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MEETING REPORT

Osteopetrosis: pathogenesis, management and future directions for research

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Meeting Report from the Osteopetrosis Workshop, Philadelphia, PA, USA, 21 October 2013.

Clinicians managing patients with osteopetrosis face a daunting challenge. Although advances in molecular genetics have led to an improved understanding of the cellular basis of the disease, clinical management remains frustrating because of the marked phenotypic variability of this condition and limited treatment options. Effective care for patients with osteopetrosis requires the coordinated efforts of a multidisciplinary team that includes endocrinologists, geneticists, hematologists, orthopedic surgeons, ophthalmologists and allied health providers. The goal of this Workshop was to convene thought leaders in the field to review the current state of the science and clinical management of osteopetrosis and to formulate a strategy to address the many unanswered research questions that confound this debilitating disease.

Dr Michael Whyte (Shriners Hospital for Children and Washington University School of Medicine, St Louis, MO, USA) presented a comprehensive overview of the clinical features of osteopetrosis. Although osteopetrosis is a heterogeneous disorder encompassing different molecular lesions and a range of clinical features, all forms share a pathogenic basis in reduced osteoclastic activity that results in excessive bone mass and a paradoxical increase in bone fragility. The clinical severity and natural history of osteopetrosis are variable but can be predicated on the basis of several key features: (1) pattern of inheritance, autosomal recessive (ARO) versus autosomal dominant (ADO); (2) molecular genotype, which gene is involved; (3) clinical phenotype, with ARO tending to present during infancy with severe disease and ADO having a variable phenotype; and (4) functional defect, osteoclast-rich (intrinsic defects in osteoclast function) or osteoclast-poor (defects in osteoclastogenesis). A molecular diagnosis is now possible for most patients; however, variable expressivity and incomplete penetrance reduce the overall accuracy of the predicted phenotype. All forms of osteopetrosis are uncommon, with estimated incidences in the United States of 1 in 500 000 and 1 in 100 000 for ARO and ADO, respectively. The major clinical morbidities are consequences of skeletal overgrowth and include fragility fractures, visual and hearing loss, choanal atresia (narrowing of nasal airway) and bone marrow failure. ARO caused by mutations in *OSTM1* or *CLCN7* may be accompanied by seizures and neurodegeneration. Osteoclast failure due to defects in *TCIRG1* is often associated with hypocalcemia and impaired mineralization (osteopetrorickets). Characteristic radiographic findings include 'Erlenmeyer flask' deformity of the femurs, a 'bone in bone' appearance and diffuse sclerosis.

Dr Laura Tosi (Children's National Medical Center, Washington, DC, USA) focused on the differential diagnosis of high bone density, and emphasized the importance of a thorough history, physical exam and careful review of skeletal radiographs. Other inherited skeletal dysplasias such as pyknodysostosis and progressive diaphyseal dysplasia should be excluded, as well as acquired conditions such as renal osteodystrophy, hypervitaminosis A and D, fluorosis and lead poisoning. Variable increases in bone density can also occur with infections such as hepatitis C.[1] Key radiographic findings that can differentiate osteopetrosis from other conditions include the lack of a visible marrow cavity in severe disease and generalized skeletal involvement. Transient hypersclerosis of infancy is a poorly understood condition that can be distinguished from ARO by molecular genetics and resolution with age.

Dr Michael Econs (Indiana University, Indianapolis, IN, USA) reviewed the genetics of osteopetrosis in mice and humans. Many spontaneous gene mutations have been identified in mice that impair development or function of osteoclasts. Molecular defects can occur in the osteoclast lineage cells or in the mesenchymal cells that form and maintain the microenvironment required for osteoclast function. In many cases, a corresponding mutation in the human homolog has not yet been determined.

An understanding of each patient's molecular defect enables optimized clinical management. Hematopoietic stem cell transplant (HSCT) can be curative in patients with osteoclast-rich osteopetrosis and osteoclast-poor osteopetrosis due to receptor activator of nuclear factor-kappa B (RANK) mutations, but will fail in osteoclast-poor osteopetrosis due to RANK ligand

(RANKL) mutations. In addition, HSCT will not reverse or prevent the neurodegeneration seen in some forms of ARO. Defects in the endosomal and lysosomal trafficking pathways disrupt ruffled border formation and underlie the resorption defect in osteoclast-rich osteopetrosis. Disease-causing mutations have been described in *TCIRG1* (coding for α3-subunit of proton pump), *CLCN7* (chloride channel), *OSTM1* (preventing chloride channel degradation), *PLEKHM1* (lysosomal/endosomal trafficking) and *SNX10* (function unclear). Mutations in *TNFRSF11A* (RANK) and *TNFSF11* (RANKL) inhibit osteoclastogenesis and underlie osteoclast-poor osteopetrosis. *CA2* mutations result in carbonic anhydrase isoenzyme II deficiency and lead to a distinct form of osteopetrosis associated with renal tubular acidosis and cerebral calcification. This enzyme catalyzes the formation of carbonic acid, an essential step in the acidification of the resorption lacunae. Activating mutations in *LRP5* are associated with a benign condition previously termed ADO type 1 (now more appropriately termed high bone mass). Heterozygous mutations in *CLCN7* cause the more severe and highly variable disorder ADO type 2. Additional molecular defects and genetic modifiers likely exist. Owing to the large number of different genes involved, analyses of gene panels or whole-exome sequencing (WES) provide the most expedient approach to molecular diagnosis. Whole-genome sequencing will likely uncover regulatory mutations missed by WES.

Dr Dolores Shoback (University of California, San Francisco, CA, USA) reviewed the cellular and histological manifestations of osteopetrosis. Biopsy studies in osteoclast-rich forms reveal osteoclasts that are bigger, more numerous and longer-lived, likely due to the absence of pro-apoptotic compounds released during resorption. Osteoclast persistence and elevated parathyroid hormone levels may stimulate further bone formation. Circulating levels of tartrate-resistant acid phosphatase (TRAP) and creatine kinase-BB (CK-BB) are elevated in osteoclast-rich osteopetrosis. Osteoclast-poor osteopetrosis is distinguished by an absence of osteoclasts and a loss of TRAP staining on biopsy.

Dr Edwin Horwitz (Ohio State University, Columbus, OH, USA) presented 20 years of experience with HSCT for osteopetrosis. HSCT can be curative for osteoclast-rich ARO[2] and should be performed as soon as possible, as outcomes worsen with age. HSCT is generally contraindicated in patients with neurodegeneration.[3] HLA-matched sibling donors provide the best outcomes; however, matched-related, matched-unrelated and matched umbilical cord blood can all be used. A benefit of matched sibling or umbilical cord blood is the shortened time to transplant. Pre-transplant evaluation should include genotyping, brain MRI and assessments by neurology, ophthalmology and otolaryngology. Complications of HSCT include graft failure (and subsequent aplasia), graft versus host disease, pulmonary hypertension, hepatic veno-occlusive disease (from the transplant conditioning regimen) and hypercalcemia[4] (from resorption of excess bone). Cure rates can approach 80% with matched sibling donors. Benefits of transplant in older children with intermediate disease and *TNFRSF11A* mutations are less evident. Interferon gamma can be used as a therapeutic bridge to transplant and may be useful in other situations.[5,6]

Dr Linda DiMeglio (Indiana University) and Dr Michael Levine (CHOP and University of Pennsylvania, Philadelphia, PA, USA) used case reports to highlight clinical dilemmas. Uncertainty surrounds the surveillance and management of visual loss. Orbital CT, MRI and evoked visual potentials were discussed as screening modalities. The majority agreed that if optic nerve compression was seen on one side, the contralateral optic canal should also be unroofed. Complex cases of individuals with osteopetrosis were presented to generate discussion and illustrate the lack of consensus regarding the management of individuals with less severe disease.

Workshop attendees then divided into smaller working groups to develop future strategies for addressing three key areas in the management of osteopetrosis: (1) improving recognition of disease through clinician education, (2) areas for future research and (3) development of clinical practice guidelines. Recommendations are summarized below.

(1) Improving recognition of disease:

- Publication of osteopetrosis-related review articles
- Inclusion of osteopetrosis-related questions in board review materials

(2) Areas for future research:

- Genotyping of all affected individuals
- Observational studies to more clearly delineate the natural history of osteopetrosis and to identify clinically evaluable risk factors (baseline functional status, skeletal and brain imaging, skeletal biomarkers, circulating osteoclast precursors, bone densitometry)
- Human clinical trials to evaluate risks and benefits of innovative treatments including calcitriol, interferon gamma, parathyroid hormone and gene therapy
- Basic research studies focused on *in vitro* studies of osteoclast activity and *in vivo* mouse models

(3) Development of clinical practice guidelines:

- Rarity and variable expressivity of osteopetrosis make the prospect of developing practice guidelines difficult, if not impossible, at present
- Recent reviews of the European experience with osteopetrosis[7–9] provide information to clinicians caring for affected patients.

Finally, all groups agreed that a patient registry would be helpful. Ideally, this registry would be developed as a research protocol so that the data collected would be HIPAA compliant and suitable for epidemiologic-, natural history- and outcome-based research. The high cost and regulatory burdens of creating this type of registry were raised as hurdles; partnerships between academic institutions, patient advocacy groups and the pharmaceutical industry could be explored to defray the cost. Collaborations with the existing Rare Diseases Clinical Research Network should be explored. There is a clear need to promote awareness, research and clinical care in osteopetrosis. It is hoped that this working group can help coordinate these activities.

Conflict of Interest

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References

1. Gregson CL, Hardcastle SA, Cooper C, Tobias JH. Friend or foe: high bone mineral density on routine bone density scanning, a review of causes and management. *Rheumatology (Oxford)* 2013;**52**:968–985.
2. Driessen GJ, Gerritsen EJ, Fischer A, Fasth A, Hop WC, Veys P *et al.* Long-term outcome of haematopoietic stem cell transplantation in autosomal recessive osteopetrosis: an EBMT report. *Bone Marrow Transplant* 2003;**32**:657–663.
3. Steward CG. Hematopoietic stem cell transplantation for osteopetrosis. *Pediatr Clin North Am* 2010;**57**:171–180.
4. Martinez C, Polgreen LE, DeFor TE, Kivisto T, Petryk A, Tolar J *et al.* Characterization and management of hypercalcemia following transplantation for osteopetrosis. *Bone Marrow Transplant* 2010;**45**:939–944.
5. Key Jr. LL , Ries WL, Rodriguiz RM, Hatcher HC. Recombinant human interferon gamma therapy for osteopetrosis. *J Pediatr* 1992;**121**:119–124.
6. Key Jr. LL , Rodriguiz RM, Willi SM, Wright NM, Hatcher HC, Eyre DR *et al.* Long-term treatment of osteopetrosis with recombinant human interferon gamma. *New Engl J Med* 1995;**332**:1594–1599.
7. Schulz AS, Moshus D, Steward CG, Villa A. Osteopetrosis—Consensus Guidelines of the ESID and the EBMT Working Party. [Updated 21 February 2011; cited 22 January 2014]. Available from http://masonshafferfoundation.org/wp-content/uploads/2012/06/Osteopetrosis-Guidelines-2011.pdf.
8. Sobacchi C, Schulz A, Coxon FP, Villa A, Helfrich MH. Osteopetrosis: genetics, treatment and new insights into osteoclast function. *Nat Rev Endocrinol* 2013;**9**: 522–536.
9. Askmyr MK, Fasth A, Richter J. Towards a better understanding and new therapeutics of osteopetrosis. *Br J Haematol* 2008;**140**:597–609.