Atlas of Genetic Diagnosis and Counseling
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Isolated Growth Hormone Deficiency in Children

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Among children with significant short stature (height of ≤ -2.5 standard deviations (SD)), 16–20 % have growth hormone deficiency (GHD), which may be isolated (IGHD) or combined (CGHD) with deficiency of other pituitary hormones (Desai et al. 1991). Congenital IGHD occurs in 1 in 4,000 to 1 in 10,000 live births, with prevalence of 1 in 3,500 in school-age population (Lindsay et al. 1994). It is often sporadic and nonfamilial (NFIGHD) but may be familial (FIGHD) in 3–30 % (Mullis 2007; Rimoin and Phillips 1997) (Figs. 1, 2, and 3).

Synonyms and Related Disorders

Dwarfism of Sindh; Hypogammaglobulinemia and isolated growth hormone deficiency, X-linked; Isolated growth hormone deficiency, Types IA, IB, II, and III; Pituitary dwarfism due to isolated growth hormone deficiency, autosomal dominant; Pimordial dwarfism

Genetics/Basic Defects

1. Causes of IGHD (Dattani and Preece 2004; Wit et al. 2011; Alatzoglou and Dattani 2012; Desai et al. 2013)
    1. Congenital: often due to genetic mutations
        1. Associated with structural defects of the brain
            1. Agenesis of the corpus callosum
            2. Septo-optic dysplasia
            3. Holoprosencephaly
            4. Encephalocele
            5. Hydrocephalus
        2. Associated with midline facial defects
            1. Cleft lip or palate
            2. Single central incisor
    2. Acquired
        1. Trauma
        2. Infections
        3. CNS tumors
        4. Langerhans cell histiocytosis
        5. Postcranial irradiation
        6. Postchemotherapy
        7. Pituitary infarction

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8. Neurosecretory dysfunction
9. Psychosocial deprivation
10. Hypothyroidism

2. Gene implicated in the etiology of IGHD
    1. Growth hormone 1 gene (*GH1*)
        1. Located on chromosome 17q22-q24
        2. Mutating the coding region and/or either entire or partial deletions of the *GH1* gene lead to IGHD
    2. Mutations in the receptor of growth hormone–releasing hormone gene (*GHRHR*)
    3. Mutations caused by other genetic factors
        1. Genetic defects associated with multiple pituitary deficiencies: e.g., PROPHET OF PIT1 gene (*PROP1*) and POU Domain, Class 1, Transcription Factor 1 gene (*POU1F1*)
        2. Rare causes: mutations in the transcription factors
            1. Homeobox Gene Expressed in Es Cells gene (*HESX1*): associated with septo-optic dysplasia (McCabe et al. 2011) or may cause IGHD with or without optic nerve hypoplasia
            2. SRY-Box 2 gene (*SOX2*): usually associated with anophthalmia/severe microphthalmia and part of the endocrine spectrum (hypogonadotrophic hypogonadism), a hypoplastic anterior pituitary, and growth hormone deficiency (Kelberman et al. 2006)
            3. Homologue of Orthodenticle, Drosophila, two gene (*OTX2*): variable phenotype ranging from IGHD to hypopituitarism with or without ocular malformations (Ashkenazi-Hoffnung et al. 2010; Dateki et al. 2010; Tajima et al. 2009)
    4. Mutations in known genes account only for a small percentage of cases; other as yet unidentified factors may be implicated in its etiology
3. Classification of four genetic forms of IGHD
    1. Autosomal recessive type IA
        1. Gene: *GH1* (17q23.3)
        2. Phenotype
            1. Undetectable GH
            2. Anti-GH antibodies on treatment
    2. Autosomal recessive type IB
        1. Gene: *GH1*, *GHRHR* (7p14.3), Growth Hormone Secretagogue Receptor gene (*GHS*R), *HESX1*
        2. Phenotype
            1. Low detectable GH
            2. No antibodies to recombinant human GH (rhGH) treatment
    3. Autosomal dominant Type II
        1. Gene: *GH1*
        2. Phenotype
            1. Less severe short stature
            2. Variable phenotype
    4. X-linked recessive Type III
        1. Gene: *SOX3*, Bruton tyrosine kinase gene (*btk*) (Xq22.1), or other yet unknown genes (Stewart et al. 2008)
        2. Phenotype
            1. With or without mental retardation
            2. Ectopic posterior pituitary

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Clinical Features

1. Principal mode of presentation of IGHD: proportional short stature and a low/decreased growth velocity for age and pubertal stage (Pinto et al. 1999; Shalet et al. 1998; Alatzoglou and Dattani 2012)
2. Additional criteria
    1. Absence of bone dysplasias
    2. Absence of chronic disease
    3. Skeletal maturation: usually delayed in proportion to height retardation
3. Age of presentation
    1. Highly variable from the first few months of life to adolescence
    2. Highly influenced by the time of onset and the degree of GFD (Adan et al. 1994)
4. IGHD Type IA
    1. At birth: may or may not have short length
    2. By the first 6 months of life: present with severe growth failure (height SD < -4.5)
    3. Infancy: may or may not have hypoglycemia
    4. Puppet (baby doll) facies
5. IGHD Type IB
    1. Less severe and more variable phenotype compared to those with type IA
    2. Marked short stature
    3. Poor growth velocity
6. IGHD Type II
    1. Commonest genetic form of IGHD
    2. Exhibiting significant variability in time of presentation and severity of GHD
7. IGHD Type III
    1. Variable phenotype: ranging from IGHD to hypopituitarism
    2. With or without mental retardation
    3. Infections
        1. Sinusitis
        2. Chronic otitis media leading to hearing loss
        3. Conjunctivitis
        4. Pneumonia
        5. Enteroviral hepatitis
        6. Diarrhea
        7. Epididymitis
        8. Prostatitis
        9. Urinary tract infections
        10. Septic arthritis
        11. Pyoderma
        12. Meningitis/encephalitis
    4. Immunology
        1. Frequent bacterial infections
        2. Severe enteroviral infections
        3. Absent B lymphocytes in all organs
        4. Absent antibody production
        5. Small tonsils
        6. Panhypogammaglobulinemia
        7. Susceptive to infections starting in the first week of life

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8. Consensus statement criteria to initiate evaluation for GHD (Consensus Guidelines for the Diagnosis and Treatment of GHD in Childhood and Adolescence from the GH Research Society (2000))
    1. "Severe" short stature [height < -3 standard deviation (SD) below mean]
    2. Height less than -1.5 SD below midparental height
    3. Height less than -2 SD below mean and either height velocity less than -1 SD below mean over past year or decrease in height SD of more than 0.5 SD over past year
    4. In the absence of short stature, height velocity less than -2 SD below mean over 1 year OR less than -1.5 SD below mean over 2 years
    5. Signs of an intracranial lesion
    6. Signs of multiple pituitary hormone deficiency
    7. Neonatal signs and symptoms of GHD, including hypoglycemia, prolonged jaundice, microphallus, or craniofacial midline abnormalities

Diagnostic Investigations

1. Consensus Guidelines for the Diagnosis and Treatment of GHD in Childhood and Adolescence from the GH Research Society (2000)
    1. The degree of short stature
    2. Growth velocity
    3. Radiographic assessment of bone age
        1. Bone age: delayed
        2. Degree of delay: related to the severity and duration of GHD
    4. Measurement of insulin-like growth factor I (IGF-I) and IGF-binding protein 3 (IGFBP-3)
        1. Considerable overlap between IGF-I and IGFBP-3 values in children with GHD compared to normal children
        2. These measures have reasonable specificity and are useful in conjunction with other diagnostic criteria
    5. Provocative growth hormone (GH) testing (postexercise, L-DOPA, insulin tolerance, arginine, insulin–arginine, clonidine, glucagon, and propranolol protocols): The results are poorly reproducible and dependent on
        1. The assay used
        2. The pubertal and nutritional status of the child
        3. The GH secretion pattern prior to testing
    6. Testing for concomitant deficiencies of LH, FSH, TSH, and ACTH
2. If growth hormone deficiency is congenital and complete, the diagnosis is relatively easy to confirm (Rogol 2014)
    1. Affected children present with severe growth failure and very low serum concentrations of growth hormone, insulin-like growth factor I (IGF-I), and its major binding protein, IGFBP-3.
    2. If diagnosed in infancy, they may also manifest hypoglycemia, prolonged jaundice, microphallus in males, and giant cell hepatitis.
    3. In those diagnosed late, delayed bone age is characteristic.
3. MRI of the hypothalamic–pituitary region: detects anomalies in about 12 % of patients with IGHD
    1. Abnormal findings on pituitary MRI indicate
        1. A relatively high likelihood that GHD will persist in adulthood
        2. That subsequent pituitary deficiencies may develop
    2. Anterior pituitary may appear aplastic or hypoplastic

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Fig. 1 A 10-year-old Caucasian boy was originally evaluated for unusual facies, small for age, and tight hamstrings and heel cords. He has been seen by an endocrinologist and received growth hormone short daily. Chromosome microarray showed Arr cgh 3q22.1 (RP11-883MS) × 1 variant

3. Posterior pituitary may be ectopically sited
4. Septo-optic dysplasia

4. Genetic testing for children with isolated GHD and a family history of GHD (Stanley 2012)
   1. Screening for growth hormone 1 (GH1) and growth-hormone-releasing hormone receptor (GHRHR) mutations (Wit et al. 2011; Kempers et al. 2013)
   2. Other genetic testing is not yet widely applicable in the diagnosis of GHD but may contribute to the diagnosis in the future
5. If there is no clue for a specific gene, consider a whole genome approach, using an SNP array or Array CGH

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Acquired: not increased
      2. Autosomal recessive: 25 % of siblings affected, 50 % of siblings carriers, and 25 % of siblings normal
      3. Autosomal dominant: not increased unless a parent is affected, in which case the recurrence risk is 50 %

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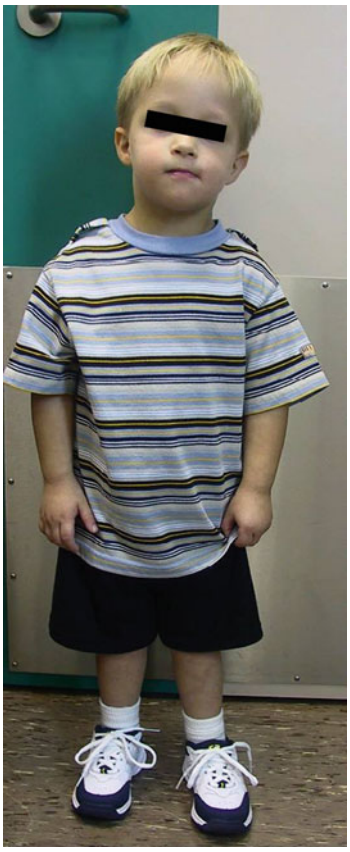

Fig. 2 This 2 year and 8 month old Caucasian boy was evaluated for growth hormone deficiency. He received Humatrope 0.5 mg IM/day since 2 years and 3 month. At 11 years of age, He was receiving 2.4 MG a day (growing at 8 cm a year) and Lupron 15 MG/28 days for his early puberty. His bone age was 13.5 years and IGF-1 was 962NG/ML. He also had acanthosis nigricans

    4. X-linked recessive
        1. If the mother is a carrier: 50 % of brothers affected and 50 % of sisters carriers
        2. If the mother is not a carrier: the recurrence risk is probably low
2. Patient's offspring
    1. Acquired: not increased
    2. Autosomal recessive: not increased unless the spouse is also a carrier, in which case the recurrence risk is 50 %
    3. Autosomal dominant: 50 %
    4. X-linked recessive: None of the sons will be affected; all daughters will be carriers.
2. Prenatal diagnosis by molecular genetic analysis
    1. Prenatal testing for pregnancies at increased risk is possible if the family's specific disease-causing mutation is known
    2. Molecular characterization in a case of isolated growth hormone deficiency leading to prenatal diagnosis of an unknown sibling (Nadar et al. 2013)
3. Management (Rogol 2014)

1. Growth hormone promotes linear growth in children by stimulating cartilage growth, particularly at the epiphyseal plate. In addition, growth hormone increases lean body mass and bone mass and reduces fat mass while increasing plasma and liver lipid content.
2. Replacement using exogenous, biosynthetic (recombinant) growth hormone

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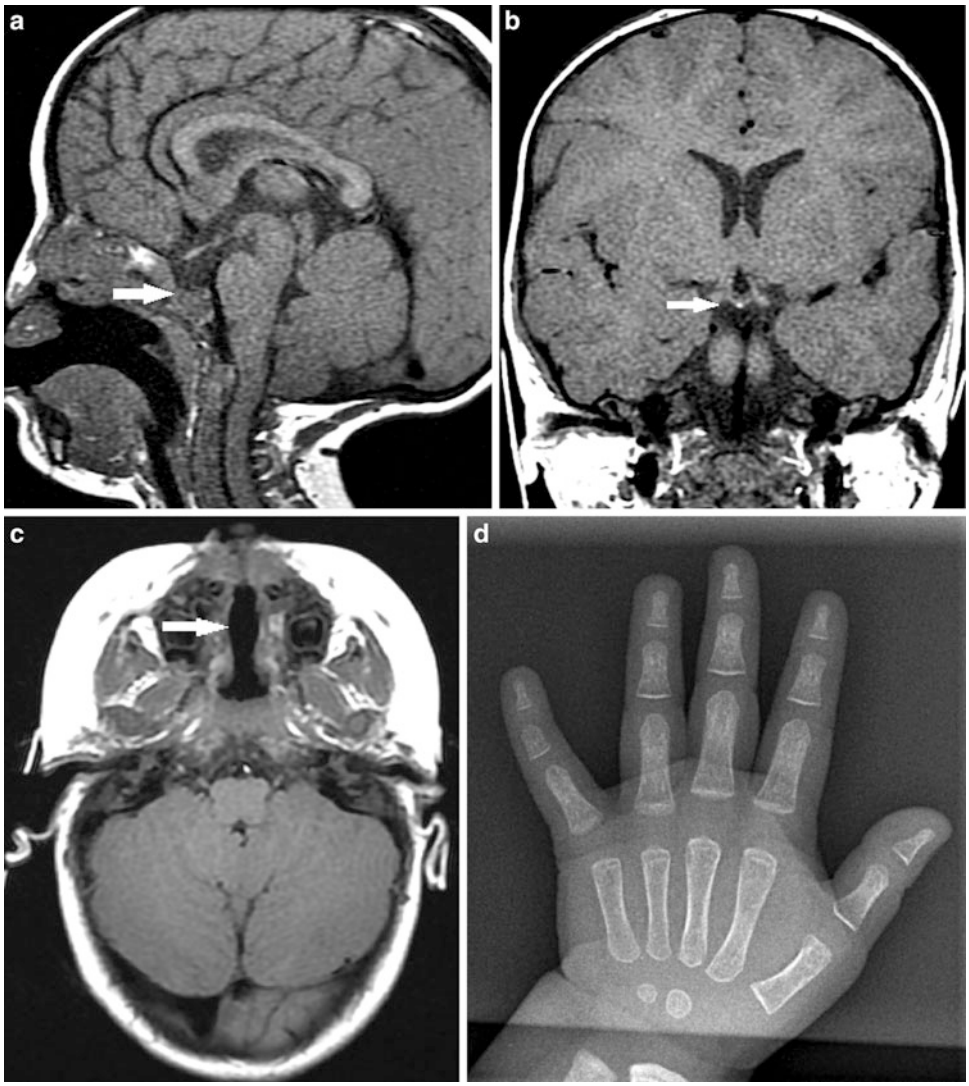

Fig. 3 (**a**–**d**) A 3-years-old girl was diagnosed with isolated growth hormone deficiency. She initially presented for small stature and abnormal MRI of her pituitary gland. Her height was 66.9 cm, which is less than the 3rd percentile. The weight was 7.3 kg, which is less than the 3rd percentile. Blood pressure 88/56, pulse 86. Systemic review was unremarkable for any systemic symptoms. There is decreased level of Insulin-like growth factor 1 (*IGF-1*) and IGF binding protein (*IGFBP-3*). Chromosomal study was reported as normal. MRI images showed hypoplasia of the pituitary lobes which lies within a shallow/small pituitary fossa (*arrow*) (**a**). Marked thinning of the pituitary stalk was noted with ectopic posterior pituitary which is located at the level of the infundibular recess of the third ventricle (*arrow*) (**b**). These findings are compatible with the pituitary stalk interruption syndrome. Cleft lip and cleft palate were also seen (*arrow*) (**c**). PA view of the left hand (**d**) was performed for bone age evaluation. It showed markedly delayed bone age (female standard for 9 months) (Courtesy of Dr. Grace Guo)

3. A majority of children with idiopathic isolated growth hormone deficiency (67–78 %) with partial growth hormone deficiency initially had normal serum growth hormone responses to insulin-induced hypoglycemia at the completion of their growth hormone therapy (Wacharasindhu et al. 1996; Tauber et al. 1997).

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