Myeloproliferative disease in children: a demographic study

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SUMMARY Over eight years, eight cases of childhood myeloproliferative disease were recognised in the northern region of England (population 3.1 million). Five were classic chronic myeloid leukaemia (CML) and the three others, forms of myeloproliferative disease. No case of juvenile CML was recognised. With the exception of CML, “adult” type myeloproliferative disease of children is under-represented in the literature and its natural history remains unknown.

Myeloproliferative disease in children is rare. In the early published reports discussion focused on idiopathic myelofibrosis.1 Considerable effort has since been taken to differentiate classic from juvenile chronic myeloid leukaemia (CML)2 and juvenile CML from the myeloproliferative syndrome associated with monosomy 7.3 The association of Epstein-Barr virus with myeloproliferative disorders and monosomy 7 has also been noted.4 More recently a myeloproliferative disorder associated with eosinophilia and a translocation between chromosomes 1 and 5 has been described.5 The other forms of myeloproliferative disease are often dismissed in a single sentence. We report here all children in whom a diagnosis of myeloproliferative disease has been made since 1980 in the northern region of England.

Patients and methods

All cases of myeloproliferative disease diagnosed in children under the age of 15 since 1980 were recorded. The cases came to light either by direct referral to one of the Newcastle hospitals, by notification to the Northern Region Children’s Malignant Disease Registry, and after direct contact with the haematologists of the northern region. All pathological material was reviewed by one of us (MMR). Bone marrow aspirates and trephine biopsy specimens were obtained from all children, but the biopsy specimen from one child with CML was inadequate. Cytogenetic analysis was performed on peripheral blood in this child and on bone marrow samples from all others. The incidence was calculated using the Office of Population Censuses and Surveys (OPCS) mid-year estimates.6

Results

Myeloproliferative disease was diagnosed between 1980 and 1987 in eight children in the northern region (population 3.1 million of which 617 000 are under the age of 15). Five patients had classic CML, an incidence of one case per million children per year. In four, the Philadelphia (Ph) chromosome was detected. In one Ph negative case molecular investigation of marrow cells obtained at diagnosis showed a rearranged bcr gene and the characteristic abnormal abl-related 210-Kd protein (data not shown), confirming “molecular” CML. The clinical features of these cases will not be discussed further. Myeloproliferative disease other than CML was diagnosed in three further children—an incidence of 0.6 per million children per year. Their case histories are described and the presenting haematological and clinical features are shown in the table.

Case reports

CASE 1

This 8 year old boy was noted by his general practitioner to have an enlarged spleen while suffering from chickenpox. A blood count showed thrombocytosis and moderate leucocytosis. A bone marrow aspirate showed myeloid hyperplasia but normal maturation of erythroid and myeloid cells. Megakaryocytes were increased in number. Histological examination of the bone marrow showed 80% cellularity, myeloid hyperplasia, strikingly increased numbers of megakaryocytes and a modest increase in reticulin. Cytogenetic investigations showed a normal karyotype. Three years later his spleen remained enlarged, his platelet count remained over 1000 × 10⁹/l, and many of the platelets were

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abnormally large. Histological analysis of the bone marrow remained unchanged. At the time of writing he remained well and was receiving no treatment.

CASE 2
Splenomegaly was first detected shortly after birth. Increasing splenomegaly subsequently occurred. He was assessed haematologically at 14 years of age, by which time his spleen was massively enlarged and his liver palpable at the edge. There was no biochemical evidence of liver dysfunction, a liver biopsy specimen showed no evidence of hepatitis or cirrhosis, splenic venogram and portal pressure were normal. Peripheral blood did not show a leucoerythroblastic picture, but poikilocytes were present. Bone marrow aspirate showed myeloid hyperplasia but no dyserythropoiesis. Megakaryocytes were increased. Histological examination of the bone marrow showed a normal karyotype. There was no evidence of a storage disease. At the time of writing he remained well at 17 years of age, with a normal white cell and platelet count but haemoglobin fluctuating between 9 and 11 g/dl. There was no haematocrit deficiency. The massive splenomegaly may have been contributing to his mild anaemia.

CASE 3
A 7 month old boy presented with a four week history of abdominal swelling, general malaise, and pallor. Fine purpura and hepatosplenomegaly were present. His peripheral blood smear showed anisocytosis, teardrop poikilocytes, and a leucoerythrobastic picture. The possibility of a non-haemopoietic tumour was considered. An intravenous pyelogram suggested a mass above the left kidney. A bone marrow aspirate showed cellular smears, no dyserythropoiesis or dysmyelopoiesis, but myeloid hyperplasia. No primitive cells were found. Histological examination of the bone marrow showed massive cellular marrow (>90%) with increased numbers of megakaryocytes but no increase in reticulin. Cytogenetic investigations showed a normal karyotype. Urinary vanillyl mandelic acid (VMA) excretion was normal and a laparotomy showed hepatosplenomegaly, but no other mass was found. His thrombocytopenia resolved spontaneously and the platelet count has continued to fluctuate between 100 and 200 × 10⁹/l. The red cell abnormalities persisted, and at the time of writing his liver was palpable 4 cm and spleen 6 cm below the costal margin. A repeat marrow trephine biopsy specimen showed no change. He has received no specific treatment and at 9 years of age remained well.

Discussion
In most patients with karyotypically normal haemopoiesis there are no readily available markers to differentiate reactive from clonal haemopoiesis. Unless a characteristic cytogenetic or molecular defect, as in CML, or an objective abnormality, such as increased red cell mass in polycythaemia, is present the diagnosis of myeloproliferative disease usually rests on a combination of clinical and haematological features, careful histological examination of marrow aspirate, and exclusion of other known causes of the haematological picture.

Thus while there were no difficulties in making a firm diagnosis in the five children with CML, apart from having to resort to molecular investigations in one, it was more difficult in the other three. Case 1, however, clearly had essential thrombocytopenia and it would be unreasonable to argue that the persistent thrombocytosis and marrow expansion, still present three years after initial presentation, were reactive. Cases 2 and 3 had long standing splenomegaly and myeloid hyperplasia. One, case 3, also had the classic peripheral blood appearances of myelofibrosis, though neither had clinically important reticulin in the marrow. While Pelger cells may sometimes be found in the peripheral blood of patients with myeloproliferative disease, they are not always present, and prominent dyserythropoiesis is usually a feature of myelodysplastic rather than myeloproliferative disease. Up to one third of patients with agnogenic myeloid metaplasia have only minimal or no increase in reticulin in their marrow.

The study dates from 1980: before that date no case of myeloproliferative disease other than CML had been recognised in a child in the northern region. These cases represent all subsequently recognised myeloproliferative disorders of children in our region. It is possible that some await recognition and others may have died unrecognised. It is unlikely that a recognisable myeloproliferative disorder is hidden behind a diagnosis of leukaemia, as one of us (MMR)
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has reviewed the pathological material or case records of all cases of leukaemia occurring in patients under the age of 25 in the northern region since 1968, as part of the recommendations of the committee chaired by Sir Douglas Black, which has been investigating the incidence of leukaemia in our region.

Little is known of the incidence of myeloproliferative diseases in a defined population. The Manchester registry recorded an incidence of 0.5 cases and the Greater Delaware Valley registry 0.86 cases of CML per million white children per year. The present study suggests an annual incidence of about one case of classic CML per million children and a somewhat lower rate for the other heterogeneous group of diseases. In the 15 years from 1968 to 1982 only four cases of CML were recorded by the Northern Region Children’s Malignant Disease Registry (0.45 cases/106 children/year), none of which is included in the present series. The apparent increase in incidence may be spurious. Nevertheless, classic CML is the single most common myeloproliferative disease in childhood. If the incidence of these diseases is similar elsewhere in the United Kingdom, well over 100 cases of childhood myeloproliferative disease have occurred in the country since 1980. It is striking that no case of juvenile CML has ever been recognised in our region, despite its well described clinical and laboratory features. This contrasts sharply with the experience of Hardisty et al2 and their review of the literature.

The behaviour of myeloproliferative diseases in children and young people remains unclear, with the exception of classic and juvenile CML. For example, does essential thrombocythaemia behave in the same way as in elderly patients? The single biggest series of young patients with this disorder comes from the Mayo Clinic,11 the youngest of which was aged 15. The stability and lack of clinical problems in the Mayo Clinic series suggests a course of masterly inaction, at least initially, but this recommendation is based on small numbers. Although death has usually rapidly followed diagnosis of myelofibrosis in children, this is not always the case.12 The theoretical risk of transformation to acute leukaemia in children with “adult” types of myeloproliferative disease seems to be less than in CML13; the three children without CML described here have been affected for at least three, eight, and 17 years without any sign of transformation.

In summary, although myeloproliferative diseases are rare in childhood, classic CML is by far the most common; other “adult” diseases do occur; and the specific childhood diseases of juvenile CML and monosomy 7 myeloproliferation are very rare. We suspect that haematologists and pathologists are reluctant to make diagnoses of “adult” types of myeloproliferative disease other than CML and that juvenile CML and other clinically similar disorders have been over-represented in the literature because of their unique features. Registries of malignant diseases of children will often fail to “capture” these diseases as the term leukaemia is not always attached to the diagnosis. Unless myeloproliferative disorders are collected by registries in the same systematic way as leukaemia and other cancers their natural history will remain obscure, and haematologists and paediatricians will have little information on which to base their therapeutic advice.

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References


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