SURVIVAL IN MALIGNANT OSTEOPTROSIS: CASE REPORT

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ABSTRACT

Introduction

Malignant infantile osteopetrosis is a rare autosomal recessive congenital disorder of bone resorption. It has a high morbidity and mortality and the sole curative treatment is a bone marrow transplant. We present a case of a child with severe infantile osteopetrosis who despite a failed bone marrow transplant as an infant has reached the age of twelve years.

Case presentation

We present the case of a child with infantile osteopetrosis to illustrate the increasing survival of children this condition. We describe the presentation, clinical course and associated complications of this child’s illness.

Conclusion

Children with severe chronic conditions are living to a greater age. There is limited information relating to the long term morbidity and mortality of children with infantile osteopetrosis.

INTRODUCTION

Malignant infantile osteopetrosis is a rare autosomal recessive congenital disorder of bone resorption. Osteoclasts fail to resorb bone, causing abnormal bone marrow cavity formation and impaired bone remodelling. This results in bone marrow failure, narrowing of cranial nerve foramina with optic nerve compression and an increased tendency to fracture.

Mortality is high in this condition. Haematological dysfunction is a prognostic indicator of poor outcome\(^1,2\) with children with severe disease (haematological dysfunction at less than three months of age and visual
impairment) dying in infancy. There is little information available regarding the long term prognosis of children who survive infancy with this disorder. Probability to survival to the age of six years has been reported as 30% in one case series of thirty-three patients. In this series, one patient was noted as surviving to fifteen at the time of publication but had had no evidence of severe haematological impairment.

Bone marrow transplant is the only curative option with haplo-identical bone marrow transplant having a reported disease free survival rate of 79% at five years.

The patient in our case has shown all of the attendant complications of infantile osteopetrosis, including presentation in infancy with haematological dysfunction, but has reached the age of twelve years despite a failed bone marrow transplant, and is currently attending school.

**CASE REPORT**

The patient is the second child of healthy consanguineous Pakistani parents. He presented to hospital at five weeks of age with suspected sepsis. He was treated for a urinary tract infection and referred to King’s College Hospital for further investigation of a mild conjugated hyperbilirubinaemia and thrombocytopenia.

On further assessment he was found to have evidence of craniofacial dysmorphism and a persisting thrombocytopenia. Chest X-ray and pelvic X-ray revealed hyper-dense bone. Bone marrow aspirate showed abnormal hyperplastic leukaemoid marrow appearance. These findings are compatible with a diagnosis of osteopetrosis.

He initially had a normal CT scan of the head, MMR of the brain and optic nerves and normal ERGs with slightly small and late VEPs. Serial assessments over the next two months revealed progression of the disease: He had poor visual fixation with deteriorating VEPs and cranial imaging suggestive of raised intracranial pressure.

Bone marrow transplant was recommended in view of the aggressive nature of his disease. The patient had a haploidentical PBSCT and BMT. His initial course was unremarkable but he unfortunately proceeded to secondary graft rejection after three months. No further donor was found and it was felt a secondary graft would have a minimal chance of success. The patient’s genetic diagnosis was confirmed at the age of six years as a mutation in the gene encoding the vacuolar proton pump.

The patient has been managed supportively. He has had aggressive nutritional support with gastrostomy feeds, physiotherapy, speech and language therapy, ophthalmology and audiology input. He has required regular immunoglobulin, packed cell and platelet infusions. The patient has
suffered complications of the disease including extreme short stature with global developmental delay and severe visual impairment.

At the age of two he required cranial vault expansion due to raised intracranial pressure as a result of his craniosynostosis. He had a complicated post-operative course with evidence of hypoxic insult to the brain. He has had multiple pathological fractures of the humerus and femur.

X-ray of right humerus. This shows a pathological fracture in a dense bone lacking a normal architecture. Callus formation is florid but does not result in effective bony union.

He presented with bleeding from both ears at the age of nine. CT did not show evidence of a basal skull fracture but did show recent parietal contusion. The patient was advised to wear a protective helmet at this point (although
since then he has never worn it!). The patient developed septic arthritis of the right hip at the age of twelve and received a six-week course of intravenous antibiotics following drainage of the joint. This patient has survived to the age of twelve despite a failed bone marrow transplant at a young age. He attends a special needs school and has had only one hospital in-patient stay in the last year.

DISCUSSION

This patient is testament to the improving survival of children with conditions previously considered to cause death in infancy. There is little information currently available regarding the long term prognosis of children with infantile osteopetrosis. Why are children surviving to an older age with conditions with a high morbidity and mortality?

Chronic ill health is more effectively managed with a holistic multi-disciplinary approach. Physical and occupational therapy can help children optimise their developmental potential. Nutritional and medical input can maximise growth and manage the inevitable complications of the illness.

Supplementary treatments such as immunoglobulin and blood products are more readily available. This supportive therapy can reduce the risk of infections such as pneumonia and septicaemia which are a common cause of death. Children may become transfusion dependent whilst waiting for a BMT or in the event of failure. Some children have been noted to regain haemopoietic competence. Day care paediatric units allow supportive therapy and medical review to be given in an easily accessible fashion. One can speculate on the role of improved nutrition, vaccination against pneumococci and influenza too: these presumably play an important part in protecting such children against the more common infections.

Human genetics of infantile osteopetrosis have been described in the last decade. The most common defect affecting 50 – 60% of children is a homozygous or compound heterozygous mutation in the gene coding for the alpha 3 component of the osteoclast specific proton pump subunit involved in acidification at the bony interface (TCIRG1, or T-cell immune regulator-1). This is part of an ATPase, a large multi-unit complex. Other ATPase vacuolar complexes are involved in urinary acidification, sperm maturation and renal tubular acidosis. This defect accounts for the severe form of the disease presenting in infancy: one mutation is found at high frequency in a population in the Chuvash Republic of Russia. Inhibition of the vacuolar ATPase might be of value in for instance, managing osteolytic processes, and a better understanding of gene modifiers in this condition would be of great use. It would also be useful to further assess phenotypic variation from this
known genetic defect to gauge differences in clinical picture and prognosis between patients.

There is little information available on which we can draw to plan for this adolescent’s future. Current treatments are limited to being supportive, or directed at iatrogenic problems such as iron accumulation following transplantation.

CONCLUSION

This case illustrates improved survival in a child with infantile osteopetrosis. He survives despite a failed bone marrow transplant and multiple complications of the disorder. This may be in part due to the improved multi-disciplinary health care offered to support his development, the supportive therapy provided and management of his complications. There is little information available regarding long-term prognosis and health care requirements in children with this disorder. Data from a case series would be the first step in optimising care of similar patients as they enter adulthood. This type of patient certainly offers many opportunities too to ask important questions of the underlying biology of his condition.

REFERENCES