear in a neonate with Down Syndrome (DS).

Keywords

Transient leukaemia of down syndrome; acute leukaemia; gata 1 mutation; down syndrome.

Introduction

Down syndrome, or constitutional trisomy 21, is the most common human chromosomal abnormality with an incidence of approximately 1 in 700 live births. Greater than 95% cases are secondary to chromosomal non-disjunction. Down syndrome is associated with various hematopoietic and non-hematopoietic malignancies. Patients with Down Syndrome are at increased risk of developing acute leukaemia, predominantly myeloid type. Acute Myeloid Leukaemia (AML) in patient's with Down Syndrome is also known as Myeloid leukaemia of Down Syndrome (ML-DS) [1].

Historically, pre-leukaemic and leukaemic phases of disease have been described during infancy and early childhood. The ''pre-leukaemic'' phase also known as Transient Leukaemia of Down Syndrome

manifests at or soon after birth.

The majority of affected patients are clinically asymptomatic at presentation and are detected incidentally by findings of abnormal blood counts and circulating blasts in the peripheral blood film. In most cases, TL-DS is self limiting and remission occurs during first 3 months of life without any therapy [2]. However, though less commonly neonates with TL-DS may present with haematological manifestations, hepatosplenomegaly, jaundice and rarely, effusions with hydrops fetalis [3].

We present a case of DS, who presented with progressively worsening TL-DS with absent blasts in peripheral blood film.

Case Report

This neonate was admitted to our hospital with an antenatal diagnosis of trisomy 21 (non-disjunction). Mum was being managed for chronic hypertension and had an uneventful pregnancy up until 28 weeks, with a normal 20-week scan. She presented at 28 weeks with decreased foetal movements; an ultrasound scan suggested features of hydrops foetalis (pleural, pericardial effusions, ascites) and anaemia with 20% blasts seen on foetal blood sample. This necessitated three In-Utero Transfusions (IUT) and ultimately, preterm delivery. Baby was suspected to have in-utero TL-DS.; blood films from the first and third IUT showed an absence of nucleated red cell precursors, low platelets and myeloblasts. GATA1 mutation was identified antenatally. This clonal GATA1 mutation suggested Transient Leukaemia of Down Syndrome (TL-DS) (atypical due to the absence of megakaryoblasts on film). In addition, antenatal scans suggested a cerebral cyst and VSD with overriding aorta.

She was born at 31/40 weeks with birth weight 1205 grams via emergency Caesarean section. She was admitted to Neonatal Intensive Care Unit (NICU) for preterm care which included mechanical ventilation, surfactant administration and further management of suspected TL-DS. She had dysmorphic features consistent with Down Syndrome.

Blood investigations on Day 1 of life were suggestive of anaemia (Hb: 84g/dl), thrombocytopenia(58 X 109/L), lymphocytosis (TLC: 28000/mm^3) with coagulopathy (PT-24sec, INR - 2.1, aPTT- 85, Fibrinogen-0.8). However, there was no evidence of blast cells on peripheral blood smear. She required frequent transfusion of blood products since Day 1.

She also had features of significant ascites and skin oedema with mild pleural and pericardial effusions consistent with hydrops foetalis. Her postnatal Echo confirmed antenatal findings of large sub-aortic VSD with some degree of aortic override and mild pericardial effusion. Her cranial ultrasound suggested small right cerebral cyst. She had no features of hepato-splenomegaly until about 7 weeks of life.

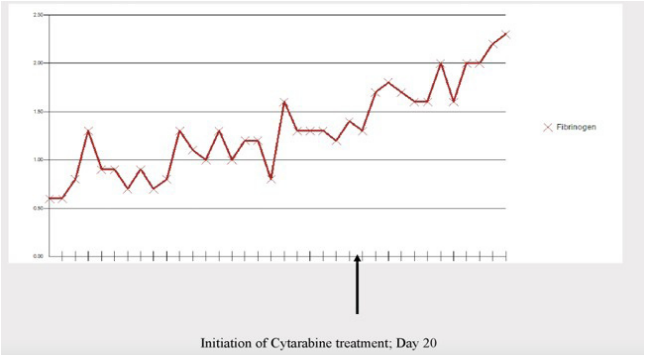
TL-DS was evident by features such as anaemia, thrombocytopenia, lymphocytosis and coagulopathy with associated antenatal and postnatal GATA1 positive; however, there was absence of blast cells on postnatal blood films and no initial hepato-splenomegaly. Bone marrow sampling could not be attempted during the early postnatal period due to low birth weight and prematurity.

She was commenced on Day 20 of life with a week course of cytarabine while awaiting extended genetic myeloid panel results to look for possible leukaemic transformation.

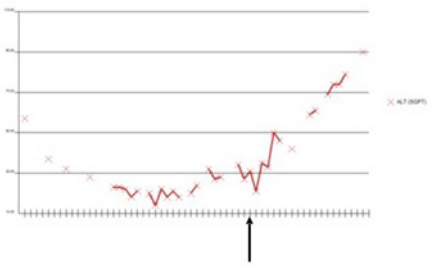
Investigations for alternate causes of foetal hydrops were undertaken with the guidance of the Metabolic team. However, no other cause was found. She was managed for hypothyroidism from 4 weeks of life. Her maximum TSH levels were 39mIU/L.

`She did respond to the initial course of Cytarabine with improvement in haematological parameters (Figure 1). Her requirement for fresh frozen plasma and platelet concentrate requirement reduced from twice a day to once in 3 days while packed RBC requirement reduced from once in two days to almost once a week. However from 7th week of life she had gradually progressive ascites and hepatosplenomegaly with 7 cm liver and 6 cm spleen size, both firm in consistency. She also developed progressive conjugated hyperbilirubinaemia first noticed on Day 51 of life (Figure 2). This was associated with resurgence of frequent need of blood products. Abdominal ultrasound confirmed hepatosplenomegaly with massive ascites. Investigations performed for conjugated hyperbilirubinaemia were inconclusive. These included serum ammonia, urine for reducing substance, alpha 1 antitrypsin 1 phenotype, galactose-1-phosphate uridyl transferase, CMV and HSV viral PCR and urine for organic acids. Extended genetic myeloid panel did not suggest features of acute leukae-mia.

As part of further management possibility of a liver biopsy, bone marrow aspiration and second course of Cytarabine were considered; however, it was declined by parents, wanting to focus on supportive management and quality of life in context mitigating burden of investigations and to avoid causing her any further suffering, parents decided discharge home for end of life care.



Initiation of Cytarabine treatment; Day 20



Day 51 of life

Discussion

One of the unique haematologic abnormalities seen in neonates with DS is transient leukemia (TL-DS) which is characterised by presence of megakaryoblastic TL-DS cells which originate in the foetal liver, spill into the peripheral blood and infiltrate throughout the liver as well as distant tis-sues. No single clinical feature is entirely specific to TL-DS [4]. However, there are several features that are seen relatively frequently in TL-DS, including organomegaly, hepatopathy (raised transami-nases with conjugated hyperbilirubinaemia), pericardial and pleural effusions, extreme leucocytosis and coagulopathy. Presence of one or more of these features in the absence of a clear alternative ex-planation should lead to the early consideration of a diagnosis of TL-DS [5,6]. In our case, this neo-nate presented with anaemia, thrombocytopenia,

leucocytosis, features of hydrops and hepato-splenomegaly with hepatopathy.

TL-DS is characterised by transient appearance of blast cells in the peripheral blood which disappear spontaneously [7]. However, absence of blast cells in peripheral blood film is not uncommon especially in neonates with Intrauterine Growth Restriction (IUGR) or other history of placental insufficiency as these babies may have lower blast counts despite large mutant GATA1 clones [5]. In our case, absence of blast cells on peripheral blood films can possibly be explained by growth restriction and maternal hypertension. We could not perform bone marrow sampling and liver biopsy during the early postnatal period due to low birth weight, prematurity and coagulopathy; later parents did not consent and decided for compassionate care. However, bone marrow examination is not gener-ally useful in TL-DS as blast cells are believed to originate in the liver and marrow blasts are variable and less prevalent than in peripheral blood [6].

TL-DS is marked by the presence of an acquired N-terminal mutation in exon 2 or exon 3 of the key haematopoietic transcription factor gene GATA1, resulting in a truncated GATA1 protein [8,9]. TL-DS is defined as presence of a GATA1 mutation along with peripheral blood blasts more than 10% and/or clinical features suggestive of TL-DS in a DS or mosaic Trisomy 21 patients [10]. This neo-nate had antenatal and postnatal GATA1 positive with clinical features suggestive of TL-DS.

The differential diagnosis for TL-DS includes leukaemoid or leukoerythroblastic reaction and congenital leukaemia [2,11]. Causes of leukaemoid reaction such as intrauterine infections, neonatal sepsis and erythroblastosis foetalis were ruled out. Extended genetic myeloid panel did not suggest features of acute leukaemia.

Management of TL-DS in DS requires a multi-disciplinary approach between a foetal medicine specialist, neonatologist and a paediatric haematologist. Various prognostic factors and treatment indi-cations have been extensively studied. TL-DS resolves spontaneously in the majority of cases, how-ever, early death and development of myeloid leukaemia, especially AML may occur. Nearly 22% of patients with TL-DS die during infancy [6]. The risk factors for mortality in TL-DS are prema-turity, low birth weight, ascites, white blood cell count >100 X10/l, bleeding diathesis, Cytarabine treatment, direct bilirubin ≥83 micromol/l. In our case all the above factors were present including early gestational age (31 weeks), high TLC (150 X 10/l) and conjugated bilirubin 124 micromol/l which correlates with early death of the baby and support the studies [5,12].

All neonates with TL-DS or presumed TL-DS with associated Life Threatening Symptoms (LTS) should be urgently considered for treatment with one week course of low dose cytarabine [14]. LTS in neonates with TL-DS includes multi-organ failure, white blood cell count >100 X 10/l, conjugated bilirubin >83 micromol/l, ascites or massive hepato-splenomegaly, hydrops foetalis, disseminated intravascular coagulation. In some cases, a single course of cytarabine is not sufficient to control TL-DS entirely. Repeat courses of cytarabine should be carefully considered to achieve control where severe liver dysfunction persists, however, study data are limited on repeated courses [3]. In our case, despite an early diagnosis of TL-DS we commenced the neonate on low dose Cytarabine on Day 20 of life because of lack of literature on its use in preterm babies. There was only transient improve-ment after a week of treatment and was fol-

lowed few weeks later by features of hepatic failure and DIC. Other treatment modalities including second course of Cytarabine was discussed with parents who in view of guarded prognosis decided for redirection of care.

Conclusion

In conclusion, TL-DS is a pre-leukaemic disorder that occurs only in neonates with constitutional trisomy 21. Neonates with this condition may have varied presentation ranging from no symptoms to fulminant course as seen in our case. Furthermore, though peripheral blasts are often seen in neo-nates with TL-DS however it is not an essential criteria and TL-DS is defined as presence of a GA-TA1 mutation along with peripheral blood blasts more than 10% and/or clinical features suggestive of TL-DS in a DS.

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