Trisomy 21 associated transient neonatal myeloproliferation in the absence of Down’s syndrome

M Richards, J Welch, A Watmore, D Readett, A J Vora

Abstract
Although usually associated with Down’s syndrome, transient neonatal myeloproliferation (TMD) can occur in the absence of a constitutional trisomy 21. This report describes two such cases, both of whom had a trisomy 21 restricted to clonal cells. Unlike in previous such reported cases, spontaneous morphological, cytogenetic, and molecular remission in both cases was followed by re-emergence, in one case, of an evolved clone with a more malignant phenotype which required pharmacological intervention. Awareness that trisomy 21 bearing leukaemia in the neonatal period can be transient even in the absence of Down’s syndrome is important to prevent unnecessary treatment. Equally, such cases require indefinite follow up as a proportion may have a recurrence which may require treatment. (Arch Dis Child Fetal Neonatal Ed 1998; 79:F215–F217)

Keywords: transient myeloproliferative syndrome; trisomy 21; leukaemia

Neonates with Down’s syndrome occasionally present with features of congenital leukaemia that undergo spontaneous remission. This has been described as transient neonatal myeloproliferative disorder (TMD). A similar condition may arise in babies without morphological features of Down’s syndrome, but such cases often have constitutional trisomy 21 or mosaicism. We describe two cases of TMD occurring in the absence of constitutional trisomy 21, one of whom had a recurrence with a more aggressive phenotype and an evolved karyotype which required the treatment given for acute myeloid leukaemia.

Case reports
CASE 1
A 1 week old baby girl presented with swelling of her feet and right forearm and an erythematous macular–papular rash over the face, trunk, and limbs. Examination of the patient showed that she was otherwise normal; in particular, she had no dysmorphic features. The baby had no dysmorphic features. The baby had no dysmorphic features.
the first course. She received four further courses of intensive combination chemotherapy and remained in remission four months later.

CASE 2
A 6 day old boy presented with respiratory and feeding difficulties and drowsiness. Examination showed that he had moderate respiratory distress, hepatomegaly, splenomegaly, conjunctivitis and an erythematous maculopapular facial rash. There were no phenotypic features of Down’s syndrome. He had a total nucleated cell count of \( 53 \times 10^9/\text{l} \) including \( 32 \times 10^9/\text{l} \) blast cells, haemoglobin concentration of 216 g/l and a platelet count of \( 39 \times 10^9/\text{l} \). A bone marrow aspirate revealed 60% blast cells. Marrow karyotype analysis revealed an abnormal chromosome 6 (apparent duplication within the region q25.3-q26) in all cells analysed plus trisomy 21 in 16/24 cells. Phytohaemagglutinin stimulated blood cells only had the abnormal chromosome 6, suggesting that this was a constitutional abnormality and that trisomy 21 was acquired and restricted to the proliferating myeloid clone. Karyotype analysis of skin fibroblasts were not, however, performed. After 2 months of follow up and no treatment, his blood counts returned to normal and a repeat bone marrow aspirate revealed 5% blast cells with no evidence of a residual trisomy 21 clone (even by FISH analysis as for case 1), although the constitutional chromosome 6 abnormality persisted in all cells. Duplication of this region of chromosome 6 is associated with mental and physical developmental anomalies but has not been reported to be associated with abnormalities of haemopoiesis. His parents have a normal karyotype.

Discussion
Down’s syndrome is associated with an increased risk of neonatal leukaemia which is estimated to be 14 to 30 times higher than in neonates with a normal karyotype. In 1964 estimated to be 14 to 30 times higher than in decreased risk of neonatal leukaemia which is Down’s syndrome is associated with an increased risk of transient myeloproliferative disorder (TMD) or transient abnormal myelopoiesis (TAM) was described. The syndrome is characterised by leucocytosis associated with moderate anaemia, thrombocytopenia, and neutropenia. Hepatosplenomegaly is common and occasionally a coagulopathy resembling disseminated intravascular coagulation is present. Bone marrow examination reveals an excess of blast cells often with large nuclei, few nucleoli, and basophilic cytoplasm which is frequently budding. Immunophenotypic analysis indicates that the blast cells are often of megakaryocytic lineage of variable maturity. Confirmation of the diagnosis of TMD occurs at the time of spontaneous regression which can take place weeks or months after presentation. Although TMD is thought of as a benign disorder, one series identified an 11% mortality associated with the initial presentation. Acute leukaemia of the same phenotype develops within two years in 33% of TMD patients with Down’s syndrome.

The monoclonal nature of TMD in patients with Down’s syndrome has been established by analysis of X chromosome inactivation in female patients by restriction fragment length polymorphism analysis of cytosine methylation sites. The blast cells, as well as morphologically and phenotypically normal myeloid and lymphoid cells, display a monoclonal pattern indicating that the clone originates from a multipotent stem cell. Blast cell karyotype is trisomy 21, tetrasomy 21\(^6\) or pentasomy 21,\(^7\) suggesting that an extra chromosome 21 favours proliferation of the abnormal clone. Other additional chromosomal abnormalities have been described including t(X;8) and del(5q).

The cases described in this report confirm that TMD can occur in the absence of constitutional trisomy 21, but in such cases is associated with a leukaemia related trisomy 21 which disappears or regresses with restoration of normal haemopoiesis. Nineteen similar cases have been reported before.\(^4\)\(^6\)\(^8\)\(^9\)\(^11\) These all achieved complete haematological and cytogenetic remission, without evidence of recurrence or evolution to acute leukaemia at periods of follow up varying from six months to six years. This contrasts with the prevalence of acute myeloid leukaemia following TMD in Down’s syndrome patients, variously reported as 25%\(^13\) and 33%.\(^7\)

Unlike in patients with Down’s syndrome, recurrence requiring therapeutic intervention has not yet been reported in patients with TMD and a normal constitutional karyotype, although it has been seen in a case of constitutional trisomy 21 mosaicism without phenotypic features of Down’s syndrome.\(^15\) There was no evidence of mosaicism in the tissues examined in our cases. Our first case is therefore unique in that there was re-emergence of an evolved clone more than two years after its disappearance had been documented by cytomorphology, cytogenetics, and molecular techniques. Presumably the trisomy 21 bearing clone persisted at minimal residual levels below the threshold of our FISH technique. Another, less likely, explanation could be recurrent clonal expansion of a small population of trisomy 21 bearing primitive haemopoietic stem cells which it was necessary to treat because of the acquisition of new mutations at recurrence conferred a more aggressive clonal phenotype.

The cases described emphasise that a patient with features of congenital leukaemia and trisomy 21 restricted to cells of haemopoietic origin may have TMD even in the absence of phenotypic features of Down’s syndrome or constitutional trisomy 21. The outlook for such patients is good but the rare case of subsequent acute leukaemia highlights the importance of close long term follow up.

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