IMAGe Syndrome: Case Report With a Previously Unreported Feature and Review of Published Literature

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IMAGe syndrome is a rare condition, first reported by Vilain et al., in 1999, characterized by intrauterine growth restriction, metaphyseal dysplasia, congenital adrenal hypoplasia, and genital anomalies. Patients with this condition may present shortly after birth with severe adrenal insufficiency, which can be life-threatening if not recognized early and commenced on steroid replacement therapy. Other reported features in this condition include, hypercalciuria and/or hypercalcemia, craniosynostosis, cleft palate, and scoliosis. We report on a 7-year-old boy with IMAGe syndrome, who in addition to the features in the acronym also has bilateral sensorineural hearing loss which has not been reported in previously published cases of IMAGe syndrome. We discuss the clinical presentation in our patient and review the literature in this rare multisystem disorder.

How to Cite this Article:

CLINICAL REPORT

The propositus is the first-born child of healthy, nonconsanguineous parents with no significant family history. The father is a contiguous gene deletion syndrome together with glycerol kinase deficiency and Duchenne muscular dystrophy. An autosomal recessive form of CAH (OMIM #240200) has also been described. This is also referred to as the “miniature adult form” due to the small size of the adrenal glands.

The cause of IMAGe syndrome is unknown. Several candidate genes have been postulated, these include, DAX1, SF1, ACD, and STAR. However, no mutations have been identified to date [Hutz et al., 2006; Tan et al., 2006], Vilain et al. [1999], Lienhardt et al. [2002], Ferey et al. [2003], Pedreira et al. [2004], Bergada et al. [2005], and Amano et al. [2008] have analyzed the DAX1 and SF1 genes and no mutations were identified. In the present report, we describe a 7-year-old child with IMAGe syndrome, who in addition has the previously unreported feature of bilateral sensorineural hearing loss. We review the published literature and describe the radiological features of this condition, with particular relevance to our patient.

INTRODUCTION

Vilain et al. [1999] reported on three boys with congenital adrenal hypoplasia (CAH), intra-uterine growth restriction, metaphyseal dysplasia, and genital anomalies. Since then there have been nine further articles describing IMAGe syndrome. Lienhardt et al. [2002] and Tan et al. [2006] have suggested an autosomal recessive pattern of inheritance based on family history. Bergada et al. [2005] postulated genomic imprinting mechanism based on their family pedigree.

CAH is relatively rare, with an estimated frequency of 1:12,500 live births. It can be a life-threatening, critical disorder, presenting immediately after birth with primary adrenal insufficiency. Prompt replacement with steroids is essential for survival. There are two distinct forms, X-linked CAH (also referred to as the cytomegalic form) is an inherited disorder of adrenal cortical development (OMIM #300200). It is frequently associated with hypogonadotropic hypogonadism and often presents with primary adrenal insufficiency. X-linked CAH has been associated with mutations in the DAX-1 gene located at Xp21 region. It can also occur as part of
Chinese, the mother is Caucasian. There was increased nuchal fold thickening and severe intrauterine-growth restriction was identified at 20 weeks gestation. chorionic villous sampling showed normal male karyotype and TORCH screen was negative. The pregnancy was closely monitored and delivery was induced at 32 weeks gestation. He was delivered by caesarean with a birth weight of 936 g (<0.4th centile), head circumference of 29 cm (25th centile), and length 35.9 cm (<=0.4th centile).

He was ventilated immediately after birth until 9 days of age. On day 3 of life, he had an adrenal crisis with severe hyponatremia. He was diagnosed with CAH and commenced on replacement therapy. His skin was noted to be hyperpigmented and he was also noted to have coronal hypospadias with mild chordee and right undescended testis. He had hypercalciora. He stayed in the special care baby unit for 77 days, mainly due to severe feeding problems and failure to gain weight. He was subsequently discharged home on nasogastric tube feeding.

The propositus was subsequently followed up in the endocrine clinic and a possible diagnosis of IMAGe syndrome was considered, based on the clinical features. Studies looking for DAX1 and SF1 mutations were negative. SNP microarray was negative. Other investigations included: a normal male karyotype and normal pituitary function tests. His renal ultrasound showed no evidence of nephrocalcinosis. Initial skeletal survey at 2 years of age revealed slender ribs and clavicle and small proximal femoral epiphysis with no evidence of metaphyseal dysplasia. He also had delayed bone age.

On subsequent reviews, he was noted to have severe failure to gain weight. At a chronological age of 13 months, corrected gestation of 11 months, his weight was 5.86 kg and length 61.5 cm (<0.4th centile), head circumference of 46.5 cm (25th centile). He was noted to have mild global developmental delay, functioning below the 0.4th centile with poor linear growth. At the age of 3 years 11 months, his weight was 12.5 kg (<0.4th centile), height was 80.5 cm (10 cm below the 0.4th centile), and head circumference was 52.5 cm (50th to 75th centile). He remained on adrenal replacement therapy. On examination, our patient has a prominent forehead with a depressed nasal bridge and short nose. He has simple cupped ears, which are slightly low-set (Fig. 1). He has relative macrocephaly and mild fifth finger clinodactyly. He went on to have an orchidopexy for his right undescended testis at 2 years of age. The genital anomalies are not of major concern at the moment, but are being followed-up by relevant professionals.

In terms of his hearing, he had passed the newborn hearing screen. There was no evidence of auditory neuropathy due to prematurity. He only had one episode of infection during his course in the neonatal period needing antibiotics. However, on follow-up he failed a distraction test, which subsequently indicated evidence of bilateral sensorineural hearing loss. He was provided with hearing aids at 3 years of age. The thresholds in the right ear range from 55 dBHL for the low frequencies down to 70–75 dBHL for the higher frequencies on the right and 60–75 dBHL on the left. Sondfield performance testing and binaural threshold ranging from 55 to 70 dBA were recorded across the speech frequencies. He was also noted to have very shallow conchae, needing more appropriate fitting of his hearing aids. His tympanograms were reported as normal. Connexin-26 testing was negative.

Developmental assessment of our patient revealed delayed milestones, in that he sat at 10–11 months of age, took his first steps at 22 months, did not crawl and was a bottom-shuffler. His speech was also delayed, although he had very good understanding. At 3 years 11 months, his functioning was at a 2.5-year level. On ophthalmic assessment, he was noted to have good binocular function and there was no evidence of squinting. He was reported to have healthy retinas.

Genetics evaluation at 6 and 7 years of age, revealed similar examination findings as before. His growth was still delayed with weight of 15.6 kg (<0.4th centile), height 90.4 cm (<0.4th centile), and head circumference of 52.5 cm (25th centile). Bone age was delayed demonstrating a bone age of 3.4 years at a chronological age of 8 years. Repeat skeletal survey at 7 years of age showed evidence of flattened distal femoral epiphysis with epiphyseal dysplasia. The hip X-ray at 7 years showed flattening and fragmentation of the proximal femoral epiphysis with broad proximal femoral metaphysis. There was normal appearance to the acetabulum and evidence of epiphyseal dysplasia in the left femoral head. There were accessory ossification centers of the metaphyses in the index and middle fingers. Accessory ossification centers were also noted in the epiphyses of the 2nd, 3rd, and 4th metatarsals. There was some evidence of mild metaphyseal dysplasia and progression of epiphyseal dysplasia was noted (Fig. 2). He continues to have mild global developmental delay, in particular speech delay and delayed linear growth. He has been commenced on growth hormone (GH) therapy, despite normal pituitary function tests, which has contributed to better linear growth.

DISCUSSION

IMAGe syndrome is a rare, but well-recognized multisystem disorder of unknown etiology. It has a broad phenotype and early recognition is important to avoid major and possibly life-
threatening complications due to CAH. This condition was first recognized as an entity by Vilain et al. [1999]. However, previous case reports have alluded to a similar phenotype. Blethen et al. [1990] reported a prenatal and postnatal growth deficient child with CAH, GH deficiency, psychomotor delay, and multiple congenital anomalies. Hall and Stelling [1991] described a 7.5-year-old male with adrenal insufficiency, facial dysmorphism, genital abnormalities, and abnormal epiphysis. To our knowledge, there are only 20 published cases of IMAGe syndrome in medical literature.

Postulated candidate genes for IMAGe syndrome included, DAX1, SF1, ACD, and STAR, but no mutations have been identified to-date. An autosomal recessive pattern of inheritance is suggested as the mode of inheritance by some authors, due to sib-pairs being reported with this condition [Lienhardt et al., 2002; Ferey et al., 2003; Tan et al., 2006]. However, in the family pedigree reported by Bergada et al. [2005] they suggest the possibility of genomic imprinting with expression through maternal transmission involving an autosomal dominant gene.

Amano et al. [2008] demonstrated the radiological evolution in IMAGe syndrome. They mentioned metaphyseal dysplasia being important for the diagnosis of IMAGe syndrome. However, metaphyseal dysplasia varies among previously reported patients with IMAGe syndrome. Delayed epiphyseal ossification and epiphyseal dysplasia has also been a consistent finding in previous children reported with this condition. In our patient, skeletal survey done at 2 and 7 years of age have consistently demonstrated epiphyseal dysplasia and delayed epiphyseal ossification. Another interesting feature, not previously described is the presence of accessory ossification centers in the metacarpals and metatarsals in our patient. The significance of this finding is unclear, but whether this may be another feature of IMAGe syndrome remains to be seen.

Accessory ossification centers can be a variant of normal in children and adolescents. Other conditions where this is seen include Cleidocranial dysplasia, oto-palato-digital syndrome, and trisomy 21, where it is seen more commonly. It is rarely also seen in brachydactyly Type C, Wolf–Hirschhorn syndrome, diastrophic dysplasia, Dyggve–Melchior–Clausen syndrome, Fanconi anemia, hand–foot genital syndrome, Larsen syndrome (especially in the calcaneus), peripheral dysostosis, spondylo-epiphyseal dysplasia, and trisomy 9p. Accessory ossification centers primarily affecting the second metacarpal are also seen in 3-M syndrome, XXXXY syndrome, Cockayne syndrome, and Gordon syndrome [Reeder and Felson, 2003].

The metaphyseal dysplasia in IMAGe syndrome may be very mild and not recognized easily. Previous case reports have demonstrated the mild nature of metaphyseal dysplasia in this condition [Bergada et al., 2005; Tan et al., 2006; Amano et al., 2008]. Most patients with IMAGe syndrome have had both epiphyseal and metaphyseal changes on skeletal survey. Amano et al. [2008] have shown that metaphyseal changes, particularly longitudinal metaphyseal striations can appear by late infancy and then progress with age.

Epiphyseal dysplasia has also been consistently reported as a feature in IMAGe syndrome and should be considered as a diagnostic feature in the absence of clear evidence of metaphyseal dysplasia, as the metaphyseal changes may be variable and confined to the short tubular bones or relatively mild as in our patient.

In view of the life-threatening nature of adrenal insufficiency in IMAGe syndrome, it is important for neonatologists to be aware of this entity, particularly when dealing with acute clinical deterioration of babies with severe IUGR or babies that are small-for-gestational age. In most case reports of IMAGe syndrome, the adrenal insufficiency has manifested as adrenal crisis in the first few days of life, except in the case report by Pedreira et al. [2004]. GH deficiency has also been reported in some of the reports [Pedreira et al., 2004; Hall et al., 1991]; however, this is not an invariable feature in IMAGe syndrome. In our patient, GH therapy was commenced at 2 years of age, although he did not demonstrate GH deficiency and had normal pituitary function tests. In these patients, GH therapy may help accelerate linear growth, particularly if there is any suggestion of GH deficiency. In patients with some of the clinical features of IMAGe syndrome, GH deficiency, presence of epiphyseal dysplasia, hypercalciuria are other features, which may help make a diagnosis of IMAGe syndrome.

Table I shows a comparison of previously reported cases with IMAGe syndrome. Dysmorphic features in IMAGe syndrome include prominent forehead, low-set ears, flat nasal bridge, and short nose. Genital abnormalities in IMAGe syndrome seem to be confined to males and include micro penis, undescended testes, and hearing loss is not a previously reported feature of this association. Although, this could be co-incidence, it is possible that this may be
## TABLE I. Clinical Features of Patients Reported With IMAGe Association

<table>
<thead>
<tr>
<th>Gender</th>
<th>IUGR</th>
<th>Postnatal growth</th>
<th>Adrenal crisis</th>
<th>Genital features</th>
<th>Renal anatomy</th>
<th>Epiphyseal dysplasia</th>
<th>Metaphyseal dysplasia</th>
<th>Delayed bone age</th>
<th>Macroecephaly</th>
<th>Facial features</th>
<th>GH deficiency</th>
<th>Hypercalcemia/hypercalciuria</th>
<th>Hearing loss</th>
<th>Dev. outcome</th>
<th>Inheritance</th>
</tr>
</thead>
</table>

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**Note:** +, present; —, absent; N/A, not applicable or not available; ?, not specified.
an additional feature in IMAGe syndrome. Further case reports are needed to identify if this is an additional feature in this condition.

In summary, we report on another child with IMAGe syndrome, who in addition to previously reported features also has bilateral sensorineural hearing loss. This case report expands the phenotypic spectrum of this condition and raises the possibility of making this diagnosis based on the presence of epiphyseal dysplasia in the absence of features of metaphyseal dysplasia, as this may be very mild and evolution of features may be age-dependant.

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REFERENCES


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