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Autosomal Dominant Osteopetrosis

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Abstract

Autosomal dominant osteopetrosis (ADO) is the most common form of osteopetrosis. ADO is characterized by generalized osteosclerosis along with characteristic radiographic features such as a “bone-in-bone” appearance of long bones and sclerosis of the superior and inferior vertebral body endplates. Generalized osteosclerosis in ADO typically results from abnormalities in osteoclast function, due most commonly to mutations in the chloride channel 7 (CLCN7) gene. A variety of debilitating complications can occur over time due to bone fragility, impingement of cranial nerves, encroachment of osteopetrotic bone in the marrow space, and poor bone vascularity. There is a wide spectrum of disease phenotype, even within the same family. Currently, there is no disease specific treatment for ADO, so clinical care focuses on monitoring for disease complications and symptomatic treatment. This review describes the history of ADO, the wide disease phenotype, and potential new therapies.

Keywords

osteopetrosis / epidemiology; osteopetrosis / genetics; osteopetrosis / pathology; osteopetrosis / history; osteopetrosis / therapy; genes / dominant

History

Autosomal dominant osteopetrosis (ADO) is the most common form of osteopetrosis, with an incidence of approximately 1:20,000.[1] The first clinical report of osteopetrosis was in 1904 by German radiologist Dr. Albers-Schonberg[2] where he described the characteristic radiographic findings of osteopetrosis. Early on, ADO was thought to include

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two phenotypes, ADO1 and ADO2. ADO1 was characterized by generalized osteosclerosis, most pronounced at the cranial vault, with no increased risk of fracture or osteomyelitis. In contrast, the osteosclerosis of ADO2 is most pronounced in the spine and long bones and is characterized by an increased risk of fracture and osteomyelitis, particularly of the mandible.

Over time, genetic testing has allowed for more precise characterization of ADO. Once the causative genes were identified,[3,4] it became clear that ADO1 and ADO2 were mechanistically two distinct diseases, driven by abnormalities in the function of different bone cell types. The generalized osteosclerosis in ADO1 results from activating mutations in the LRP5 gene causing increased osteoblastic bone formation (OMIM #607634). Generalized osteosclerosis due primarily to increased osteoblast function such as that caused by LRP5 mutations would then be separated into an independent group of osteosclerotic, osteoblast-driven, disorders, which would also include recessive disorders such as sclerosteosis. In contrast, the osteopetrosis in ADO2 results from mutations in genes responsible for osteoclast differentiation and/or function, most commonly CLCN7 (OMIM #166600). Thus, we believe more accurate naming is to drop the number and use ADO to indicate osteopetrotic diseases resulting from primary osteoclast dysfunction with autosomal dominant inheritance. Mutations in other genes impairing osteoclast function also cause an osteopetrotic phenotype, usually in a recessive manner. The increase in bone mass in osteopetrosis is primarily due to lower resorption and consequent accumulation of mineral over time.

Clinical Overview

The clinical diagnosis of ADO is made by identifying generalized osteosclerosis and pathognomonic radiographic features identifiable on standard radiographs. Therefore, a skeletal survey is all that is required to make the diagnosis of osteopetrosis. However, genetic testing is recommended to determine the type of osteopetrosis and distinguish it from other osteoslerotic diseases.[5] The age of onset of ADO is typically in young adulthood but can present in childhood as well. Disease severity varies significantly even within families due to incomplete penetrance and variable expressivity.[6]

The autosomal dominant form of osteopetrosis has historically been called “benign autosomal dominant osteopetrosis. However due to the significant complications of the disease, either in childhood or as adults, we recommend dropping the use of the term “benign”, as being inaccurate and misleading. A variety of debilitating complications occur over time due features such as impingement of cranial nerves, encroachment of osteopetrotic bone in the marrow space, and poor bone vascularity. Complications of ADO are summarized in Table 1. The most common complications are fractures, pain, and osteonecrosis/osteomyelitis, particularly of the mandible. Vision loss is a serious complication occurring in 19% of ADO (typically presenting in childhood, with onset in adulthood being exceedingly rare).[7–9] Bone marrow failure and transfusion dependence can happen in severely affected individuals[7].

Fractures were the most common complication in two large ADO case series.[7,8] Fractures occur in approximately 53% of children and 98% of adults with ADO with fractures of

the pelvis/hip/femur and arms are most common.[7] Impaired bone vascularity can result in poor healing and infection[8]. Surgical intervention is difficult and there is an increased risk of implant failure, refracture, defective remodeling, and osteomyelitis compared to patients without osteopetrosis. Osteomyelitis in ADO is often quite difficult to treat, and all too often requires multiple surgical interventions and chronic antibiotic treatment.

Radiology

Characteristic radiographic features of ADO are often most obvious in the spine and long bones of the arms and legs. Besides the generalized osteosclerosis, there can be a distinctive “bone-in-bone” appearance (Fig. 1A), also called “endobones”. Vertebrae range from mild sclerosis of the superior and inferior endplates, to an anvil appearance, then to uniformly dense (Fig. 1B). “Club-shaped” flaring of the metaphysis of long bones with cortical thinning (“Erlenmeyer flask bone deformity”, Fig. 1C) and transverse metaphyseal lucent bands reflect a failure of metaphyseal remodeling, but are not exclusive to osteopetrosis [10]. Skull changes include basilar thickening as well as poor sinus development, however the skull thickening is generally less severe than in other osteosclerotic diseases.

Treatment

Currently, there is no disease specific treatment for ADO. Treatment is only symptomatic. Various medical approaches have been tested, such as high dose calcitriol (mainly in ARO) or interferon gamma-1b, however none have delivered any significant improvement in disease.[11–15] In fact, studies in ADO mice with CLCN7 mutations have shown that high dose calcitriol might be detrimental and actually increase bone mass.[16]

Hematopoietic cell transplantation (HCT) is standard of care for infants with most forms of autosomal recessive osteopetrosis. Alam et at[17] showed improvement, but not complete resolution, in bone parameters in our murine ADO model in 3- and 9-month-old mice. However, there are limited data regarding HCT in patients with ADO. Stepensky et al[18] reported on 7 patients with attenuated autosomal recessive osteopetrosis (none with heterozygous CLCN7 mutations) who were transplanted at a median age of 15 years (range 5–30 years); 6 of 7 survived 1–9 years post HCT at last follow-up, with 100% donor chimerism. Another report of HCT treatment of osteopetrosis by Zhu et al[19] included 4 patients with heterozygous mutations in CLCN7 all of whom were alive at 60 months post HCT follow-up. The specific age at HCT of this subset of ADO patients was not given, but the oldest age of HCT in the entire cohort reported was less than 9 years. These two reports include a small number of patients, treated with HCT at a relatively young age for patients with ADO, and at centers with extensive experience treating patients with osteopetrosis. Unfortunately, all we have to direct therapy of older patients with ADO is anecdotal evidence suggesting increased fatality and risk of HCT-related complications (our unpublished observations). Thus, we believe that sufficient concern exists at this time to not routinely recommend HCT for patients with ADO. The decision to move forward with HCT in ADO should be done on a case-by-case basis and with the understanding that mortality appears to be very high in older patients.

Interest in interferon gamma-1b (IFN-γ1b) for treatment of ADO stems from studies conducted by Dr. Lyndon Key[20,21] in the early 1990s that led to the FDA approval of IFN-γ1b for the treatment of "severe infantile osteopetrosis". Insufficient numbers of individuals with non-infantile ADO were included in the studies to determine if this treatment was effective in ADO. Interferon gamma is a naturally occurring cytokine that has been shown to have anti-microbial and anti-viral immunomodulatory effects,[22] and is a potent stimulator of superoxide anion production which in turn promotes the formation and activation of osteoclasts.[23] IFN-γ1b has been shown to increase osteoclast size, tartrate acid phosphatase staining, and superoxide anion production in cell cultures from patients with osteopetrosis.[24] In addition, IFN-γ1b results in increased marrow space in osteopetrotic mice.[25] In Key's studies, IFN-γ1b treatment resulted in decreased trabecular bone area measured by bone biopsy, decrease in lumbar spine bone mineral density, and improvement in hemoglobin concentration.[20,21]

More recently, two studies were conducted to test the effects of IFN-γ1b in patients with ADO. One was a 14-week, open label, pilot study, evaluating tolerability and impact on bone biomarkers.[11] Fasting C-telopeptide of < 25% above baseline was used to guide dose titration to a goal of 100 mcg/m^2 three times per week. The study recruited nine adult patients and three pediatric patients with ADO. They found no clear changes in biochemical markers of bone resorption or formation. There was also no change in measures of quality of life except for a potential worsening in mental health, postulated to be due to symptoms caused by the treatment or patient perception of overall disease burden. The other study was a 52-week, open label, pilot study evaluating tolerability and effects on bone mineral density, pain, and quality of life.[12] This study recruited 4 adults and 1 adolescent patient with ADO. The dose of IFN-γ1b was titrated over three weeks to a goal of 100 mcg/m^2 three times weekly based on tolerability. Four of the five participants enrolled withdrew from the study between 3–9 months due to intolerability of the flu-like effects caused by IFN-γ1b. The fifth participant was treated with prednisone on the day of injection, which negated the flu-like side effects and resulted in tolerability of IFN-γ1b for the full 12-month treatment period. BMD measured by dual energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) were stable over 6–12 months, and there were no clear trends in bone biomarkers or quality of life measures. Based on these two studies of IFN-γ1b in individuals with ADO, IFN-γ1b does not reverse disease or improve quality of life. While IFN-γ1b might stabilize BMD if tolerated, additional data would be needed to confirm this. What is clear, is that IFN-γ1b treatment is largely intolerable to individuals with ADO and that co-administration of prednisone is needed to achieve tolerability.

A novel approach to treatment currently under investigation is gene silencing using specific small interfering RNA (siRNA). Most individuals with ADO have a dominant mutation of the CLCN7 gene making it amenable to this therapeutic approach. Preclinical data has shown that mutation specific siRNA treatment increased the bone resorption marker collagen type I crosslinked C-telopeptide (CTX) and reduced bone mass in pre-pubertal and adult ADO mice.[26,27] Based on the preclinical data, in 2020 the pharmaceutical company SiSaf established a collaboration and licensing agreement with the University of L'Aquila

(PI: Anna Teti, PhD) to develop this approach for ADO. Please see the review by Dr. Maurizi in this issue for a detailed description of this novel therapeutic approach to ADO.

Summary

Autosomal dominant osteopetrosis is an osteosclerotic disorder due to defective osteoclastic bone resorption, most commonly arising from missense mutations in the CLCN7 gene. There is incomplete penetrance with approximately one third of people with a mutation not showing evidence of disease. There are also large differences in disease severity, even between members of the same family. The most common complications are fractures, pain, and osteonecrosis/osteomyelitis, particularly of the mandible. Vision loss and bone marrow failure can also occur in patients with severe disease. New approaches to therapy are on the horizon. Conflict of Interest Statement: Dr. Econs is a consultant for SiSaf, which is developing a therapy for ADO. Drs. Imel and Polgreen have no relevant conflicts to report.

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Highlights

- This article reviews the history, nosology, and disease phenotype of autosomal dominant osteopetrosis (ADO).
- A distinction between primarily osteosclerotic/osteoblast-driven and primarily osteopetrotic/osteoclast-driven disease is delineated.
- Potential therapies for ADO are described.

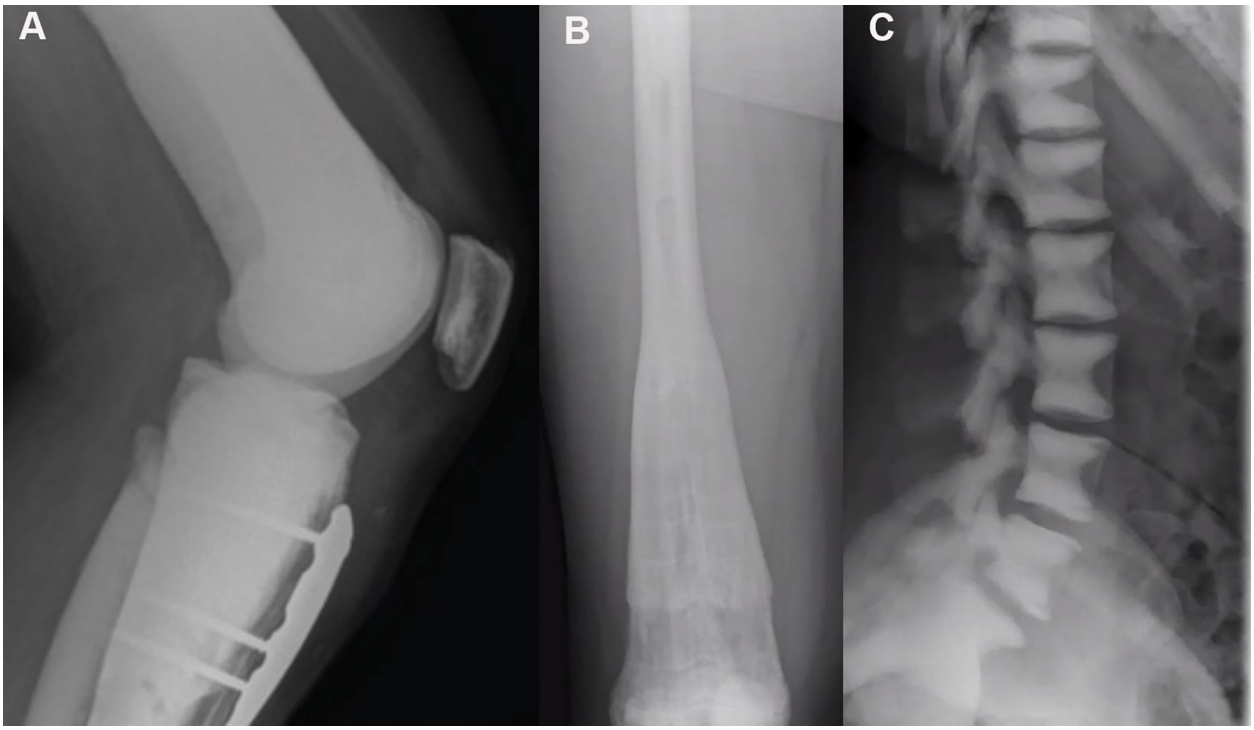

Figure 1. Classic radiographic features of osteopetrosis:
A) bone within a bone appearance ("endobones"), B) sclerosis of the superior and inferior endplates ("sandwich vertebrae" or "rugger jersey spine"), and C) club shaped flaring of the metaphysis with abnormal cortical thinning resulting in an Erlenmeyer flask-like appearance.

Table 1.

ADO2 Disease Complications by Subspecialty

Dentistry	Tooth decay/caries
	Osteomyelitis of the mandible and/or maxilla
Hematology	Anemia (including transfusion dependence)
	Thrombocytopenia
	Leukopenia
	Hepatosplenomegaly due to extramedullary hematopoiesis
Neurology/Neurosurgery	Facial nerve palsy
	Hearing loss
	Optic nerve atrophy
	Hydrocephalus
	Chronic pain
Ophthalmology	Vision loss
Orthopedics	Hip osteoarthritis
	Thoracic and/or lumbar scoliosis
	Spondylolysis
	Pectus carinatum
	Avascular necrosis
	Osteomyelitis
Otolaryngology	Nasal stuffiness
	Narrow palate
	Tooth crowding