

Case Report

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Transient Myeloproliferative Disorder in Neonates with Down syndrome: Case Report and Review

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Abstract

Down syndrome (DS) or trisomy 21 is the most prevalent chromosomopathy. Interesting associations have been documented between DS and various hematopoietic and non-hematopoietic malignancies. Transient myeloproliferative disorder (TMD) is a clonal proliferation of megakaryoblasts, typically occurring in newborns with DS. It is believed that TMD occurs in the presence of GATA-1 mutation together with trisomy 21. The disorder resolved in the majority of patients during the first six months of life, however, 30% of patients can develop acute leukemia or a myelodysplastic syndrome in the first five years of life. In most instances, this unique disorder has the ability to spontaneously "turn off" the overproliferation and enter a state of remission. Only supportive care is recommended for TMD during the first months of life unless the clinical condition requires intervention.

This is the report of a preterm newborn with Down syndrome diagnosed with TMD that required chemotherapy on the first days of life due to a poor clinical course and other risk factors for early death. As more cases of this disorder are presented, it is important to share our experience to aid in management and diagnosis.

Introduction

Down syndrome or trisomy 21 is the most prevalent chromosomopathy with an incidence of approximately 1 per 700 live births. Prevalence correlates with advanced maternal age. More than 95% of cases are secondary to meiotic non-disjunction, and rarely, it may be due to mosaicism or translocation [1,2]. Interesting associations have been documented between Down syndrome (DS) and various hematopoietic and non-hematopoietic malignancies. Throughout their lives, patients with DS have a reduced overall risk of solid tumors. In contrast, a 500-fold increased risk of acute megakaryoblastic leukemia (AMKL) is observed during early childhood (1-5 years of age) [1-3].

Transient abnormal myelopoiesis (TAM) is seen exclusively in Down syndrome and affects approximately 4 to 10% of newborns. The true incidence is unknown since patients may be asymptomatic and it is not always necessary to perform routine laboratory tests. The average age of presentation is between 3 to 7 days, but there are patients diagnosed up to 2 months of age [2]. The pathogenesis of transient myeloproliferative disorder is complex, with multiple processes which lead to the presence of megakaryocytic lineage blasts in peripheral blood of infants with trisomy 21. Although some steps have been elucidated in this pathway, many remain unknown [1-3]. The development of this disorder seems to require the acquisition of a somatic mutation of the gene encoding the hematopoietic transcription factor GATA-1. GATA-1 mutations result in the expression of a GATA-1 protein truncated at the amino terminus (GATA1s). The functional consequence is poor megakaryocytic

differentiation and uncontrolled proliferation of a blasto population [3]. The number of blasts is often higher in the peripheral blood than in the bone marrow (the site of postnatal hematopoiesis), a finding that is consistent with the origin of the disorder in the tissues of fetal hematopoiesis (e.g. fetal liver) [1].

The Transient Myeloproliferative Disorder (TMD) is resolved in the majority of patients during the first three months of life. In approximately 20% of cases, after an apparent clinical resolution, acute myeloid leukemia appears in the first 4 years of life [1,2]. The most common clinical manifestations include hepatomegaly (60%), splenomegaly (35%-40%), jaundice (15%), pericardial effusion (15%), pleural effusion (10%-15%), ascites (10%), respiratory distress (10%) and hemorrhagic diathesis (10%). Less common features include liver fibrosis, fetal hydrops and renal failure [1,4,5].

The characteristic hematological findings include leukocytosis (100000/IL in 20%-30% of cases), thrombocytopenia (40% of cases) and a greater number of circulating blasts. Approximately 10% to 25% of patients are asymptomatic; therefore, the diagnosis can be established as an incidental finding during the laboratory evaluation for some other cause. Occasionally, the finding of myeloproliferative syndrome may even be the first indication that a patient has trisomy 21 [1,5]. The diagnosis of TMD is commonly suspected in new-borns with Down syndrome who have blasts in the peripheral blood smear and abnormal cell counts [6,7].

When TMD is clinically suspected, a cytogenetic karyotypic analysis should be performed to establish constitutional trisomy 21, whereas

analysis of the GATA1 mutation is also recommended to document clones of the blasto population. The presence of a mutation or mutations acquired in exon 2 or 3 of the GATA1 gene on the X chromosome establishes a diagnosis of TMD and serves as a potential marker for the future control of the disease in the development of AMKL [1,6,8]. Bone marrow examination is usually not indicated since the findings in it are similar or less pronounced than those in the blood [6].

The natural history of transient myeloproliferative syndrome is quite variable. The majority of neonates (80% of those with documented TMD) experience spontaneous remission within 3 to 6 months of age. At the other end of the spectrum of the disease, neonatal (or even fetal) death occurs in approximately 10% of patients secondary to diffuse organ infiltration by megakaryoblasts, associated parenchymal fibrosis and subsequent multisystem failure. Approximately 20% of patients with TMD develop AMKL in their first 4 years of life and this may be preceded by a myelodysplastic syndrome [1,9].

Independent risk factors that predict early mortality include white blood cell counts above 100000/L, premature births (37 weeks), effusions (pleural, pericardial, ascites or hydrops), coagulopathy, hemorrhagic diathesis, platelet count greater than 100000/L, low birth weight and failure to eliminate peripheral blasts. When these high-risk characteristics are present, the intervention is justified by chemotherapy. The cytidine deaminase gene participates in the catabolism of cytarabine and its transcription decreases in patients with Down syndrome, which leads to a decrease in the metabolism of the drug intracellularly with the subsequent increase in the efficacy of the drug [1,10,11].

It has been shown that a short cycle of low-dose cytarabine decreases the risk of death in TMD, but does not appear to prevent progression to acute myeloid leukemia. For infants with one or more risk factors for early death, cytoreductive therapy should be offered with low doses of subcutaneous cytarabine (10 mg/m per dose) every 12 h for a total of seven days [9,12-14].

Case Report

Preterm new-born of 35 weeks of post-menstrual age, with premature rupture of membranes of approximately 7 hours of evolution, with antecedents of controlled pregnancy with negative serology, maternal age of 40 years, 4 previous healthy children, with both healthy parents, not consanguineous. Ultrasound of first and second trimester without pathological findings, nuchal translucence within normal range. In third-trimester ultrasound, uterus gestase with single fetus, live, amniotic fluid in sufficient quantity, fetal morphological examination with moderate hepatosplenomegaly with decreased echogenicity of both organs.

A girl of 2225 g, size 43 cm, head circumference 30.5 cm, Apgar 8/8, with good adaptation to extra-uterine life, without oxygen requirement is born by vaginal delivery. It presents phenotype compatible with trisomy 21 and severe hepatosplenomegaly. Neonatal admission is decided and empirical antibiotic therapy (Ampicillin - Gentamicin) and parenteral hydration are indicated.

Laboratory was performed and it was observed: erythrocyte 5.24 million/ul, hemoglobin 17.6 g/dl, haematocrit 53.7%, leukocytes 48,100/ul (presence of immature elements, 60 erythroblasts per 100 white blood cells), platelets 280,000/ul, PCR 5 mg/l (VN: <5), GPT 261 U/l, GOT 392 U/l, GGT 585 U/l, FAL 897 U/l.

Interconsultation is carried out with genetic service which takes samples for karyotype where trisomy 21 is confirmed. Interconsultation is performed with oncohematology service, who decides to adopt expectant management and assess clinical and laboratory evolution.

An echocardiogram is performed where persistent ductus arteriosus and pulmonary hypertension is reported, cerebral ultrasound showed marked bilateral symmetric periventricular hyperechogenicity and abdominal ultrasound showed marked hepatomegaly (crosses the midline and occupies right hypochondrium), moderate splenomegaly, hyperechoic kidneys without cysts and gallbladder with biliary mud inside.

At 24 hours of age, severe indirect hyperbilirubinemia (total bilirubin 24.85 mg%, bilirubin direct: 2.43 mg%, bilirubin indirect: 22.42 mg%, LDH 16.260 U/l, maternal blood group O+, blood group of new-born A+) is observed in the laboratory. It requires phototherapy and exchange-transfusion where two volemias are replaced. After this procedure, laboratory is checked and Gammaglobulin EV passage is indicated at 1 g/kg.

At 48 h of age, it begins with haematological alterations and coagulation disorders (Platelets 51,000/ul, PT 26%, APTT 48 s). Vitamin K EV is indicated and transfusions of fresh frozen plasma are performed as needed. After a transient improvement, on the sixth day of life she presents episode of low digestive hemorrhage and oligoanuria with generalized edema. Doses of furosemide VO (2 mg/kg) were made and it was decided to start with ursodeoxycholic acid by pattern of persistent cholestasis in the laboratory.

On the ninth day of life it presents a feverish record of 38.4°C. A sample is taken for uroculture, blood culture and retro-culture of central venous access and empirical antibiotic therapy is started with Vancomycin+Amikacin EV. The girl evolves unfavorably, with greater respiratory effort that worsens with the passing of hours, active bleeding by high digestive tract with fresh blood debits in moderate amount. She presented impending respiratory claudication, so intubation with TET No. 3 was decided, it was placed in mechanic ventilation (mode pressure controlled ventilation) and inotropic support was started at high doses due to refractory hypotension (Adrenaline, Dopamine, Hydrocortisone). She required TET replacement due to total obstruction with blood and secretions.

Cerebral ultrasound is repeated where grade II intraventricular hemorrhage is reported and abdominal ultrasound shows ascites, hepatosplenomegaly, globular kidneys with normal Doppler, significant persistent ductus arteriosus. On the tenth day of life she presents pulmonary hemorrhage and coagulopathy that requires transfusions with cryoprecipitates and fresh frozen plasma every 8 h. Due to a poor clinical course, with hyperleukocytosis in the laboratory (leukocytes 137,400/ul), chemotherapy with Citarabine EV 8 mg/day was decided jointly with the oncohematology service.

At 11 days of age, uroculture informed no inflammatory response, with development of gram-negative bacillus (*Klebsiella pneumoniae* BLEE). It was decided to rotate therapeutic scheme to Vancomycin +Meropenem EV. At 14 days of age the girl presents a cardiac arrest. Advanced resuscitation is performed for 15 min without obtaining favorable response, declaring her death.

Discussion

Neonatal TMD is considered a serious disease requiring intensive care shortly after birth. As such, diagnosis and assessment of its severity must be immediate. Without cordocentesis, prenatal diagnosis is very difficult. Two cases of fetal TAM were reported that were diagnosed on the basis of ultrasonographic evidence of hydrops and hepatosplenomegaly. There was the first published report suggesting a relation between fetal TMD and hepatosplenomegaly. Smrcek and colleagues showed in a retrospective study that fetal hepatosplenomegaly and/or hydrops in the second half of pregnancy is a sign of myeloproliferative disorder in fetuses with trisomy 21 or mosaic trisomy [15].

Fetal hepatomegaly is a specific finding in cases of severe isoimmunization disorder, *in utero* infection, fetal congestive heart failure, and metabolic disorder. If these conditions are excluded then fetal hepatomegaly associated with Down syndrome should be regarded as diagnostic of TMD and an indication for the need to prepare for neonatal intensive care [15]. In previous case series, TMD was found to have a high case fatality rate, despite the generally accepted approach of supportive care until the disease's spontaneous resolution. This has led to significant confusion and unease among clinicians as to the proper route of action when a patient with TMD presents [8]. In the Children's Oncology Group Study A2971, 78% of children with TMD had mild symptoms and spontaneous resolution of their disease without intervention, similar to a recent report from the BFM (84%). This ranged from those who only had transient blasts in the peripheral blood (31%) to those with mild organomegaly, such as hepatomegaly (58%), abnormal liver function studies (41%), and splenomegaly (36%), similar to other recent reports. In comparison, those patients who presented in moribund condition or with lysis tumoral syndrome were likely to lead to mortality if intervention is not implemented. Organ infiltration, primarily hepatic, may be severe, progressive, and fatal. Hayashi et al found 10 of 15 TMD patients died within the first few months of disseminated intravascular coagulation, hepatic failure, or renal failure. Zipursky et al. [3] identified 7 of 13 severe TMD patients in the literature died, of whom 5 were stillborn, and 2 died later. Hydrops fetalis was a predominant symptom in these patients, with prominent blast infiltration of the heart and liver found at autopsy with associated fibrosis, whereas none of these findings were found in the marrow. Three of the 4 reviewed patients died within 24 h of birth [8]. Subsequently, Al-Kasim et al. [14] further described the central role of hepatic involvement in those with a fatal outcome. Nine of 48 patients enrolled had life-threatening disease, 7 with hepatic fibrosis and 2 with cardiorespiratory failure. Without intervention all died, whereas 3 children in whom short courses of low-dose cytarabine were administered survived. More recently, Klusmann et al. [12] reported the BFM registry experience, which identified that high-risk patients (high WBC, prematurity, ascites, and failure of TMD resolution) had an improved outcome if intervention was given (72% vs. 24%, $P=0.001$). Intervention clearly appears to have a role in supporting these children through a critical period of their disease [6]. Because of this wide range of presentations and their incumbent mortality risks, it is important to better ascertain who may require intervention before spontaneous resolution. The Children's Oncology Group Study A2971 proposes a mortality risk-based classification system to stratify the treatment of TMD patients. They identified 3 distinct TMD risk groups. High-risk patients have early evidence of LTS and a TMD-associated mortality rate of 55% at 3 years. Most infants with TMD (41%) belong to the intermediate-risk group, specifically those with hepatomegaly although without LTS. These

infants rarely die from acute complications of TMD; however, they have a 23% 3 year mortality rate. This is double the overall mortality rate of the low risk group and is disproportionately greater than the mortality rates of DS infants without TMD. The rest (38%) are the classic "low-risk" patients in whom the disease spontaneously resolves without therapeutic intervention. Low-risk patients have less than a 2.3% chance of dying from acute complications of TMD [8].

Conclusion

Transient myeloproliferative syndrome, also called transient neonatal leukemia or transient anomalous myelopoiesis, is described in most cases in new-borns with trisomy 21. The approximate incidence is 10% [7,13]. The disorder is detected in approximately 80% of the cases in the third trimester, and in the rest of the cases it is performed postpartum. Among the suggestive echographic findings, it can be noted: hepatosplenomegaly (79.5%), fetal hydrops (30.8%), pericardial effusion (23.1%) and alteration in the volume of amniotic fluid (15.4%). Prenatal diagnosis requires high presumption and diagnostic suspicion and therefore the prognosis is worse, and it has high mortality [16]. Its clinical expression is variable, although there are asymptomatic cases, other patients present symptoms caused by organ infiltration or tumor lysis, accompanied by intense leukocytosis, leukostasis, organic failure with hemodynamic and respiratory compromise [7,17]. The circulating blasts in the peripheral blood exhibit immunophenotypic markers of myeloblastic, megarioblastic and erythroblastic precursors. The clinical course is usually self-limiting during the first six months. However, 30% of patients can develop acute leukemia (MAM-M7) or a myelodysplastic syndrome in the first five years of life [14,16].

It is important to make a differential diagnosis with other entities that have leukemoid reactions, thrombocytopenia and anemia, such as congenital viral infections (TORCH), neonatal hemolytic processes (Rh incompatibility), neonatal leukemia, histiocytosis, neuroblastoma or situations that occur with perinatal hypoxia [9,11,18].

The initial treatment is supportive therapy. Chemotherapy is used in patients with severe manifestations, such as compromised liver or cardiorespiratory function that are accompanied by visceromegaly or serous effusion, as well as severe leukocytosis [19]. The actual incidence of TAM is difficult to determine without performing a prospective screening of all infants with down syndrome. Although the diagnosis of TMD is usually made with clinical and haematological findings, molecular diagnosis by demonstrating the GATA1 mutation(s) will clarify the diagnosis in clinical and hematologically silent cases [17]. Given the variable clinical presentation of TAM, it is important to identify the factors that reliably predict the outcome and, therefore, the patients who are likely to benefit from the treatment. It will also be important to consider which babies deserve treatment and to establish the most effective treatment regimens [14,17].

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