

COMMENTARY

IMAGE, a New Clinical Association of Intrauterine Growth Retardation, Metaphyseal Dysplasia, Adrenal Hypoplasia Congenita, and Genital Anomalies

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ABSTRACT

We report three boys with adrenal hypoplasia congenita (AHC) and additional findings that represent a new syndrome, IMAGE: Intrauterine growth retardation, Metaphyseal dysplasia, AHC, and Genital anomalies. Each presented shortly after birth with growth retardation and severe adrenal insufficiency. Each of the three patients had mild dysmorphic features, bilateral cryptorchidism, a small penis, and hypogonadotropic hypogonadism. Skeletal surveys revealed metaphyseal dysplasia in all three and epiphyseal dysplasia in two. The patients had documented or suspected hypercalciuria and/or hypercalcemia, resulting in nephrocalcinosis in one and in prenatal liver and spleen calcifications in another. AHC presents most often either

as an isolated abnormality, caused by mutations in the DAX1 gene, or as part of an Xp21 contiguous gene syndrome, caused by a deletion of the Duchenne muscular dystrophy, glycerol kinase, and DAX1 genes. All three patients with the IMAGE association had normal creatine kinase levels and no evidence of glycerol kinase deficiency. Sequence analysis of DNA from these patients revealed no mutation in the DAX1- or steroidogenic factor-1-coding sequences, nor was a deletion of DAX1 detected. Identification of the molecular basis of the IMAGE association will give new insight into the pathogenesis of this syndromic relationship involving bone, adrenal cortical, and pituitary development. (*J Clin Endocrinol Metab* 84: 4335–4340, 1999)

DISEASES leading to adrenal insufficiency are life-threatening disorders that require early recognition and ongoing steroid hormone replacement, with acute increases in the therapy during stress. Among the various etiologies of adrenal insufficiency, X-linked adrenal hypoplasia congenita (AHC) has become a focus of interest because of recent advances in understanding its molecular pathogenesis.

The X-linked or cytomegalic form of AHC is an inherited disorder of adrenal cortical development (1, 2), and is characterized by the absence or near absence of the permanent or adult zone of the adrenal cortex and by structural disorganization of the fetal cortex with abnormally large cells (3, 4). It differs from the autosomal recessive miniature adult form of AHC, in which the adrenal cortexes have the normal adult structure but are very small (5). X-Linked AHC results in severe primary adrenal in-

sufficiency involving glucocorticoids and mineralocorticoids and failure to respond to the elevated levels of ACTH (2). Symptoms usually have a sudden onset and are precipitated by stress, such as an intercurrent infection or surgical procedure. Symptoms include hypotension, dehydration, shock, abdominal pain, and fever, accompanied by hyponatremia and hyperkalemia. If untreated, the disorder is lethal. The age of onset is usually in the neonatal period or during infancy. However, in some patients, age of onset is later, up to several years of age, presumably due to residual functional cortex (2). Hypogonadotropic hypogonadism, manifesting clinically with cryptorchidism and delayed puberty, is also frequently associated with AHC (6–8).

AHC may occur as an isolated disorder or as part of a contiguous gene syndrome with glycerol kinase deficiency and Duchenne muscular dystrophy (9). Intragenic mutations in DAX1 (Dosage-sensitive sex reversal, Adrenal hypoplasia congenita on the X-chromosome, gene 1), a gene encoding a new member of the nuclear hormone receptor superfamily, were shown to be responsible for both AHC and hypogonadotropic hypogonadism (10–12). DAX1 is located in the Xp21 dosage-sensitive sex reversal region, the duplication of which is associated with female or ambiguous genitalia in XY individuals (13, 14). Analysis of

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DAX1 has shown that many AHC patients have *DAX1* mutations, but some individuals with AHC have no detectable *DAX1* mutations (2, 10). The mouse *DAX1* homolog, *Ahch*, is expressed in the adrenals on embryonic day 12.5, 1 day after the development of the adrenal primordium from the urogenital ridge, and expression persists (15). Point mutations in *DAX1* in patients with AHC, and murine expression profile of *Ahch* suggest that *DAX1* is required for the normal development of the adrenal cortex. *DAX1* may interact in a concerted fashion with steroidogenic factor-1 (*SF1*), another member of the nuclear hormone receptor superfamily (16).

We report three unrelated boys with a previously unrecognized syndrome that we will refer to as the IMAGE association for Intrauterine growth retardation, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital abnormalities. We will describe additional clinical, radiological, and molecular genetic findings in these boys, including an absence of mutations in the *DAX1* gene.

Materials and Methods

Patients were identified and followed at three institutions: Hôpital Necker (Paris, France), Hôpital Charles Nicolle (Rouen, France), and Baylor College of Medicine (Houston, TX).

Blood samples for investigational studies were obtained from patients with informed consent. Genomic DNA samples were extracted using standard procedures. For *DAX1* amplification, primers and cycle conditions were those that have been previously described (17, 18). For *SF1* amplification, the following intronic primers were used for the protein coding exons: 5'-CACAGAGAGGGGATTACGCGA-3' and 5'-GTACTATCCCCTCAGCCCT-3' for exons 2 and 3, 5'-CCATGAAA-GGGTGTGAGCA-3' and 5'-GATGGCCCTATCCAAAGGACA-3' for exon 4, 5'-ACGCCTAGTTGGGTCTCAGT-3' and 5'-ACAGCAGGGC-TACCTCTCCA-3' for exon 5, and 5'-GTGCACCTCCAATCCATGCCC-3' and 5'-ACTCTGGCCACAGCAGGGCTA-3' for exon 6. Amplification conditions for *SF1* were 5-min initial denaturation at 94 C, followed by 1-min denaturation at 94 C, 1-min annealing at 57 C, and 1-min extension at 72 C for 30 cycles, followed by a 7-min final extension at 72 C.

Direct sequencing was performed on the amplification products by automated cycle sequencing, using an ABI 377 (PE Applied Biosystems, Foster City, CA). Southern blots were performed (19); *DAX1* exon 2 (17) was used as a probe, with patients' genomic DNAs digested with *TaqI*.

Results

The patients' clinical and radiological findings are summarized Table 1. Normal values may vary according to age or to laboratory.

Patient 1

This French Caucasian boy presented at birth with intrauterine growth retardation and left hydronephrosis. He had bifrontal bossing, a flattened nasal bridge (that progressively improved), low set ears, bilateral cryptorchidism, and a micropenis (length, 2 cm; <5th percentile); (Fig. 1a). He was hypotonic. On day 13, a nephrostomy drainage tube was inserted under general anesthesia, and acute adrenal insufficiency was revealed by generalized weakness, vomiting, and a dehydrated appearance immediately after the surgery. Hyponatremia, hyperkalemia, and hypernatruria were noted. His plasma ACTH level was 720 pg/mL (normal, 10–60 pg/mL). Replacement doses of fludrocortisone and

TABLE 1. Summary of physical and laboratory findings in three patients with IMAGE association

	Case 1	Case 2	Case 3
Intrauterine growth retardation	+	+	+
Adrenal crisis	+ (day 13)	+ (day 4)	+ (day 7)
Adrenal hypoplasia	Probable	+	+
Hypercalciuria	+	+	Probable
Bifrontal bossing, abnormal ears and nose	+	+	+
Short arms and legs	+	+	+
Craniosynostosis	–	–	+
Micropenis	+	+	Small penis
Bilateral cryptorchidism	+	+	+
Osteopenia	+	+	+
Delayed bone age	+	+	+
Small epiphyses	+	–	+
Striated, irregular metaphyses	+	+	+

hydrocortisone, and sodium supplementation were initiated. An ACTH stimulation test was performed, and intermediates in the mineralocorticoid and glucocorticoid biosynthetic pathways were either low or within normal limits: 17-hydroxyprogesterone, 30 ng/dL (normal, 7–77 ng/dL); androstenedione, 100 ng/dL (normal, 20–290 ng/dL); dehydroepiandrosterone, 35 ng/dL (normal, 50–760 ng/dL); 11-desoxycortisol, 30 ng/dL (normal, 13–147 ng/dL); deoxycorticosterone, 5 ng/dL (normal, 7–49 ng/dL); and 17-hydroxypregnenolone, 20 ng/dL (normal, 36–769 ng/dL). He had a normal testosterone response after hCG stimulation. The proposed diagnosis was AHC.

The boy had hypercalciuria that was noted at 2 yr of age and progressively worsened: the calcium/creatinine ratio was 0.21 at 2 yr, 0.64 at 3 yr, 0.91 at 4 yr, and 1.15 at 4 yr, 3 months of age (normal, <0.25). Standard values for urinary calcium/creatinine ratio vary by age (20). The serum ionized calcium level was 1.27 mmol/L (normal, 1.09–1.29 mmol/L), and the PTH level was 26 pg/mL (normal, 10–65 pg/mL) at 4 yr of age. 1,25-Dihydrovitamin D₃ was 49 pg/mL (normal, 20–80 pg/mL) and 25-hydroxyvitamin D₃ was 8 ng/mL (normal, 5–30 ng/mL).

He had normal creatine phosphokinase levels at 18 U/mL. There was no glyceroluria on urinary organic acid chromatography, and triglycerides were normal, suggesting normal glycerol kinase activity.

The GH level measured at 2 yr, 5 months of age after stimulation by clonidine was 36.7 ng/mL (normal, >10 ng/mL). At 4 yr of age, after stimulation by ornithine, it was 20.3 ng/mL. The level of insulin-like growth factor I at 4 yr of age was 3.8 U/L (normal, 3–5.5 U/L).

Family history was unremarkable. High resolution chromosome analysis revealed a normal 46,XY karyotype. No mutation was identified in either the *DAX1*- or *SF1*-coding sequences. A Southern blot performed with *DAX1* exon 2 as probe to look for a deletion or rearrangement was normal. Intellectual development was normal. Growth retardation and muscular hypotonia persisted, and metaphyseal and epiphyseal dysplasia was first noted at 2 yr of age, associated with progressively severe scoliosis (Fig. 1b). X-Rays performed at 6 yr of age showed small, irregular and flattened femoral and tibial epiphyses and enlarged, striated, and irregular femoral metaphyses (Fig. 1c).

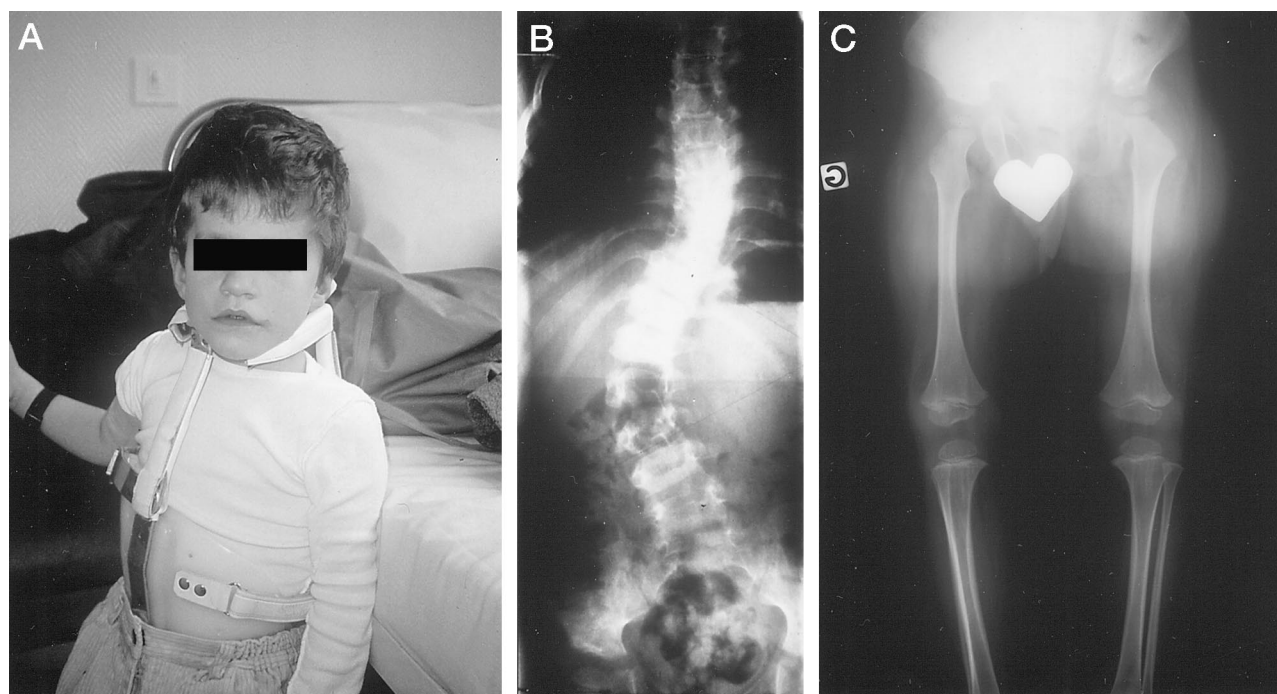


FIG. 1. Photograph and x-rays of patient 1 at 6 yr of age. a, He showed mild bifrontal bossing and low set ears. b, X-ray of the spine revealed severe scoliosis. c, X-ray of the pelvis and legs showed small, irregular, and flattened femoral and tibial epiphyses, and enlarged, striated, and irregular femoral metaphyses.

Patient 2

This French Caucasian boy was diagnosed with intrauterine growth retardation during the second trimester of pregnancy. He was delivered at 33 weeks gestation, and Apgar scores were 3 and 6. He developed respiratory distress requiring intubation. He was noted to have micrognathia, low set ears, and a flattened nasal bridge (Fig. 2a). His phallus was small (1.8 cm; <5th percentile), and he had bilateral cryptorchidism. On day 4, hyponatremia, hypernatruria, and hyperpigmentation were noted. ACTH was elevated to 1600 pg/mL (normal, 10–80 pg/mL). Intermediates in the mineralocorticoid and glucocorticoid biosynthetic pathways were low, with 17-hydroxyprogesterone at 2 ng/dL (normal, 26–568 ng/dL) and 11-desoxycortisol undetectable (normal, 48–57 ng/dL). His skin darkened progressively over the next 2 weeks. Abdominal ultrasound and abdominal computed tomography scan did not reveal the presence of adrenals. A diagnosis of AHC was proposed.

He had hypercalcemia (up to 3 mmol/L during the first month of life; normal, 2.2–2.6 mmol/L) and nephrocalcinosis. Creatine phosphokinase levels were normal. Serum triglyceride and urinary glycerol levels were normal.

The family history was unremarkable. High resolution chromosome analysis showed a normal 46,XY karyotype. No mutation was identified in either the *DAX1*- or *SF1*-coding sequences. A Southern blot performed with the *DAX1* exon 2 probe was normal.

Intellectual development was normal. Adrenal insufficiency was treated on day 17 with replacement doses of hydrocortisone and fludrocortisone and increased sodium chloride intake. A metaphyseal dysplasia was noted at age 3 yr, 8 months when x-rays showed striated, irregular, and

flared femoral and tibial metaphyses (Fig. 2b). Spinal x-rays revealed osteopenia but no scoliosis (Fig. 2c). Bone age was delayed.

Patient 3

This American Latino boy presented at birth with severe intrauterine growth retardation, dysmorphic features, and marked hyperpigmentation leading to the diagnosis of charcoal-baby syndrome and a subsequent report (21). He had a prominent forehead, secondary to overriding, but movable sagittal and coronal sutures, and bilateral epicanthal folds (Fig. 3a). His ears were low set. He had micrognathia and a slightly high arched palate with a uvula that had a very short cleft. He had bilateral cryptorchidism with a small penis (3 cm at 6 months of age; 10th percentile). Liver and spleen calcifications that had been seen on ultrasound prenatally were confirmed postnatally by ultrasound.

On day 7 of life, he had an adrenal crisis revealed by low blood pressure, respiratory distress, hyponatremia, and hyperkalemia. He required mechanical ventilation for 2 days and was treated successfully with replacement doses of hydrocortisone and fludrocortisone and supplemental sodium chloride. Abdominal ultrasound did not reveal the presence of adrenals. At 3 months of age, this boy underwent surgery for craniosynostosis with appropriate steroid adjustments and experienced no complications. Skin hyperpigmentation progressively decreased.

At 2 yr of age, femoral metaphyses were noted to be irregular and flared, and epiphyses were small (Fig. 3b). His intellectual development was normal. Family history was unremarkable. High resolution karyotype was 46,XY with no abnormalities. No mutation was identified in either the

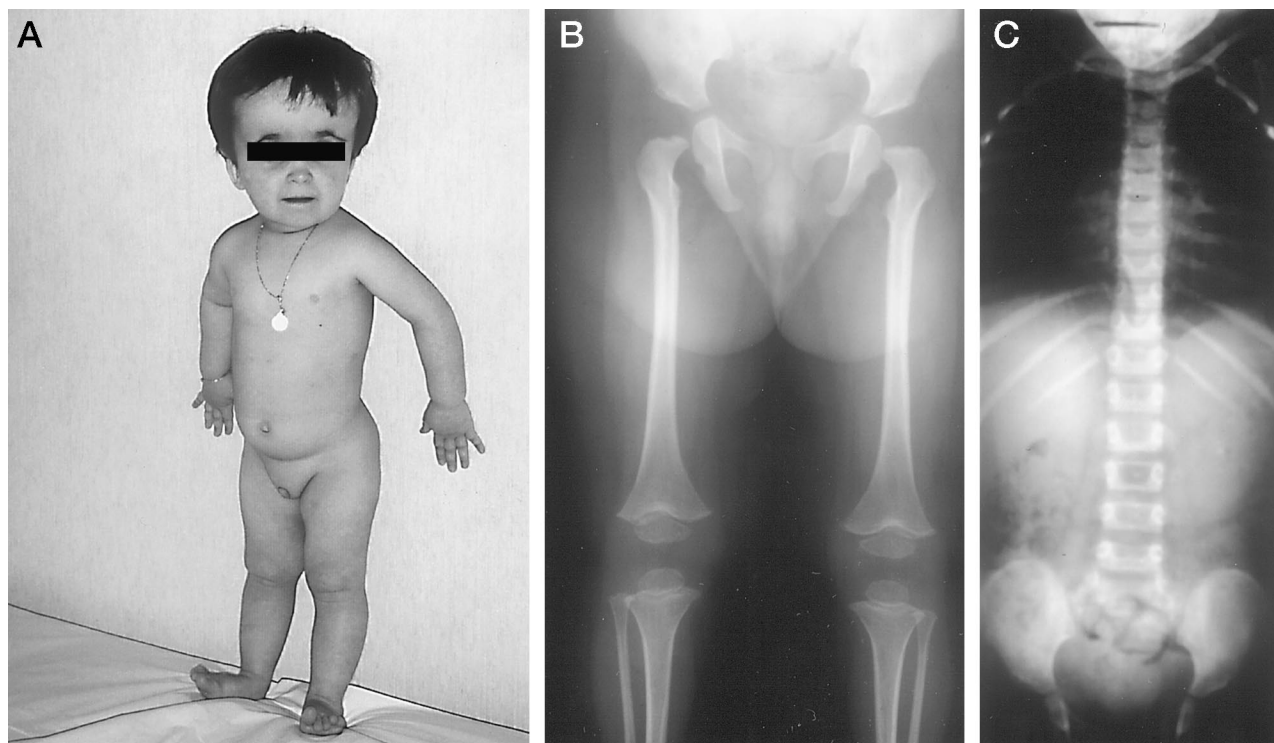


FIG. 2. Photograph and x-rays of patient 2 at age 3 yr, 8 months. a, He showed micrognathia, low set ears, bifrontal bossing, and a flattened nasal bridge. He had a microphallus with bilateral cryptorchidism. b, X-ray of the pelvis and legs revealed irregular and flattened tibial epiphyses, absence of femoral epiphyses, and enlarged, striated, and irregular femoral metaphyses. c, X-ray of the spine showed osteopenia without scoliosis.

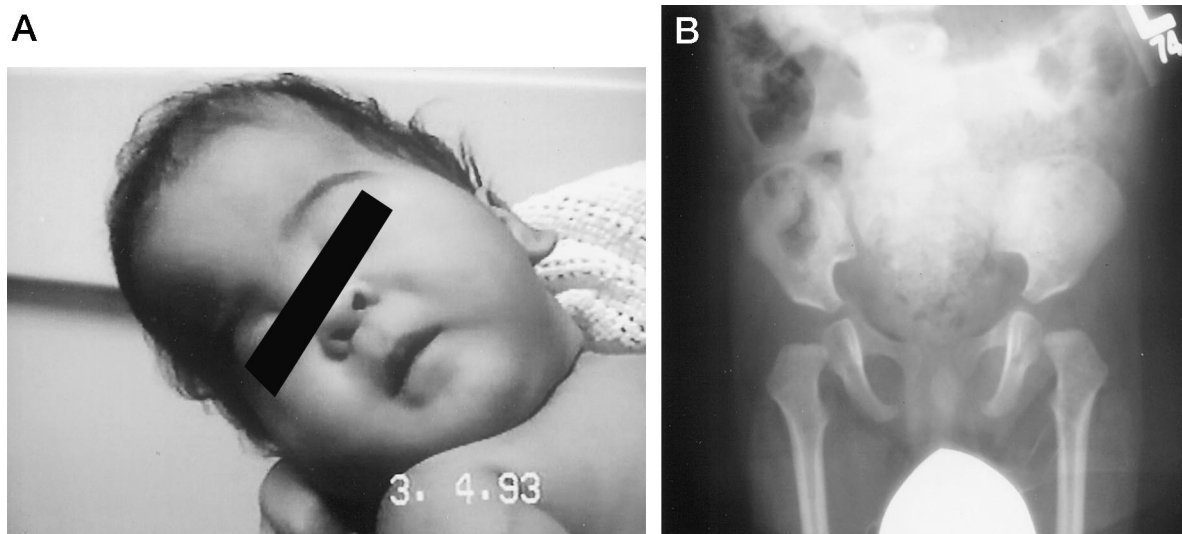


FIG. 3. Photograph and x-ray of patient 3 at 6 months of age. a, He showed a prominent forehead, bilateral epicanthal folds, low set ears, and micrognathia. b, X-ray of the pelvis showed absence of femoral epiphyses and irregular, mildly enlarged femoral metaphyses.

DAX1- or *SF1*-coding sequences. A Southern blot performed with the *DAX1* exon 2 probe was normal.

Discussion

We present three boys with intrauterine growth retardation, metaphyseal dysplasia with or without epiphyseal dysplasia and associated soft tissue calcifications, AHC with severe neonatal adrenal cortical insufficiency, and genital

abnormalities with bilateral cryptorchidism and a small phallus. We refer to this previously unrecognized syndrome as the IMAGe association. Two other patients, both boys, with AHC and similar associated features were described independently (22, 23). They both had intrauterine growth retardation, dysplastic hips, growth retardation with GH deficiency, dysmorphic features, developmental delay, microphallus, and bilateral cryptorchidism. Our patients differ

from these previously reported boys, because GH deficiency and developmental delay were not present in our patients. In addition, the soft tissue calcifications, hypercalcemia, and/or hypercalciuria, present in all three of our patients, were not described in either of the previously reported boys. The two patients reported earlier may represent a different association, but they may also be clinical variants of the IMAGE association. High resolution karyotypes for all three of our patients were normal. Molecular studies of our three patients revealed no mutation in the coding sequences for *DAX1* or *SF1*, a nuclear hormone receptor that maps to 9q33 (24) and is involved in adrenal development (25).

The skeletal anomalies observed in our patients do not have specific characteristics of well defined chondrodysplasia. The normal hand size rules out pathologies caused by mutations in *COMP*, such as multiple epiphyseal dysplasia (OMIM 132400). An association between skeletal dysplasia and congenital adrenal hypoplasia has not been described previously. However, patients with the Xp21 contiguous gene syndrome involving AHC, glycerol kinase deficiency, and Duchenne muscular dystrophy may have osteoporosis and pathological fractures (26). The abnormalities in calcium metabolism observed or presumed in our patients are also remarkable, because it is extremely rare for chondrodysplasia to be associated with calcium metabolism abnormalities. The Jansen-type metaphyseal chondrodysplasia, caused by a mutation in the gene encoding the PTH receptor (27), is the only well characterized example of the association of chondrodysplasia with an abnormality in calcium metabolism (28). Because of the low incidence of AHC or metaphyseal/epiphyseal dysplasia, this association in three unrelated patients is unlikely to be coincidental and may be explained by a unifying molecular mechanism.

The genital anomalies may be the consequence of hypogonadotropic hypogonadism, as cryptorchidism and micropenis are frequently observed in this condition, as with AHC consequent to *DAX1* mutations. Stimulation tests, difficult to interpret in the prepubertal period, were not performed in our patients to confirm this possibility.

Two hypotheses may explain the pathophysiology of this newly recognized clinical association. 1) A mutation in an autosomal gene may be responsible for the AHC present in these patients. This autosomal gene could be directly involved in both adrenal and bone development or could be localized near a second, discrete locus responsible for the bone dysplasia and involved in a contiguous gene syndrome with the autosomal AHC locus. According to this hypothesis, the fact that these three patients as well as the two others reported previously (22, 23) are male would be coincidental. It is possible that AHC in females is underreported, because localization of the *DAX1*-AHC locus on the X-chromosome has focused attention of clinicians on adrenal insufficiency in boys (2).

2) A mutation in the *DAX1* gene region, leaving the *DAX1* open reading frame intact, may occur. According to this hypothesis, AHC would be explained by a position effect leading to a low expression of *DAX1*. Decreased *DAX1* protein production would also be responsible for the genital anomalies, because mutations in *DAX1* are known to be

present in patients with AHC and hypogonadotropic hypogonadism. The bone abnormalities would be explained by the presence of a locus involved in bone development near *DAX1*. *DAX1* expression may be disrupted by a distant rearrangement, as one patient with AHC has a breakpoint localized up to 100 kb centromeric of *DAX1* (11). The presence of a bone development locus in Xp21.3 is plausible, because approximately half of the patients with large deletions of the region have osteoporosis and pathological fractures (26). Precise characterization of the Xp21.3 deletions in patients with and without bone involvement may help to define a critical region on the X-chromosome crucial for normal bone development and/or susceptibility to osteoporosis.

In summary, we report three boys with a new syndrome, the IMAGE association, who have intrauterine growth retardation, metaphyseal dysplasia, AHC, and genital abnormalities. Identification of additional patients with these clinical features will help delineate the clinical spectrum of this syndrome and may give us insight into its molecular pathogenesis.

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The Austrian Society for Bone and Mineral Research Announces Its 2000 Research Prize

The prize, a continuation of the *Chemofux* prizes, honors a novel finding or concept. It will be awarded to an individual who in recent years has published outstanding work on molecular, cellular, (patho)physiological, or clinical aspects of bone and mineral metabolism. Individuals are invited to submit up to three related publications that have appeared since 1997. Papers in press are acceptable if accompanied by an acceptance letter from the journal. Publications must be in English in refereed journals listed in *Current Contents*.

Applicants should describe their finding or concept and its background in a brief statement, not to exceed 300 words, emphasizing the importance of their contribution to progress in bone and mineral metabolism. The letter of application should also include a brief biographical sketch, along with letters by co-authors that they agree to the submission and either wish to share the prize money or waive their claim to it.

The prize of ATS 100,000—will be awarded in connection with the International Conference featuring the work of the prize winner, to be held in Vienna, Austria, November 30–December 2, 2000.

Applications must be submitted no later than March 15, 2000, to: Dr. Klaus Klaushofer, Ludwig Boltzmann Institute of Osteology, 4th Medical Department, Hanusch Hospital, Heinrich Collin-Str. 30, A-1140 Vienna, Austria. All entries that comply to the aforementioned regulations will be forwarded to an International Jury, which will independently select the prize winner.

The jury consists of: K. Klaushofer (Vienna, Chair), E. M. Brown (Boston), G. Karsenty (Houston), D. J. Martin (Fitzroy), M. Peterlik (Vienna), C. van Os (Nijmegen), L. Raisz (Farmington), P. Stern (Chicago), A. Teti (Rome), and M. Thomasset (Paris).

The jury's decision is final and cannot be appealed. The winner will be notified by the end of June 2000.

Previous prize winners: 1988, T. J. Martin; 1991, M. Thomasset and A. Teti; 1994, E. M. Brown; 1997, G. Karsenty.

On the occasion of the Award Ceremony of the 2000 International Research Prize of the AuSBMR, the **International Conference on Progress in Bone and Mineral Research 2000**, organized by the AuSBMR and Ludwig Boltzmann Institute of Osteology, will be held in Vienna, Austria, November 30–December 2, 2000.

Conference Secretariat: Vienna Medical Academy, Alser Strasse 4, A-1090 Vienna, Austria.

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Dates to remember: **March 15, 2000**—deadline for applications for the “2000 International Research Prize”; **June 30, 2000**—deadline for receipt of abstracts.