

Clinical Report
Two Sisters With IMAGE Syndrome:
 Cytomegalic Adrenal Histopathology,
 Support for Autosomal Recessive Inheritance
 and Literature Review

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Received 29 March 2006; Accepted 17 May 2006

Adrenal hypoplasia congenita (AHC) is a rare condition and causes primary adrenal insufficiency. X-linked (OMIM 300200) and autosomal recessive (OMIM 240200) forms are recognized. Recently, an association between Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital abnormalities (IMAGE syndrome; OMIM 300290) has been described. We present the clinical features of two sisters with intrauterine growth restriction, AHC, and dysmorphic features. Interesting histopathologic findings of one sister are also presented.

We suggest that IMAGE syndrome is the most plausible diagnosis and that autosomal recessive inheritance is likely. We analyzed genes that were postulated candidates for IMAGE syndrome (*SFI*, *DAX-1*, and *STAR*), and no mutations were found. Other cases of IMAGE syndrome are reviewed. © 2006 Wiley-Liss, Inc.

Key words: adrenal hypoplasia congenita; autosomal recessive; cytomegalic adrenal cells; adrenal insufficiency

How to cite this article: Tan TY, Jameson JL, Campbell PE, Ekert PG, Zacharin M, Savarirayan R. 2006. Two sisters with IMAGE syndrome: Cytomegalic adrenal histopathology, support for autosomal recessive inheritance and literature review. *Am J Med Genet Part A* 140A:1778–1784.

INTRODUCTION

IMAGE syndrome (OMIM 300290) comprises Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital abnormalities. The term was first coined by Vilain et al. [1999] and to date only 16 cases have been described in the literature [Blethen et al., 1990; Hall and Stelling, 1991; Vilain et al., 1999; Lienhardt et al., 2002; Ferey et al., 2003; Pedreira et al., 2004; Bergada et al., 2005]. The cause of IMAGE syndrome is unknown, although autosomal recessive inheritance is postulated. We present clinical and histopathologic data of two sisters in whom we propose the diagnosis of IMAGE syndrome and review previous cases.

CLINICAL REPORT

Patient 1

The probanda was the third child to healthy unrelated Caucasian parents, aged 37 and 38 years at the time of her birth. Two male siblings aged 4 and 6 years are well, with normal growth and

Grant sponsor: NIH; Grant number: R01 HD044801.

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DOI 10.1002/ajmg.a.31365

development. Pregnancy was complicated by a flu-like illness with fevers at 6 weeks of gestation treated with oral antibiotics. There was occasional maternal use of antihistamines, but no exposure to known teratogens. Antenatal karyotype done for advanced maternal age was 46,XX. Antenatal ultrasound at 18 weeks of gestation showed growth consistent with 17 weeks of gestation. At 30 weeks of gestation, fundal height was reduced, and antenatal ultrasound diagnosed intrauterine growth restriction which persisted until delivery by elective caesarean at 37 weeks of gestation. Birth weight was 1.4 kg (1 kg below 10th centile); head circumference 29 cm (1.5 cm below 10th centile); length 39 cm (6.5 cm below 10th centile). Apgar scores were 6 at 1 min and 8 at 5 min. Respiratory distress was managed with continuous positive airway pressure and oxygen. Echocardiography showed a patent ductus arteriosus and mild pulmonary hypertension. Hyperbilirubinemia was treated with phototherapy. There was an episode of minimal hypoglycemia (blood glucose 2.9 mmol/L) on day one of life that responded to intravenous 10% dextrose and did not recur.

Initial assessment showed a symmetrically growth restricted infant with tiny low-set ears, smooth philtrum, small upturned nose, micrognathia, and short palpebral fissures. She had fine facial features that were somewhat crowded. Genitalia were normal female. There was no clinodactyly or body asymmetry. Her limbs were of normal length. She had bilateral “cocked-up” great toes and a small café-au-lait spot. She was noted to have a high-pitched cry. At age 8 weeks, her tone, tendon reflexes, and motor milestones were normal. Her growth parameters were well below the 10th centile. Audiologic assessment was normal.

At age 3 months, she developed symptoms of a mild upper respiratory tract infection and did not feed well. She was admitted to hospital after a week of feeding difficulties. Over 24 hr, she became progressively lethargic and rapidly deteriorated while waiting for transfer to a tertiary center. She was not able to be resuscitated. Perimortem investigations and postmortem findings are presented.

Patient 2

The sister of the proposita was born at 34 weeks of gestation by caesarean for intrauterine growth restriction first detected on ultrasound scan at 18 weeks. Karyotype analysis of chorionic villous cells was 46,XX. The pregnancy was otherwise unremarkable. No resuscitation was required at delivery. Apgar scores were 7 and 8 at 1 and 5 min, respectively. Birth weight was 1,255 g (445 g <10th centile), length 38 cm (4 cm <10th centile), and head circumference 28 cm (2 cm <10th centile). She developed respiratory distress and required

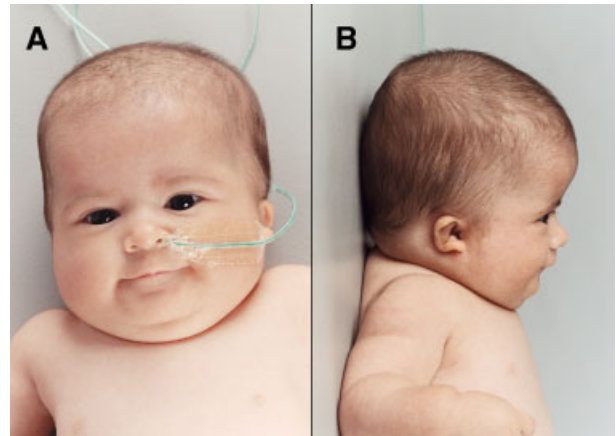


FIG. 1. Clinical features of Patient 2. Note low-set tiny ears, frontal bossing, flat nasal bridge, and micrognathia.

continuous positive airway pressure and ventilatory support for 3 days. One dose of surfactant was given. Jaundice of prematurity was treated with phototherapy. Parenteral nutrition was required for 2 days. A short course of intravenous antibiotics was given for suspected infection.

The facial features of Patient 2 (Fig. 1) were remarkably similar to the facial features of the proposita. She was generally fine-featured, with some midfacial crowding. Her ears were low-set and below the 3rd centile in length. Her nasal bridge was depressed, philtrum was smooth, and her lips were thin. Her palate and uvula were intact. She had mild micrognathia. Her limbs were not shortened. She had bilaterally “cocked-up” great toes. Her genitalia and anus were normal.

At age 6 months, her weight was 3,830 g, length 51 cm, and head circumference 35.5 cm (all parameters well below the 3rd centile). She had two café-au-lait spots, and a 1 cm leg length discrepancy. She was found to have bilaterally dislocated hips and surgical intervention is planned. Development was age-appropriate.

LABORATORY INVESTIGATIONS

Patient 1

Blood films of the proposita showed macrocytosis and Howell–Jolly bodies suggestive of hyposplenism. Direct Coombs antibody test and glucose-6-phosphate dehydrogenase analysis were normal. There were no abnormalities of thyroid function. Cranial and renal ultrasounds were reported as normal with no specific comment on adrenal gland dimensions. Serology for congenital infections (TORCH) was negative, and postnatal karyotype was 46,XX. Fluorescent in-situ hybridization studies were negative for 22q11 and 5p deletions.

Antemortem cortisol level was 443 nmol/L, but the adrenocorticotrophin level was not interpretable due to sample collection problems.

The most significant postmortem findings were the tiny adrenal glands; the right weighing 0.1 g and the left weighing 0.2 g (normal range 1.5–2.0 g each). The pituitary gland was also small, measuring 2.5 × 2.2 mm.

Microscopic findings of both adrenal cortices were similar. The bulk of the cortex was made up of large cells varying in size from 50 microns to over 100 microns in diameter. These cells formed confluent sheets replacing the normal columnar arrangement of the cortical cells. The abnormal cells had pink granular cytoplasm and irregular hyperchromatic nuclei, some of which contained vacuoles (Fig. 2). There were no mitoses. The adrenal medulla was well-formed.

Histology of the pituitary showed a small anterior lobe comprising the three cell types (eosinophil, basophil, chromophobe). Occasional cells with large nuclei (twice the diameter of the normal pituitocytes) were scattered through the gland; most of these were eosinophils. The posterior lobe was normal.

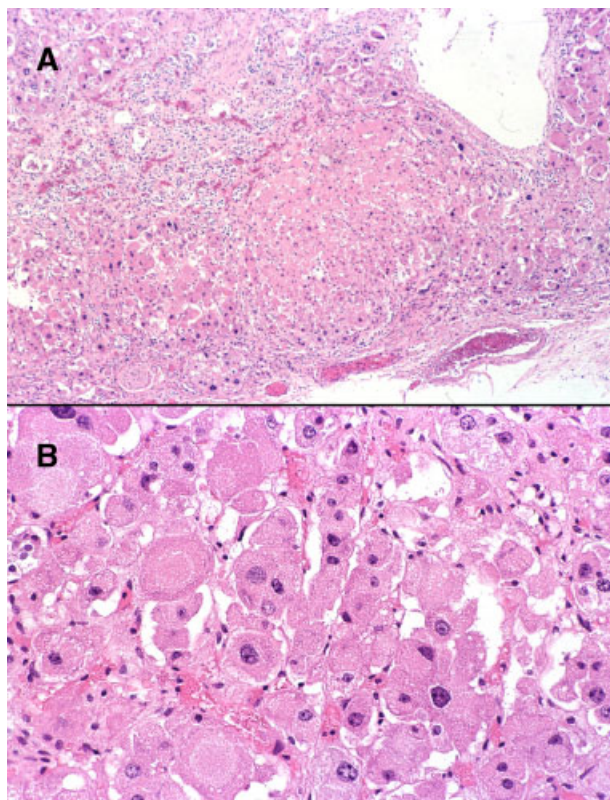


FIG. 2. Adrenal histology of Patient 1 (A) magnification 10× disorganized irregular clusters of large cells with abundant eosinophilic granular cytoplasm with intranuclear inclusions and large hyperchromatic nuclei. Note lack of normal layering. B: magnification 20× abnormal cortical cells with granular eosinophilic cytoplasm and large hyperchromatic nuclei.

The rest of the postmortem examination confirmed a small uvula with thin palatal tissue on either side. There was no palatal cleft. The larynx and epiglottis were hypoplastic but normally formed and the trachea was also hypoplastic being slender, but containing cartilage. The heart weighed 15.9 g (95% confidence interval 13–29 g). The right ventricle was slightly thicker than usual (5 mm near the apex). The lungs were congested and fleshy. *Klebsiella pneumoniae* was isolated on microbiology culture from a left lung swab. The spleen was noted to be small, weighing 4.4 g (normal 14 g). Histology of the spleen showed normal red and white pulp.

Patient 2

Primary adrenal insufficiency was diagnosed in Patient 2 on day one of life. Cortisol was 37 nmol/L (lower limit of normal is 200) and ACTH was >278 pmol/L (normal <20). Treatment was commenced with fludrocortisone and hydrocortisone. Levels of other anterior pituitary hormones were within normal limits. Serum calcium levels were not elevated. No abnormalities were seen on cranial ultrasound. There was no evidence of renal calcification on ultrasound. There were no cardiac abnormalities on echocardiogram. Postnatal high-resolution karyotype was 46,XX and no subtelomeric abnormalities were detected on multiplex ligation-dependent probe amplification (MLPA). Biparental inheritance of chromosome 7 was demonstrated on uniparental disomy studies. A 7-dehydrocholesterol level was within normal limits.

Radiographic features at 6 months of age include widened rib metaphyses, metaphyseal cupping of the metacarpals and proximal phalanges, and absence of the femoral capital epiphyses (Fig. 3). There were no abnormalities of the long bone metaphyses.

After obtaining written informed consent, genomic DNA was extracted from peripheral blood leukocytes using standard procedures. The coding sequences of *DAX-1*, *SF-1*, and *STAR* were amplified by PCR using specific oligonucleotide primer pairs and conditions described previously [Achermann et al., 1999a; Bhangoo et al., 2005]. Direct sequencing of PCR products was performed using a Taq big dye terminator sequencing kit and ABI 310 automated sequencer (PE Applied Biosystems, Foster City, CA). No mutations were found in the coding regions or splice sites of the *DAX-1*, *SF-1*, and *STAR* genes.

DISCUSSION

Congenital hypoplasia of the adrenal glands (AHC) is a rare condition described in two histologically distinct forms, X-linked (OMIM 300200) or autosomal recessive (OMIM 240200). The X-linked recessive form is characterized by lack of the

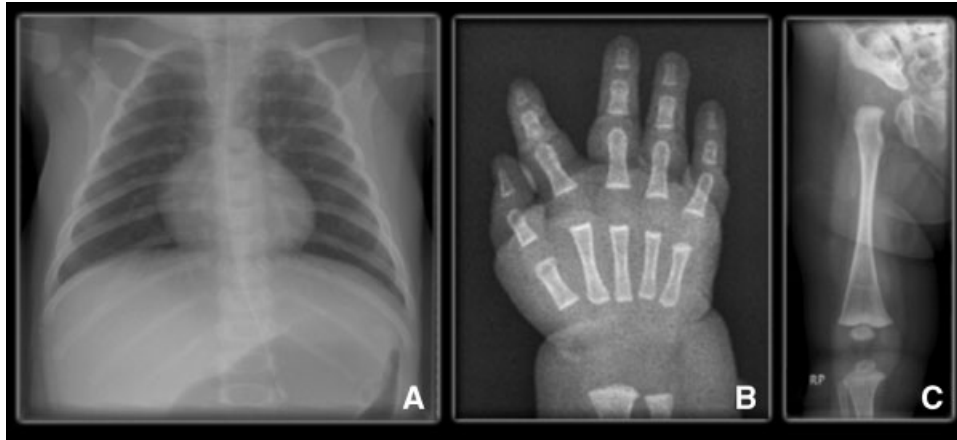


FIG. 3. Radiographic images of Patient 2 (A) chest X-ray: note widened rib metaphyses, and only 11 ribs on the right; (B) right hand X-ray: metaphyseal cupping of the short tubular bones, observed best in the metacarpals and proximal phalanges; (C) right lower limb and pelvis X-ray: note absence of capital femoral epiphyses.

permanent adult cortical zone with consequent adrenocortical failure. The remaining cortical cells are eosinophilic and large (“cytomegalic”), irregularly clumped, and contain typical nuclear inclusions [Weiss and Mellinger, 1970]. Hypogonadotrophic hypogonadism, presenting with pubertal failure, is a frequent association of the X-linked form of AHC [Hay, 1977; Hay et al., 1981]. Affected males usually present in infancy [Reutens et al., 1999] with symptoms of adrenal crises, but presentation in later life has been reported [Tabarin et al., 2000]. The gene for X-linked AHC, *NROB1* (OMIM 300473) was cloned in 1994 and codes for *DAX-1* (dosage-sensitive sex-reversal—AHC critical region on the X chromosome, gene 1) [Muscatelli et al., 1994]. *DAX-1*, a transcriptional regulator belonging to the nuclear receptor superfamily [Zanaria et al., 1994; Burriss et al., 1996; Phelan and McCabe, 2001; Zhang et al., 2001], is expressed at all levels of the hypothalamic-pituitary-adrenal-gonadal axis [Zanaria et al., 1994; Guo et al., 1995] and regulates pubertal development [Habiby et al., 1996]. Females with a *DAX-1* mutation/deletion may be affected [Bartley et al., 1982] or may have delayed puberty [Phelan and McCabe, 2001].

Another form of AHC (OMIM 240200) is also referred to as the “miniature adult” form [Phelan and McCabe, 2001] because the adrenal is undersized, composed almost entirely of permanent cortex, but appears histologically normal. It may occur sporadically or by autosomal recessive inheritance, and may be associated with abnormalities of the central nervous system such as anencephaly. It may form part of an autoimmune polyendocrinopathy [Gambelunghe et al., 1999].

AHC is genetically heterogeneous, as not all cases are found to have mutations in *NROB1*. Mutations in *NR5A1* (encoding SF1, a protein that interacts with *DAX-1*), were found in patients with adrenal insufficiency [Achermann et al., 1999b].

We analyzed the *DAX-1* and *SF1* genes and found no mutations, and no mutations in these genes have been identified in other cases of IMAGE syndrome [Vilain et al., 1999; Lienhardt et al., 2002; Ferey et al., 2003; Pedreira et al., 2004; Bergada et al., 2005]. We also analyzed the gene encoding the steroidogenic acute regulatory (STAR) protein and did not identify any mutations (OMIM 600617). Mutations in the *STAR* gene cause congenital lipoid adrenal hyperplasia, the most severe form of congenital adrenal hyperplasia [Lin et al., 1995]. Affected individuals are unable to synthesize adrenal or gonadal hormones and die of a severe salt-wasting syndrome (with hyperpigmentation and failure to thrive) in infancy if untreated. All are phenotypic females regardless of genotypic sex. Whilst we acknowledge that there are other genes associated with congenital glucocorticoid deficiency such as *MC2R* (OMIM 607397), *CYP11A1* (OMIM 118485), and *AAAS* (OMIM 605378), their clinical presentation is not consistent with the phenotypic features of the patients reported here and were therefore not analyzed.

The two sisters presented here have primary adrenal insufficiency, intrauterine growth restriction, dysmorphic facial features including small low-set ears, and radiographic abnormalities. The diagnosis that most adequately reconciles these clinical findings is IMAGE syndrome (OMIM 300290), comprising Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital abnormalities.

This entity was first recognized in three boys with dysmorphic features, intrauterine growth restriction, metaphyseal dysplasia, AHC, bilateral cryptorchidism, and hypogonadotrophic hypogonadism [Vilain et al., 1999]. Two similar males were described independently in previous reports [Blethen et al., 1990; Hall and Stelling, 1991]. Subsequently, a further 11 cases have been reported, three brother–sister

TABLE I. Clinical Features of IMAGE

	This report		Bliethen et al. [1990]		Hall and Stelling [1991]		Vilain et al. [1999]		Lienhardt et al. [2002]				Fery et al. [2003]		Pedreira et al. [2004]				Bergada et al. [2005]				Total n = 18					
	Patient1	Patient 2	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2	Case 3	Case 4	Case 1	Case 2	Case 1	Case 2	Case 3	Case 4	Case 1	Case 2	Case 3	Case 4						
																								3 months	6 months	4 years, 7 months	7 years, 6 months	6 years
Age at report	37	34	43	2,410	1,700	39	7 years, 6 months	6 years	3 years, 8 months	33	NA	NA	NA	NA	NA	NA	NA	NA	2,065	1,700	2,150	2,300	1,430	8.5 months	37	12 Male, 6 female		
Gender (M/F)	F	F	M	1,255	2,410	M	M	M	M	M	M	F	M	M	M	M	M	M	M	M	M	F	M	M	M	M	12 Male, 6 female	
Gestation (weeks)	37	34	43	2,410	1,700	39	7 years, 6 months	6 years	3 years, 8 months	33	NA	NA	NA	NA	NA	NA	NA	NA	2,065	1,700	2,150	2,300	1,430	8.5 months	37	12 Male, 6 female		
Birth weight (grams)	1,400	1,255	2,410	2,410	1,700	39	7 years, 6 months	6 years	3 years, 8 months	33	NA	NA	NA	NA	NA	NA	NA	NA	2,065	1,700	2,150	2,300	1,430	8.5 months	37	12 Male, 6 female		
IUGR	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Postnatal growth failure	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal insufficiency	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Frontal bossing	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Low-set ears	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Flat nasal bridge	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Palate/uvula abnormalities	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Micrognathia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Genital abnormalities	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Scoliosis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Asymmetry	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Visceral calcification	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypercalciuria/Hypercalcemia	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Skin pigmentation	CAL	CAL	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	CAL/+	+	+	+	+	+	+	+	+	+
Developmental delay	-	-	+	NA	NA	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Craniosynostosis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hip subluxation	-	-	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Osteopenia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Delayed bone age	NA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
Abnormal epiphyses	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Abnormal metaphyses	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GH deficiency	NA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Response to GH	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	+	+	+	+	+	+	+	+	+
Normal puberty	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DAX-1 analyzed	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SF-1 analyzed	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
STAR analyzed	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Familial	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

+, present; -, absent; NA, not available/applicable; CAL, café-au-lait spot.

pairs [Lienhardt et al., 2002; Ferey et al., 2003], one isolated case [Pedreira et al., 2004] and four cases from one pedigree [Bergada et al., 2005]. The clinical features of the previously reported cases are summarized in Table I.

The dysmorphic features of IMAGE syndrome include frontal bossing, low-set ears, and flat nasal bridge. Less common features include a high-arched palate, cleft or bifid uvula, craniosynostosis, and micrognathia. Scoliosis, although uncommon, may be severe [Vilain et al., 1999; Bergada et al., 2005]. The genital abnormalities reported in IMAGE syndrome have been limited to males and include cryptorchidism, micropenis, and hypospadias; this may be a reason for under-ascertainment of females. A rare complication, hypercalciuria and/or hypercalcemia may be associated with renal, hepatic, or splenic calcification and may reflect an abnormality of calcium metabolism. Growth hormone deficiency was detected in two patients [Blethen et al., 1990; Pedreira et al., 2004], and in three patients growth improved with the administration of growth hormone [Blethen et al., 1990; Lienhardt et al., 2002; Pedreira et al., 2004]. All patients in whom pubertal status was able to be assessed had normal onset of puberty [Lienhardt et al., 2002; Ferey et al., 2003; Bergada et al., 2005].

Ours is the first report of adrenal histopathology in IMAGE syndrome. The histologic findings in our patient are similar to those seen in the X-linked recessive cytomegalic form of adrenal insufficiency related to mutations in the *DAX-1* gene. Of particular interest is a brief report of two sisters with adrenal hypoplasia and histologic features of the X-linked recessive form of AHC [Kruger et al., 1993] (OMIM 202155). The first girl was small-for-dates and died at age 7 weeks. The second daughter was also small-for-dates and developed adrenocortical insufficiency, requiring treatment with hydrocortisone and fludrocortisone. It was reported that her adrenals could not be identified by computed tomography at age 1 year. Radiographic investigations were not reported, and a detailed report was not published. Parental consanguinity was not commented upon, but autosomal recessive inheritance was proposed. Our data suggest that there is an autosomal locus for the cytomegalic form of AHC. Having two sisters with an early onset of symptoms in the presence of two phenotypically normal male siblings without adrenal insufficiency would make skewed X-inactivation unlikely. The 2:1 male:female ratio of reported cases is likely to be coincidental, and it is possible that adrenal insufficiency/IMAGE syndrome is under-recognized in females. The pedigree reported by Bergada et al. [2005] is complex and likely to be non-Mendelian; a defect of imprinting was proposed. We maintain that autosomal recessive inheritance in IMAGE syndrome is most likely because of sibling recurrence and severely affected females.

The onset of the skeletal abnormalities in individuals with IMAGE syndrome is not known and may be variable. The epiphyseal and metaphyseal abnormalities at age 6 months in our Patient 2 is the earliest reported. Another patient exhibited humeral and tibial fractures of unknown cause at the age of 20 days, at which time she died unexpectedly with severe hyponatremia [Lienhardt et al., 2002].

The pathogenesis of the adrenal and skeletal findings of IMAGE syndrome is unknown. It is possible that IMAGE syndrome represents a contiguous gene defect, similar to that seen in patients with AHC associated with glycerol kinase deficiency and Duchenne muscular dystrophy (an association that led to the localization of the *DAX-1* gene to the Xp21 region) [Walker et al., 1992; Worley et al., 1993; Bardoni et al., 1994]. All patients reported to date have had normal high-resolution karyotypes; submicroscopic-chromosomal anomalies may be detected with more widespread use of array-based comparative genomic hybridization (CGH).

Another possibility for the etiology of IMAGE syndrome is a mutation in a gene with effects on bone and adrenal development (and possibly calcium metabolism). Adrenal insufficiency is not known to be associated with any of the well-known chondrodysplasias characterized by metaphyseal changes. A patient with an autoimmune-polyendocrinopathy-candidiasis-ectodermal dysplasia (APECED) syndrome was reported to have metaphyseal abnormalities of the tibia in addition to diabetes, hepatitis adrenal failure, and a novel mutation in the autoimmune regulator *AIRE* gene [Vogel et al., 2003]. This is not a common association, however (OMIM 607358). A unifying molecular mechanism may become clearer with further study of the phenotype, as seen in those patients reported with the skeletal abnormalities of Antley-Bixler syndrome (OMIM 207410), ambiguous genitalia and defects of steroidogenesis found to have mutations in the cytochrome P450 reductase gene [Huang et al., 2005].

We conclude that IMAGE syndrome is a rare disorder of unknown pathogenesis that may be under-recognized particularly in females, and that autosomal-recessive inheritance is most likely. The presence of cytomegalic cells on adrenal histopathology suggests that this appearance is not exclusively seen in patients with AHC associated with a *DAX-1* mutation.

ACKNOWLEDGMENTS

We thank the family for their willingness to contribute to this work and Robin Forbes for her invaluable assistance. We also thank Wen Xia Gu for the molecular analyses of the *DAX-1*, *SF-1*, and *STAR* genes.

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