Down Syndrome with Transient Myeloproliferative Disorder and Beta-Thalassemia Major

Amit Garg · Ankur Singh · Mohanaraj Ramachandran · Seema Kapoor

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Abstract Down syndrome is the most common chromosomal abnormality and is frequently associated with transient myeloproliferative disorder (TMD) and leukaemias. The coinheritance of this syndrome with beta-thalassemia major is uncommon. Only two cases of coinheritance of Down syndrome with beta-thalassemia major have been published in literature. We report an infant suffering from Down syndrome who presented with severe anemia which was later attributed to beta-thalassemia major and TMD. The infant improved after blood transfusion and other supportive management. The blasts disappeared from marrow during hospital stay. In areas of high prevalence of beta-thalassemia heterozygotes, the presence of coinheritance of the mentioned condition with another congenital disorder may be common.

Keywords Down syndrome TMD · Beta-thalassemia major

Introduction

Down syndrome is the most common chromosomal abnormality in the live newborn approximately 1 in 644–733 births [1]. It is caused by an extra whole or partial copy of chromosome 21. Children with Down syndrome have various haematological abnormalities and have an increased predisposition to transient myeloproliferative disorder and acute leukaemias. The thalassemias are a heterogeneous group of haemoglobinopathies which are

characterised by reduced or absent level of alpha or beta chain of the haemoglobin [2]. Only two cases of coinheritance of Down syndrome with beta-thalassemia major are available in literature [3, 4]. Here we report a rare case of Down syndrome associated with both beta-thalassemia major and transient myeloproliferative disorder.

Case Report

A 4 month old male child born to a 25 year old gravida two mother through uneventful vaginal delivery at term with a birth weight of 2.75 kg. There was no history of consanguinity between the parents. The parents belonged to Bihar.

Child was apparently well up to the age of 31/2 months and presented to us with complaints of low grade fever for 2 days and decreased oral acceptance for 15 days. He weighed 4.3 kg with a height of 55 cm and a head circumference of 34 cm (all below -3 SD for corresponding age and sex). On examination child was found to have depressed nasal bridge, epicanthal folds, mongoloid slant, low set ears, simian crease and left sided undescended testis. Child was having severe pallor. His liver was palpable 7 cm below right costal margin with a span of 8.5 cm, was firm in consistency and non-tender, spleen was palpable 7.5 cm below left costal margin, was firm and non-tender. An ejection systolic murmur of grade 3/6 was heard in the pulmonary area and further echocardiography revealed tiny ostium secundum atrial septal defect. The neurological examination revealed hypotonia of trunk and limb muscles. In view of anemia workup was done and investigations showed haemoglobin of 3.4 g/dl, TLC- $29.4 \times 10^9/l$, platelet count of $50 \times 10^9/l$. Peripheral smear showed microcytic hypochromic anemia with tear drop cells, nucleated red blood cells 15/100 white blood cells. Bone

A. Garg · A. Singh · M. Ramachandran · S. Kapoor (✉)
MAMC and Associated Lok Nayak Hospital, M-439, Ground
Floor, Guruharkishan Nagar, Paschim Vihar, New Delhi, India
e-mail: drseemakapoor@gmail.com

Fig. 1 a Bone marrow aspirate shows erythroid hyperplasia
b Bone marrow aspirate shows blasts(*black arrows*) and features of dyserythropoiesis in an erythroid precursor (*white arrow*)

Fig. 2 HPLC chromatogram(Bio rad variant beta-thalassemia short program) shows highly elevated HbF(*black arrow*)

marrow aspiration showed reversal of M: E ratio(1:4). Erythroid series showed normoblastic reaction with mild degree of dyserythropoiesis. 8 % blasts were seen and myeloid maturation was unremarkable (Fig 1a, b). Megakaryocytes were decreased in number with normal morphology and function bone marrow iron stores were adequate (grade 2).

High performance liquid chromatography (HPLC) revealed beta-thalassemia major with highly elevated peak of HbF (Fig. 2) with 93.7 %, HbA2-3.5 %, HbA-2.2 %. Naked eye single tube red cell osmotic fragility test was done for parents which was positive. HPLC was also done for both the parents which confirmed beta-thalassemia trait. The infant was tested for mutation which revealed him to be homozygous for IVS 1:5(G>C). Parents were carrier for mutation. Ultrasound abdomen, thyroid function tests, liver

function tests were within normal limits. Karyotyping was done using trypsin-giemsa banding which revealed Trisomy 21(47, XY, +21).

A bone marrow aspiration was repeated after 10 days to look for the status of blasts which revealed normoblastic erythroid hyperplasia(M:E ratio of 1:3),myeloid maturation was unremarkable and no blasts were seen. Megakaryocytes were adequate in number and function. The child is in our follow up and the transfusion frequency is every 3–4 months.

Discussion

In the literature reviewed till date, the coinheritance of the beta-thalassemia major/Down syndrome has been reported in two patients only. Keser et al. [3] reported a child having features of both beta-thalassemia major and Down's syndrome. They had described a 2.5-year-old girl with the above mentioned conditions who had presented with the complaints of growth retardation. Another case report is of a 3-year-old Hindu girl who was a diagnosed case of beta-thalassemia major with Down's syndrome, presented for blood transfusion at the hospital [4]. There is not a single case report of a patient having Down syndrome with transient myeloproliferative disorder (TMD) and beta-thalassemia major as present in our patient.

TMD is defined as the morphologic detection of blasts in peripheral blood in infants less than three months of age. TMD has also been referred to as transient abnormal myelopoiesis or transient leukemia. TMD is usually detected in the first week of life and spontaneously resolves within 2–194 days with a mean of 58 days [5].

The transient nature of this condition can be explained by the great capacity of TMD blasts to proliferate and differentiate into various kinds of cells including basophils, neutrophils, eosinophils monocytes and erythrocytes [6]. Gosavi et al. [7], described two newborns with a karyotype of 47, XY, +21, who presented with marked leukocytosis and many blast cells in the peripheral blood. In both the cases, the blasts disappeared and the total leukocyte count reverted to normal without any specific treatment [7]. Recent studies have shown the blasts of TMD to be clonal in origin and show GATA1 mutation in nearly all patients with TMD [1]. In our patient there were blasts in marrow which disappeared during the hospital stay thus confirming the transient nature. However we could not perform GATA 1 mutation owing to the absence of blasts in the peripheral blood.

TMD blasts are believed to be of fetal derivation and normally reside in organs of fetal hematopoiesis such as the liver, a model that may explain the higher percentage of TMD blasts in the peripheral blood compared to the bone marrow [1]. In our patient blasts were found in marrow only and not in peripheral blood. It may be explained by the resolving stage of TMD as the age of the patient was 4 months and also the hematological parameters improved during the hospital stay only.

The mechanism of TMD development or the progression to acute leukemia from TMD in DS is largely unknown [8]. However few molecular mechanisms that lead to TMD are being elucidated. TMD blasts contain extra copies of chromosome 21 and occasionally additional karyotypic abnormalities [9]. Additional non-karyotypic oncogenic events must collaborate with trisomy 21 to generate TMD because TMD is seen in only a subset of neonates with trisomy 21 and TMD can occur without additional karyotypic abnormalities.

In our patient 8 % blasts were seen in bone marrow which resolved spontaneously. This child needs to be

followed up closely to look for the progression to MDS as DS-MDS children can present with cytopenias, dyspoiesis. They are clinically well at initial diagnosis and have increased blasts in the marrow (6–29 % of the marrow cellularity). A subset has a history of TMD. In areas of high prevalence of beta-thalassemia, the presence of coinheritance of the mentioned condition with another congenital disorder may be common. Presence of thalassemia and TMD contributed to significant anemia in present case. We need to follow this case for progression of leukemia besides providing standard of care treatment for Down syndrome.

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