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Successful use of enzyme replacement therapy in infantile hypophosphatasia

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Letter to Editor – new case notes/report

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Dear Editor,

We wish to report the first successful Australian use of enzyme replacement therapy (ERT; asfotase alfa) in a patient with infantile hypophosphatasia. Hypophosphatasia is a metabolic bone disease with a wide spectrum of clinical presentations. The primary defect is a loss-of-function mutation(s) in the gene encoding tissue non-specific alkaline phosphatase (TNSALP), leading to deficient bone and tooth mineralisation and an imbalance in calcium and phosphate metabolism. The clinical manifestations vary and may include skeletal deformity, recurrent poorly healing fractures, chronic debilitating pain/weakness, tooth loss, reduced physical function, seizures, respiratory failure and/or death.

Previous therapy for hypophosphatasia has been supportive only. We report a 6-year old girl, presenting at 20 weeks gestation with bilateral femoral bowing, with an antenatal diagnosis of osteogenesis imperfecta. At birth, she was found to have an alkaline phosphatase (ALP) level of 31 IU/L (Reference Interval: 100-350 IU/L age- and gender-adjusted), elevated urinary phosphoethanolamine, consistent radiological features and was homozygous for a known TNSALP gene mutation. She had persistent hypercalcaemia, failure to thrive, and at 3 months developed severe bronchiolitis requiring intubation and ventilation for 2 weeks. Following reports of dramatic improvements in mineralization for this previously untreatable disease in animal models (1) and humans (2), asfotase alfa was commenced at 4 months (2mg/kg subcutaneously (SC) three times per week). Biochemical disturbances resolved quickly and a further episode of bronchiolitis at 5.5 months was managed with nasal prong oxygen only; no further invasive ventilation has been required. She showed marked improvement of mineralization on serial radiographs, with straightening of her femori. Her linear growth has been steady. She has been making excellent developmental progress, with no ongoing issues. She had persistent craniosynostosis which required cranial advancement surgery at aged 3, which was uncomplicated with resultant normal cranial shape. Calcification was noted on radiography at injection site but nothing was palpable clinically – this had largely resolved on follow up radiograph one year later with increased injection site rotation and switching to 1mg/kg SC, 6 times per week. Nephrocalcinosis had been noted on ultrasound prior to commencement of ERT, but had resolved by age 4. This successful outcome is reflected in the clinical trials showing improved survival and respiratory outcomes (3), with no significant side effects reported. We conclude that ERT should be strongly considered for this previously untreatable condition.

Acknowledgements – we thank the family for allowing us to publish their story, and to Alexion for ongoing compassionate supply of ERT for this patient.

Figure 1 – comparison of left femur, from (a) 2 months of age, prior to use of ERT and (b) at age 5 yrs 10 months, demonstrating significant reduction in femoral bowing

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Figure 1 JPCH case report.tif