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EXTENSIVE CLINICAL EXPERIENCE

Autosomal Dominant Osteopetrosis: Clinical Severity and Natural History of 94 Subjects with a Chloride Channel 7 Gene Mutation

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Context: Autosomal dominant osteopetrosis (ADO) is a sclerosing bone disorder caused by heterozygous mutations in the chloride channel 7 (ClCN7) gene. The clinical manifestations of this disease have not been well characterized since the discovery of the genetic basis of ADO.

Objectives: The primary objectives were to improve our understanding of ADO clinical characteristics and to study the natural history of the disease in the largest series of patients reported to date.

Design and Setting: This study was primarily a retrospective cross-sectional analysis of individuals with a ClCN7 mutation that was conducted over a 4-yr period at a tertiary referral center and through family reunions. Longitudinal data on a subset of subjects were also studied.

Patients and Interventions: We studied 311 subjects from 11 ADO families, including 62 individuals with ADO (patients with the classic clinical phenotype based on radiographs and/or biochemistries), 32 unaffected gene carriers (subjects with the gene mutation but no radiographic and/or biochemical phenotype), and 217 controls who did not harbor a ClCN7 gene mutation. Clinical data were collected through patient interviews and examinations, medical records, and/or self-reported responses on a questionnaire that was completed by all subjects.

Main Outcome Measures: The prevalence of fracture, osteomyelitis, visual loss, and bone marrow failure was determined. Differences in clinical manifestations were analyzed according to affected *vs.* carrier status, age, and underlying genotype.

Results: Ninety-two percent of ADO subjects had at least one sequela of the disease. Gene carriers did not have an increased risk of disease manifestations, although they were found to have significant increases in bone mineral density ($P < 0.05$). Compared with controls, subjects with ADO had a significantly increased prevalence of fracture (84 *vs.* 36%; $P < 0.0001$) and osteomyelitis (16 *vs.* 0.9%; $P < 0.0001$). Severe fractures (defined as ≥10 fractures of any type and/or greater than one hip/femur fracture) were identified only in ADO subjects, and osteomyelitis typically occurred in the maxilla or mandible in older adults. Visual loss, which typically had its onset in childhood, and bone marrow failure occurred in 19 and 3% of ADO subjects, respectively. Adults were more likely to manifest an ADO clinical characteristic, but no definitive genotype-phenotype relationship could be concluded. Longitudinal data suggest that the ADO clinical phenotype worsens over time.

Conclusions: ADO caused by mutations in the CLCN7 gene is a frequently symptomatic disease manifested by a high rate of fracture, osteomyelitis, visual loss, and occasional bone marrow failure. The sequelae of ADO, which can be identified as early as infancy, appear to worsen over time. Fracture is the most prevalent consequence of ADO, although other more severe manifestations of disease can occur and should not be confused with recessive forms of osteopetrosis, particularly when identified in early childhood. **(*J Clin Endocrinol Metab* 92: 771–778, 2007)**

AUTOSOMAL DOMINANT osteopetrosis (ADO) is a genetic bone disorder characterized by widespread osteosclerosis and the radiographic finding of endobones ("bone within a bone" appearance) best manifested by the classic "rugger-jersey" identified in the vertebral bodies of affected individuals (1). The osteosclerotic but fragile bones in ADO result from ineffective osteoclast-mediated bone resorption caused by inactivating mutations in the chloride channel 7 (ClCN7) gene (2, 3). Although not definitely established, these mutations are assumed to disrupt acidification of the osteoclast resorption lacunae that in turn prevents degradation of the mineral component of bone (4).

The osteopetroses in humans encompass a genetically heterogeneous group of metabolic bone disorders (5). Historically, two major types of ADO, ADO1 and ADO2, were distinguished by their radiographic and clinical characteristics (6, 7). However, ADO1 is now known to be secondary to mutations in the gene encoding the low-density lipoprotein receptor-related protein 5 (8). In light of the fact that the disease previously termed ADO1 is not secondary to primary abnormalities in osteoclast resorption (9), there appears to be only one true form of ADO, and this name will henceforth be used for the disease also known as ADO2 and Albers-Schönberg disease. A contrast must also be made between ADO and autosomal recessive osteopetrosis. Although the

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Abbreviations: ADO, Autosomal dominant osteopetrosis; BMD, bone mineral density; DXA, dual x-ray absorptiometry.

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latter may occur secondary to homozygous or compound heterozygous mutations in the ClCN7 gene (2, 10, 11), the majority of autosomal recessive osteopetrosis cases result from mutations in TCIRG1 encoding the a3 subunit of the vacuolar proton pump (11, 12).

Given the reduced penetrance of the ADO phenotype, the spectrum of disease expression can range from radiographically unaffected gene carriers to skeletally affected yet asymptomatic individuals to severely affected persons with multiple fractures, osteomyelitis, cranial nerve deficits, and bone marrow failure resulting from decreased volume of the medullary cavity (13, 14) (Fig. 1). Based on our previous observations, the classic skeletal phenotype is seen in only 66% of individuals who inherit a ClCN7 gene mutation (3). Individuals with ADO also have markedly elevated serum levels of tartrate-resistant acid phosphatase and the BB isoenzyme of creatine kinase (14, 15). Tartrate-resistant acid phosphatase levels may also correlate to and be useful for predicting the clinical severity of disease (16). Radiographically unaffected gene carriers do not show elevations in these analytes (14, 16).

The prevalence and natural history of the clinical manifestations of ADO remain poorly characterized, and there have been few previous large studies of ADO clinical characteristics, all of which were reported before the discovery of the genetic basis of ADO (7, 13, 17, 18). To define the extent of phenotypic variability in ADO and to determine whether disease severity worsens with age, we studied 94 subjects with ClCN7 mutations, the largest such group studied to date. In addition to a cross-sectional analysis, we analyzed longitudinal data on a subset of our patients to determine whether the disease worsens with age.

Patients and Methods

ADO subjects and definition of the ADO phenotype

This study was a retrospective cross-sectional analysis of a large cohort of subjects with a ClCN7 gene mutation. During an almost 4-yr period from November 1997 until October 2001, we identified individuals from 11 ADO families. The Indiana University Institutional Review Board approved the research protocol, and all subjects (or their parents/legal guardians) gave written informed consent before participating in the study. We collected clinical data through patient interviews and examinations, medical records, and/or self-reported responses on a questionnaire that was completed by all subjects. Many subjects were recruited through large family reunions specifically organized by the investigators for this research. Data obtained after the defined collection period were not included in the analysis so as not to overrepresent the prevalence of disease manifestations. Individuals with a ClCN7 gene mutation were classified according to phenotype as either being an affected ADO subject or an unaffected gene carrier (henceforth referred to only as a gene carrier), which was determined by radiographic and/or biochemical findings as described previously (3, 14). Affected subjects had radiographic and/or biochemical evidence of ADO, whereas gene carriers did not, although they too harbored a ClCN7 gene mutation. Those family members who were negative for a ClCN7 gene mutation and family members related by marriage were used as the control group.

Studies and definition of clinical manifestations

Blood specimens were drawn for DNA analysis and/or biochemistry analysis as previously reported (3, 14). When possible, an assessment of bone mineral density (BMD) was accomplished with dual x-ray absorptiometry (DXA) using GE Lunar DPX-IQ and DPX-L equipment (GE Lunar, Madison, WI). We assessed for a history of fractures, osteomyelitis, and/or osteonecrosis (for brevity, subsequently referred to only as osteomyelitis given the difficulty in determining retrospectively the exact pathophysiology of this problem), visual loss, and bone marrow failure in all subjects. Fracture history was primarily ascertained by patient history because most radiographs from fracture events were not available for review and because many mild fractures went untreated by a healthcare provider. A fracture score of "severe" was defined as 10 or more fractures of any type and/or greater than one hip/femur fracture (Fig. 1). Otherwise, fractures were characterized as either being present or absent. Particular fracture types were also recorded and included each fracture episode in a particular bone; if the exact number of fractures in a given bone was unknown, a fracture was counted only once. Similar to fractures, osteomyelitis, visual loss, and bone marrow failure were defined as being either present or absent. Osteomyelitis was considered present if: 1) the patient reported a bone infection requiring antibiotics; 2) the subject had findings of active osteomyelitis on examination; or 3) a history of gum breakdown followed by extrusion of a bony fragment

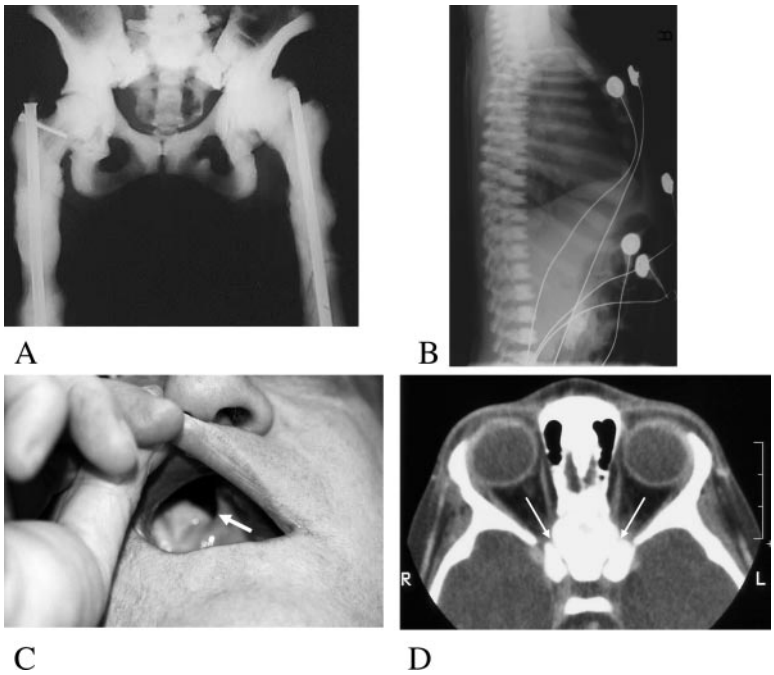

FIG. 1. Clinical manifestations of ADO. A, Pelvic x-ray of a severely affected subject demonstrating severe osteosclerosis and evidence of previous bilateral femoral fractures with associated bony deformities and loss of the joint space. B, Almost 3-month-old infant with classic radiograph findings of ADO, including diffuse osteosclerosis and the appearance of a rugger-jersey spine. C, Severe chronic maxillary osteomyelitis with associated destruction of the palate (*arrow*). D, Severe bilateral optic canal narrowing (*arrows*) in a 4-yr-old patient with complete loss of vision in the left eye and 20/80 visual acuity in the right eye.

was given, consistent with an episode of osteonecrosis. Visual loss was considered present only if there was well-documented visual impairment, which we defined as blindness or decreased vision in the setting of a diagnosis of optic atrophy. Complete blood counts were not obtained as part of the current study. Therefore, bone marrow failure was defined as having a history of decreased hematopoiesis necessitating blood transfusions.

The data were compared among three groups: ADO subjects, gene carriers, and controls. We then studied the relationship of age to clinical manifestations by comparing the phenotype in adults (>18 yr of age) to children (≤18 yr of age). We also determined whether specific mutations were associated with a particular clinical phenotype.

Longitudinal data

A subset of our subjects had previously been studied in the 1960s and reported by Johnston *et al.* (17) in 1968. In the current study, we were able to obtain over 30 yr of follow-up on some of these patients. In addition, to illustrate the clinical course of severe ADO diagnosed in infancy, we present longitudinal data on a young child who has been followed prospectively since diagnosis.

Statistics

We estimated the means of continuous outcomes and the proportions of categorical outcomes and then used two-sample *t*-tests to compare means and χ^2 tests to compare proportions between subgroups. One-sample *t*-tests were used to test whether means of Z scores for BMD were different from zero.

Results

Subject characteristics

All 62 ADO subjects and 32 gene carriers within the 11 ADO families had one of five heterozygous missense mutations in the ClCN7 gene as previously reported (3). The most common mutation in our subject population was the R286W mutation (47%) followed by the G215R (27%), R767W (18%), L213F (7%), and R762L (1%) mutations. Children age 18 or younger represented 23% of subjects with a ClCN7 gene mutation, and 19 of 22 (86%) of these children had ADO. Table 1 provides the baseline characteristics of the study subjects. The 94 subjects with mutations in the ClCN7 gene were well matched in terms of age and sex compared with controls ($P > 0.6$). The youngest age of ADO diagnosis was 2 d after birth as a result of a fractured humerus and clavicle (optic atrophy was also appreciated at that time), whereas the oldest age of diagnosis was 68 yr of age after the subject sustained a spontaneous femoral fracture. In all, six subjects were diagnosed with ADO when they were 1 yr of age or younger.

Clinical manifestations

In the current study, 92% of ADO subjects had a history of or an active diagnosis of at least one of the main clinical manifestations of their disease (Table 1). Twenty-six percent of children with ADO were asymptomatic, whereas no affected adult was without a clinical manifestation of disease. Table 2 represents the distribution of clinical manifestations among the 62 children and adults with ADO. No single subject had all four major clinical manifestations, but four subjects (6%) had three disease sequelae, three of whom were adults (Table 2).

Fracture

Fracture is the most prevalent clinical manifestation of ADO, occurring in 84% of all ADO subjects compared with 36% of controls ($P < 0.0001$). As shown in Table 1, fracture prevalence was also markedly increased in individuals with ADO compared with gene carriers ($P < 0.005$) who did not experience fractures significantly more frequently than the control group ($P = 0.07$). Almost every adult with ADO (98%) reported a fracture. In children, fractures were less prevalent but still occurred in 53% of ADO subjects compared with 16% of controls ($P < 0.005$). Severe fractures were identified only in ADO subjects (in 16% of affected children and 33% of affected adults, $P < 0.01$ and $P < 0.0001$, respectively, compared with controls) underscoring the severity of this aspect of the ADO phenotype. A history of a hip or femur fracture was documented in 16% of children and 49% of adults with ADO. Many of the fractures were described as occurring spontaneously, and at least five of the ADO subjects had a history of 15 or more fractures. Table 3 enumerates the fracture types encountered in 52 of the 62 subjects with ADO. Most fractures (86%) occurred in the appendicular skeleton. Twenty-five affected subjects (40% of the group) had 50 fracture episodes in the pelvis, hip, or femur, accounting for 32% of all fracture events. Less than 3% of gene carriers or controls had fractures of the pelvis, hip, or femur.

TABLE 1. Characteristics of 94 subjects with a ClCN7 mutation and controls

	No.	Mean age ± SD (range)	Males (%)	Mean age at diagnosis[a] (range)	FX (%)	VL (%)	OM (%)	BMF (%)
Subjects ≤ 18 yr of age								
ADO patients	19	8.9 ± 4.5 (9 months–17 yr)	58	3.8 yr (birth–9 yr)	53	42	0	5
Gene carriers	3	7.9 ± 7.3 (21 months–16 yr)	67	NA	0	0	0	0
Controls	67	7.7 ± 4.2 (12 months–17 yr)	49	NA	16	NA	0	0
Subjects > 18 yr of age								
ADO patients	43	47.1 ± 16.4 (22–79 yr)	44	20.3 yr (9 months–68 yr)	98	9	23	2
Gene carriers	29	43.3 ± 15.6 (22–76 yr)	45	NA	59	0	0	0
Controls	150	42.7 ± 15.0 (19–85 yr)	43	NA	45	NA	1	0
Total								
ADO patients	62	35.4 ± 22.5 (9 months–79 yr)	48	15.2 yr (birth–68 yr)	84	19	16	3
Gene carriers	32	40.0 ± 18.2 (21 months–76 yr)	47	NA	53	0	0	0
Controls	217	31.9 ± 20.6 (12 months–85 yr)	45	NA	36	0	1	0

For a definition of the subgroups, please refer to the text. NA, Not applicable or not available; FX, fractures; VL, visual loss; OM, osteomyelitis/osteonecrosis; BMF, bone marrow failure.

[a] Data were available for 16 of 19 children and 36 of 43 adults.

TABLE 2. Clinical manifestation profile of children and adults with ADO

	Fracture	Visual loss	Osteomyelitis	Bone marrow failure	No. (%)
Children (age ≤ 18 yr)	–	–	–	–	5 (26)
	–	X	–	–	4 (21)
	X	–	–	–	6 (32)
	X	X	–	–	3 (16)
	X	X	–	X	1 (5)
Adults (age > 18 yr)	–	–	X	–	1 (2)
	X	–	–	–	31 (72)
	X	–	X	–	6 (14)
	X	X	–	–	2 (5)
	X	–	X	X	1 (2)
	X	X	X	–	2 (5)

X, Clinical manifestation present; –, clinical manifestation not present.

Visual loss

In our population, there was a high rate of severe visual loss in ADO subjects with an overall prevalence of 19% (12 of 62). Data from the control group was not detailed enough for comparison. In 11 of the 12 cases, visual loss clearly had its onset in childhood, suggesting that visual impairment, when it occurs, has its onset early in life.

Osteomyelitis

Osteomyelitis was identified in 10 (16%) patients with ADO and only two (0.9%) members of the control population ($P < 0.0001$). No gene carrier had a history of osteomyelitis. In eight (13%) of the patients with ADO patients, the osteomyelitis was confined to the maxilla and/or mandible; in five, the osteomyelitis was chronic with the presence of a draining fistula and/or obvious bony destruction resulting in visible defects in the jaw or palate (Fig. 1). The other two affected individuals had osteomyelitis of the femur after surgical repair of a fracture. All osteomyelitis cases were identified in adults with ADO, and this manifestation was more prevalent in older adulthood with 80% of the cases identified in adults over age 45. There was only one case of chronic osteomyelitis in subjects less than 45 yr of age, and this occurred in the most severely affected individual in this study. There were only two adult control subjects with a history of osteomyelitis. One had an infection of the femur in the setting of a traumatic fracture, and the other reported osteomyelitis of the lower leg occurring at the age of 2 yr. There were no cases of osteomyelitis in the pediatric population. Subsequent to the data collection, however, there was one case of osteomyelitis that occurred in the tibial metaphysis of an affected 9-yr-old boy. It remains unclear whether this was truly related to the osteopetrosis, because this presentation is typical for childhood hematogenous osteomyelitis.

TABLE 3. Fracture types in 62 patients with ADO

Skeletal site	No.	Percentage
Skull/face	2	1
Hands/finger	18	11
Arm ("wrist," radius, ulna, and humerus)	29	18
Shoulder/clavicle	5	3
Rib	8	5
Vertebra/coccyx (including spondylolysis)	12	8
Pelvis/hip/femur	50	32
Leg (other than femur)	14	9
Foot/toe	20	13
Total	158	100

Bone marrow failure

Two patients with ADO (3%) in the current series had significant bone marrow failure necessitating hematological supportive care. The first patient was a 14-yr-old boy who was reported to be pancytopenic and requiring frequent blood transfusions. The second patient was a 31-yr-old man who had pancytopenia associated with massive hepatosplenomegaly secondary to extramedullary hematopoiesis. He had received multiple transfusions in the past and had developed an autoimmune hemolytic anemia, which precluded the ready administration of blood transfusions. His hemoglobin dropped as low as 3 g/dl at one point in his care.

Other clinical manifestations

Despite not being systematically queried, there were several other clinical manifestations reported with some regularity by the ADO subjects. These included nasal stuffiness secondary to narrowing of the nasal passageways, narrow palate and tooth crowding, frontal bossing, spondylolysis, pectus carinatum, and avascular necrosis. As would be expected, many of the affected subjects with severe fractures also reported long-term pain and disability. Most of these observations were not independently confirmed as part of the study, and at least one subject was misdiagnosed as having avascular necrosis of the hip resulting from the misinterpretation of endobones in the proximal femur on magnetic resonance imaging.

Assessment of BMD

We obtained measurements of BMD in a subset of our study population. The results of central DXA in ADO subjects (ages 17–68 yr) and gene carriers (ages 22–75 yr) are detailed in Fig. 2. Individuals with ADO showed marked elevations of BMD, with mean Z scores of the lumbar spine, femoral neck, and total body of 9.84 ± 2.17 (n = 12; range, 5.9–12.4), 10.14 ± 3.57 (n = 11; range, 3.1–14.8), and 8.23 ± 2.3 (n = 9; range, 5.2–11.9), respectively ($P < 0.0001$ at all sites). Mean Z scores for gene carriers were 2.41 ± 1.72 (n = 8; range, −0.4 to 4.61), 1.58 ± 1.06 (n = 8; range, 0.0–3.47), and 1.73 ± 0.93 (n = 7; range, −0.2 to 2.7) for the lumbar

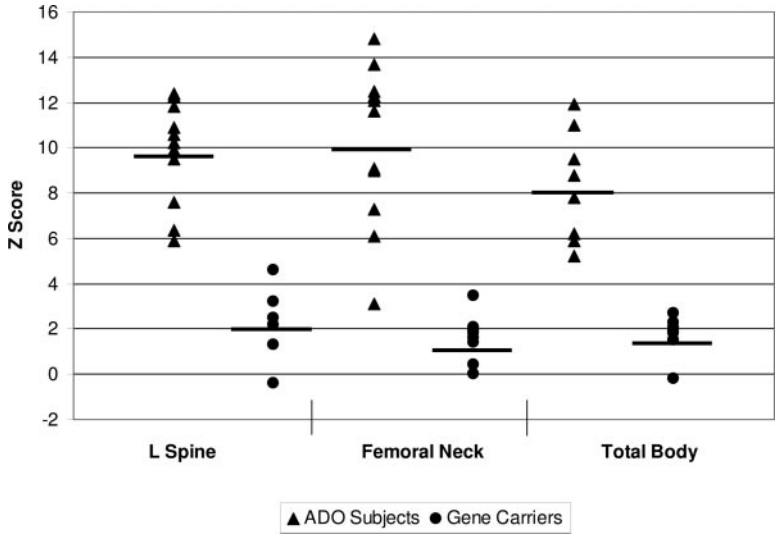

FIG. 2. Central DXA measurements in ADO subjects (*black triangles*) and unaffected gene carriers (*black circles*) with a ClCN7 gene mutation. Not all subjects had every site studied, and some results are the same and are therefore represented by one symbol only. Each *short solid line* represents the mean Z score for each data set.

spine, femoral neck, and total body, respectively ($P < 0.05$ at all sites).

Genotype-phenotype correlations

Data from ADO subjects with the three most common mutations were analyzed to determine whether there was a clear genotype-phenotype correlation. These mutations were R286W, G215R, and R767W and, as a percentage, they represented 42, 31, and 19% of the 62 ADO subjects, respectively. Asymptomatic carriers were found with all three mutations, and nonpenetrance rates were 41, 24, and 29%, respectively. Patients with the R767W genotype, which was found in only one family, appeared to manifest only fracture. Only one subject (8%) with an R767W mutation was classified as having severe fractures in contrast to the R286W (31% subjects with severe fractures) and G215R (42% subjects with severe fractures) genotypes. However, the numbers are too small to statistically address genotype-phenotype correlations. Overall disease severity in the G215R and R286W mutations was similar (data not shown). Bone marrow failure was only identified in individuals with the G215R mutation. The prevalence of osteomyelitis/osteonecrosis and visual loss was similar between the G215R and R286W mutations. Of interest, five of eight children and one of four adults with visual loss were from a single family with an R286W mutation.

Longitudinal data

In the current study, we had the opportunity to assess a subset of patients reported by Johnston *et al.* in 1968 (17). Six subjects (five with ADO and one carrier) from two ADO families were restudied over 30 yr after the preliminary report, and their clinical characteristics are detailed in Table 4. The one person who was classified as unaffected in the 1968 paper remained clinically unaffected, although she was identified in the current study as a gene carrier. Of the five subjects found to have ADO in the 1960s, the most severely affected individual continued to have severe disease that worsened over time. The other four patients all developed progressive symptoms of ADO with an increase in the number and/or severity of clinical manifestations. These data suggest that ADO appears to worsen clinically over time.

We have also followed one severely affected child prospectively since the age of 9 months. She was originally diagnosed at age 4 months via a chest x-ray, but in a retro-

TABLE 4. Natural history of ADO in six subjects with over 30 yr of follow-up

Subject no.	1960s	1990s
1	Normal (age 19)	Unaffected gene carrier (age 54)
2	Clinically affected (age 30) Asymptomatic	Clinically affected (age 65) Mild disease Knee OA, OM
3	Clinically affected (age 26) Asymptomatic	Clinically affected (age 61) Mild disease Transient OM, rib FX, "cracked vertebra"
4	Clinically affected (age 22) Mild disease "Cracked arm," back pain	Clinically affected (age 59) Severe disease Bilateral hip FX, OM
5	Clinically affected (age 23) Mild disease Metatarsal FX	Clinically affected (age 56) Severe disease Bilateral hip FX, OM
6	Clinically affected (age 15) Severe disease VL, multiple FX	Clinically affected (age 51) Severe disease VL, multiple FX, OM

FX, Fracture; OA, osteoarthritis; OM, osteomyelitis and/or osteonecrosis; VL, visual loss.

spective review of radiographs obtained since birth, the classic features of osteopetrosis were obvious earlier (Fig. 1). At the initial evaluation, she had noisy breathing secondary to narrowed nasal passageways and mild gross motor delays, but she otherwise did not have any of the four major ADO clinical characteristics. By 3½ yr of age, she developed severe visual loss in one eye secondary to optic canal narrowing, which necessitated optic canal decompression. By the age of 4 yr, the patient had sustained five fractures in the arms and legs. She has thus far had no evidence of bone marrow failure or hepatosplenomegaly. On review of all children diagnosed with ADO, there were others with classic radiographic manifestations as infants. In these cases, similar to the subject described above, clinical manifestations of ADO became severe in childhood, suggesting that the most severe cases of ADO can present in infancy and that a diagnosis of ADO in early childhood may portend a more severe prognosis.

Discussion

In the current study, we have presented data from the largest reported series of subjects with documented CLCN7 gene mutations and characterized the clinical manifestations of the metabolic bone disorder ADO. Our study demonstrates that the majority of patients with radiographic and/or biochemical evidence of ADO suffer serious sequelae of the disease. Indeed, of 62 individuals with ADO, 92% had some clinical manifestation of the disorder. Coupled with results from previous studies (7, 13, 17, 18) (Table 5), it can be concluded that fracture is the most likely consequence of ADO. Fractures overwhelmingly occur in the appendicular skeleton, typically the femur. The overall fracture rate in our population was 84%, and adults were more likely than children to have experienced a fracture. This may suggest progression of disease as one ages, but it may just reflect the fact that adults have had more time to sustain a fracture. Our rate of fracture is higher than the rate of 35–45% described by Johnston *et al.* (17) but comparable to other reports.

There are some limitations in our study of fracture in this population, which may have resulted in either over- or underestimation of the true fracture prevalence. First, radiographs were not always available to document each self-reported fracture, and many mild fractures were not well documented because medical attention was not sought at the time. Second, fractures were difficult to quantify. Many subjects with multiple fractures (some patients had over 40) could not provide a detailed list of the number and site of their fractures, and there may have been a recall bias. Third, metachronous fractures in the same person were counted as separate fracture events, although the presence of a previous fracture may have contributed more to subsequent fracture than the underlying disease itself.

There are several potential explanations for the apparent paradox of increased fracture risk despite increased BMD. First, because bone remodeling is impaired secondary to the underlying osteoclast defect in ADO, microdamage to the bone can accumulate as reported in animal models treated with bisphosphonates (19). Failure to repair areas of microdamage may then lead to clinical fracture, perhaps explaining in part why spontaneous fractures occur in ADO. Second, the biomechanics of ADO bone are dramatically altered. Because of the increased quantity of bone, the skeleton of patients with ADO is less pliable and therefore unable to absorb significant energy before breaking. Therefore, this reduced work to failure makes osteopetrotic bone more susceptible to breaking when external forces are applied (20).

Visual loss, which occurred more commonly in our study than in previous reports (Table 5), seems to have its origins in childhood, because most affected subjects with visual loss clearly lost vision before the age of 18 yr. We could not independently confirm every report of visual loss or do systematic ophthalmological evaluations on all individuals. Because of this latter limitation, the degree of visual loss in adults may actually have been underrepresented. It is unclear why visual loss occurs in childhood, but it may be related to a more critical role of bone remodeling during childhood in maintaining an appropriate optic canal caliber to keep pace with growth of the optic nerve. In our series, most cases of visual loss were attributed to narrowing of the optic canal, keeping in mind that primary retinal dysfunction or cerebral venous outflow obstruction leading to raised intracranial pressure may play a role in the most severe osteopetrosis cases (21, 22). Our study did not assess for the

TABLE 5. Clinical characteristics of patients with ADO: a comparison of studies

	No.	Fractures	Osteomyelitis[a]	Visual loss	BMF or HSM	Total symptomatic
Waguespack *et al.* (current study)	62	84% (pelvis/hip/femur most common)	13%	19%	3%	92%
Bénichou *et al.* (13)	37	76% (femur and rib most common)	13% (4 of 31 evaluable subjects)	5% (16% with cranial nerve palsy)	ND	81%
el-Tawil and Stoker (18)	28	62% (femur most common)	ND	ND	ND	ND
Bollerslev and Andersen (7)	15	67% (most in appendicular skeleton)	0%	ND	ND	67% (fractures only)
Johnston *et al.* (17)	133[b]	35–40%	10%	ND (20–25% with cranial nerve palsy)	0%	50–55%

BMF, Bone marrow failure; HSM, hepatosplenomegaly; ND, not documented.

[a] Jaw osteomyelitis and/or osteonecrosis only; in the current study, there were two cases of femoral osteomyelitis related to previous surgery, and in Bénichou *et al.*, four additional cases of nonmandibular osteomyelitis were reported.

[b] Literature review of previous reported cases of ADO, not all of which may have had ADO; does not include the 11 patients with ADO reported by Johnston *et al.*, because five of them are included in the current study.

presence of all cranial nerve palsies but instead focused on cranial nerve II. However, based on previous studies, the finding of facial nerve palsies and hearing loss would not be an unexpected component of the ADO phenotype (13, 17, 23).

Osteomyelitis was quite common in our study, specifically in older adults with ADO. The usual sites for osteomyelitis were the mandible and maxilla, and chronic osteomyelitis (often accompanied by oral cutaneous fistulas) was a consistent problem. Thirteen percent of our subjects experienced jaw osteomyelitis, which is comparable to the reports by Bénichou *et al*. (13) and Johnston *et al*. (17) (Table 5). Some subjects gave a history very descriptive of osteonecrosis, similar to that described in patients with cancer receiving frequent infusions of iv bisphosphonates (24). These data demonstrate the importance of the osteoclast in maintaining bone integrity in the jaw. The exact factor that predisposes individuals with ADO to mandibular and maxillary osteonecrosis and subsequent osteomyelitis is unknown but may be related either to the inability of these bones to adapt to the need for increased bone remodeling (*e.g.* in the setting of inflammation or dental procedures) and/or to alterations of the microscopic blood supply that occur because of ineffective osteoclastic resorption of the mineral matrix (24). Our study did not assess potential predisposing factors such as antecedent dental work. It is also unclear whether the two cases of femoral osteomyelitis were clearly related to ADO given that both subjects had previous surgical repair of a femoral fracture.

Failure of normal hematopoiesis resulting from decreased volume of the bone marrow space is the least common yet most life-threatening manifestation of ADO. This report, along with that of Frattini *et al.* (11), demonstrates that bone marrow failure can be a component of the ADO phenotype. Bénichou *et al.* (13) did not report cases of bone marrow failure because this was an exclusion criterion for their study. Therefore, more cases of bone marrow failure resulting from ADO may be recognized through genetic testing of individuals previously believed to have recessive forms of osteopetrosis. The finding of bone marrow failure in our population and the diagnosis of some of our subjects in infancy demonstrate that the presence of bone marrow failure and/or the identification of severe osteosclerosis in a young child on radiographic examination do not indicate that the individual has a recessive form of osteopetrosis. This concept is also supported by other reports in the literature (11, 25).

Nonpenetrance of the ADO phenotype has long been recognized (17), with one third of individuals who inherit a ClCN7 gene mutation not manifesting the ADO phenotype (3). The current study confirms that these gene carriers do not have clinical manifestations of disease. However, high normal Z scores on bone densitometry can be identified in some gene carriers, and the group as a whole has statistically significant higher DXA Z scores compared with the expected population mean of zero. Whether this subtle manifestation of underlying osteoclast dysfunction protects against fracture could not be demonstrated, because fracture prevalence in this group was similar to controls. It remains unclear why members within a given family can have such differential expressions of a commonly shared mutation, but it is most likely that background modifier genes, which interact directly or indirectly with the ClCN7 gene and its protein product, play a large role in determining the overall phenotype (26).

As shown by the worsening of clinical manifestations over 30 yr of follow-up and the cross-sectional differences observed between children and adults, ADO is a disease that becomes more symptomatic over time. Longitudinal data also suggest that narrowing of the optic canal does not occur over decades of follow-up, so if an affected individual is not blind by age 18 yr, he or she is unlikely to lose vision in adulthood. However, as demonstrated by the one pediatric case presented, there is still a real concern that visual loss may be progressive in childhood, thus underscoring the need for diligent monitoring of young patients with ADO, particularly those with a severe skeletal phenotype.

In summary, mutations in the CLCN7 gene cause ADO in two thirds of individuals who inherit this genetic defect. Gene carriers do not manifest ADO clinical characteristics, except for subtly but significantly increased BMD. Although historically labeled as a benign adult form of osteopetrosis, ADO is almost always associated with at least one clinical manifestation. The clinical sequelae of ADO can be quite severe and reminiscent of recessive forms of osteopetrosis. Individuals with ADO are most likely to fracture long bones and become more symptomatic from their disease over time. The most severely affected individuals can be identified in childhood. Children should be diligently followed for visual loss, and adults with ADO should be educated about osteomyelitis/osteonecrosis so that prevention and early recognition of this problem can be achieved. Patients with ADO should also be appropriately counseled regarding their likelihood to fracture and their increased risk for other ADO-related problems.

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