Malignant infantile osteopetrosis presenting with neonatal hypocalcaemia

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Abstract
Presentation characteristics were reviewed in 14 children from 12 families with malignant infantile osteopetrosis seen at two large referral centres for bone marrow transplantation. Children from six of these families presented initially with symptoms of hypocalcaemia. These comprised early or late neonatal convulsions in six cases (corrected serum calcium < 1.5 mmol/l), and vomiting and irritability (serum calcium 1.68 mmol/l) in another. One other related child had severe and persistent jittering episodes almost certainly attributable to hypocalcaemia. In seven of eight cases, these symptoms developed during the first 14 days of life. Although occasionally reported previously, malignant infantile osteopetrosis remains essentially unrecognised as a cause of neonatal hypocalcaemia, often resulting in diagnostic confusion and delay. This is important in the context of curative haemopoietic stem cell transplantation where preservation of sight may depend on early intervention. (Arch Dis Child Fetal Neonatal Ed 2000;83:F21–F23)

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Malignant infantile osteopetrosis (MIOP) is a rare inherited bone disease characterised by reduced or dysregulated activity of osteoclasts, resulting in generalised osteosclerosis (fig 1A). Overgrowth of cranial nerve foramina and the foramen magnum results in nerve compression—progressively affecting the optic, facial, oculomotor, and auditory nerves—and hydrocephalus. Other problems include irritability, snuffling because of disruption of nasal architecture, hepatosplenomegaly (the result of extramedullary haemoipoiesis), and eventually hypersplenism. Failure to thrive and increased infections because of an unexplained defect in neutrophil superoxide function are also characteristic.

In the natural course of the disease, 70% of children die within the first six years. Most of the remainder have a very poor quality of life and die by the age of 10. With the exception of a very small proportion of cases characterised by primary neurodegenerative disease, bone marrow transplantation (BMT) is curative, as osteoclasts are derived from bone marrow precursors. About two thirds of children are cured by BMT from matched sibling donors. Historically, the use of alternative (non-sibling) donors has yielded very poor results because of a combination of high rejection rates and other transplant complications. However, there are now encouraging signs that the use of high dose, highly T lymphocyte depleted, parental marrow or peripheral blood stem cell transplants can improve outcome for those lacking a family donor (W Friedrich and T Klingebiel, personal communication).

The commonest presentations result from optic nerve compression in the first year of life. This may result in failure to establish fixation and nystagmus, or slightly later development of strabismus. Unfortunately, one of the most disappointing aspects of transplantation is the rarity of reversal of these symptoms. Therefore it is crucial to identify affected children at the earliest possible stage and to perform BMT with relative urgency. This is particularly true now that suitable donors (either sibling or haploidentical) can be found for all patients with only minimal delay.

Figure 1 Representative chest radiographs before and after successful unrelated donor bone marrow transplantation. At diagnosis (A) there is generalised osteosclerosis. There is appreciable improvement in both bone density and modelling by nine months after the transplant (B).
The presence of a previous child with MIOP in this family had led to attempted antenatal diagnosis by third trimester radiography, but this was unremarkable. Hypocalcaemia prompted further radiography and hence diagnosis. Including the child with jittering episodes, eight of 14 children therefore had definite or presumed symptomatic hypocalcaemia during the first month of life. The diagnosis of MIOP was quickly established or already known in five of these eight cases. However, in the remaining children, diagnosis was delayed by 50, 68, and 200 days, by which time all three had developed visual failure.

Mean age at presentation for children with proven hypocalcaemia was 12.4 days. This contrasted with an average of 6.6 months for children presenting with more widely recognised symptoms—for example, nystagmus, hepatosplenomegaly, macrocephaly, and cytopenias.

### BONE MARROW TRANSPLANTATION

Ten children underwent BMT at the Bristol Royal Hospital for Sick Children, Newcastle General Hospital, or Hospital for Sick Children, Great Ormond Street; in seven the bone marrow was from unrelated donors, in one it was from a haploidentical donor, in one from a matched sibling, and another from a one anti-
appearances of osteopetrosis are characteristic deformity of the distal tibia. The metaphyses are within a bone appearance. Osteosclerosis and a “bone limb showing generalised Figure 2 Plain radiograph of right lower limb showing generalised osteosclerosis and a “bone within a bone” appearance. The metaphyses are irregular and there is varus deformity of the distal tibia and proximal femur. These are characteristic appearances of osteopetrosis and secondary rickets.

In the neonatal period, children are functionally relatively hypoparathyroidism. In this setting, normal osteoblast function, unbalanced by compensatory osteoclast function, pushes some osteopetrotic children into hypocalcaemia. The impact of this relative imprisonment of calcium stores is shown most notably by the development of early rickets in some children (fig 2). This has been elegantly termed a “paradox of plenty”. Our series, in conjunction with the observations of Avery et al and Gerritsen et al, show that this window during which MIOP presents with hypocalcaemia is very narrow—all cases have occurred within the first 43 days, most within the first two weeks.

It could be argued that the high incidence of hypocalcaemic presentation seen in this series reflects a common ancestry. However, the geographical distribution and family histories lend no support to this hypothesis. Clearly, genetic analysis would help to exclude such a founder defect. However, the quest for gene defects responsible for human osteopetrosis is currently proving elusive (in contrast with animal models in which a variety of gene defects—for example, CSF-1, c-src—have been established). This may reflect the presence of a number of separate defects all resulting in osteoclast dysfunction.

The importance of early diagnosis and treatment cannot be stressed too highly. Both of the patients who are alive in this series were transplanted by 6 months of age and retain perfect vision. Furthermore, although established optic atrophy is irreversible, there are well documented cases of visual improvement after transplant. These are presumably children in whom occlusion of the vascular supply to the optic nerve is compromised by bony overgrowth but not yet critically occluded.

With the advent of increasingly safe and refined techniques of haploidentical stem cell transplantation, which for the first time brings the possible rapid treatment for most children, early diagnosis is paramount. The absence of MIOP from the differential diagnosis of neonatal hypocalcaemia contributed in this series to a diagnostic delay of up to six months. This oversight must be corrected if this is to be avoided and the chances of transplantation to preserve visual and other cranial nerve function maximised. We therefore recommend that a plain radiograph of the knee or wrist be included in the routine investigation of children with “idiopathic” neonatal hypocalcaemia.

Figure 2

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