Growth Hormone & IGF Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Hypothalamic abnormalities: Growth failure due to defects of the GHRH receptor

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ARTICLE INFO

Keywords:
GH
GHRH
GHRHR
IGF-I
IGF-II

ABSTRACT

Several acquired or congenital hypothalamic abnormalities may cause growth failure (GF). We described two of these congenital abnormalities. First, a case of CHARGE syndrome, an epigenetic disorder mostly caused by heterozygous mutations in the gene encoding CHD7, a chromatin remodeling protein, causing several malformations, some life-threatening, with additional secondary hypothalamus-hypophyseal dysfunction, including GF. Second, a cohort of individuals with genetic isolated severe GH deficiency (IGHD), due to a homozygous mutation in the GH-releasing hormone (GHRH) receptor gene described in Itabaianinha County, in northeast Brazil. In this IGHD, with marked reduction of serum concentrations of IGF-I, and an up regulation of IGF-II, GF is the principal finding in otherwise normal subjects, with normal quality of life and longevity. This IGHD may unveil the effects of GHRH, pituitary GH and IGF-I, IGF-II and local GH and growth factor on the size and function of body and several systems. For instance, anterior pituitary hypoplasia, and impairment of the non-REM sleep may be due to GHRH resistance. Proportionate short stature, doll facies, high-pitched pre-pubertal voice, and reduced muscle mass reflect the lack of the synergistic effect of pituitary GH and IGF-I in bones and muscles. Central adiposity may be due to a direct effect of the lack of GH. Brain, eyes and immune system may also involve IGF-II and local GH or growth factors. A concept of physiological hierarchy controlling body size and function by each component of the GH system may be drawn from this model.

1. Introduction

Growth failure (GF) is characterized by a growth rate below the appropriate velocity for age; short stature is height less than two standard deviations below the mean, or near the third percentile. Several acquired or hereditary disorders cause GF, including hypothalamic abnormalities caused by tumors, infiltrative diseases, trauma, systemic conditions, drugs, radiotherapy or genetic disorders. This paper describes two congenital examples of these abnormalities, one involving the CHD7 protein which can lead to misregulation of the methylation of thousands of other genes [1], and the other the receptor for growth hormone (GH) releasing hormone (GHRH).

In the first case, we describe a patient with the CHARGE Syndrome, an epigenetic disorder caused by heterozygous mutations in gene encoding CHD7, a chromatin remodeling protein, which exhibits pleiotropic effects during embryogenesis, causing several malformations, some life threatening, with additional hypothalamus-hypophyseal dysfunction, including GF [1]. In this case, GF is a secondary issue in a critically ill child.

In the second, we summarize the phenotype of an extended kindred with 105 (some deceased) subjects with isolated GH deficiency (IGHD), due to a homozygous inactivating mutation (c.57 + 1G > A) in the GH releasing hormone (GHRH) receptor (GHRHR) gene (*GHRHR*, OMIM n. 612,781) [2]. Most of the affected patients reside in the rural County of Itabaianinha, a highly consanguineous and isolated area in the northeastern Brazilian state of Sergipe [2].

In this severe IGHD with almost undetectable IGF-I concentrations, GF is the principal finding in otherwise apparently normal subjects, with normal quality of life and longevity. This IGHD cohort suggests the actions of GHRH, pituitary GH, IGF-I, IGF-II and local GH and growth factor in the size and function of the body and particular systems. A concept of physiological hierarchy controlling body size and function by each component of the GH system may be drawn from this model.

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https://doi.org/10.1016/j.ghir.2017.12.011
Received 15 September 2017; Received in revised form 19 December 2017; Accepted 19 December 2017
1096-6374/ © 2017 Published by Elsevier Ltd.

1.1. CHARGE syndrome

A 3-week-old old male newborn was transferred to neonatal intensive care unit for multidisciplinary care. He was born by normal delivery, at 40 weeks of gestational age, and was the product of the first pregnancy of a 28-year-old mother with normal prenatal screenings. His prenatal ultrasounds revealed normal intrauterine growth, and no morphologic abnormalities were reported. His APGAR scores were 5 and 7, due to respiratory distress. His birth length was 46 cm and his weight 2.9Kg, both below the3rd percentile. The physical exam revealed the presence of coloboma, atrial septal defect, ventricular septal defect, choanal atresia, undescended testicles, micropenis, and normal neurological exam. The abdominal ultrasound did not show Mullerian structures, but the echocardiogram revealed atrial septal and ventricular septal defects. Brain MRI, showed no pituitary hypoplasia, nor ectopic neuro-hypophysis, but dysplastic cochlea and absent olfactory bulbs were documented, with otherwise normal brain. Laboratory workup revealed mild anemia and undetectable gonadotropins levels with apparently normal thyrotrophic, corticotrophic, and somatotroph axis. Array cGH was normal. He required continuous positive airway pressure (CPAP) for few days and was subsequently weaned off to room air. He had also a hiatal hernia surgically that needed repair on day 2 of life. The diagnosis of CHARGE syndrome, an acronym of **C**oloboma, **H**eart defects, choanal **A**tresia, growth and development **R**etardation, **G**enital and **E**ar abnormalities and deafness, was posed. CHARGE syndrome is often an autosomal dominant disorder, caused by one of more than 500 mutations in CHD7 gene, although recent studies suggested that 10 to 20% of individuals with CHARGE do not have *CHD7* gene mutations or gene dosage abnormalities [1]. Array cGH, used to discover the mutation in the CHD7 gene in CHARGE syndrome does not always show the genetic mutation, as most individuals with CHARGE have small genetic defects that do not affect the entire gene [3].

The care and follow up of the patient involved an interdisciplinary team, including respiratory care: CPAP at birth, weaned off thereafter; cardiovascular care: surgical repair to be scheduled; gastrointestinal care: G tube scheduled for appropriate feeding; nutritional support; endocrine care: testosterone injections for micropenis and growth monitoring; urology care: surgery to explore undescended; and physical occupational therapy.

Charge syndrome affects 1 in 10,000 to 1 in 8000 newborns [3,4]. Individuals with the CHARGE syndrome exhibit broad variability in clinical features, even among affected individuals from the same family who carry the same mutation. The mechanisms underlying this variability are not known, but are likely related to changes in gene expression or genetic modifiers. Roles for CHD7 in cells include formation of large protein complexes and regulation of movement of nucleosomes along DNA [5].

The diagnostic criteria have evolved over time; with the most recent revision by Sanlaville and Verloes [6]. The diagnosis requires the child to have three major criteria or two major and two minor criteria. The major criteria include ocular coloboma, choanal atresia, and semicircular canal hypoplasia. The minor criteria include rhombencephalic dysfunction, hypothalamus-hypophyseal dysfunction, ear malformation, mediastinal organ malformation, and mental retardation. This child had all three major criteria (already diagnostic), and at least three minor criteria, despite the lack of neurologic findings at this age of life, since development and growth delays, speech and hearing impairments often occurs in later childhood:

The proven hypothalamus-hypophyseal dysfunction in this child was hypogonadotropic hypogonadism, with microphallus that was treated with testosterone injections. Growth is being monitored to verify a possible lack of catch-up. In this case, a low IGF-I level, at age 4 years, associated to low GH response to stimulatory GH tests will be required to establish the diagnosis of GH deficiency. If GHD is confirmed, GH replacement therapy will be started as it has been shown to be beneficial for CHARGE patients with GH deficiency [7]. In addition, immunological dysfunction, which predominantly affects T-cell function, has occasionally been described in patients with CHARGE syndrome [8] and deserves to be assessed in this child. CHARGE syndrome exemplifies how disrupted chromatin remodeling can impact human health, causing a multiple anomaly condition associated to hypothalamus-hypophyseal dysfunction. In this case the treatment of the life-threatening conditions was the priority, with a subsequent growth surveillance to cope a possible GF.

Now, we will move to another model in which, a resistance to a hypothalamic factor (GHRH) occurs due to an inactivating mutation (c.57 + 1G > A) in the GHRHR gene.

2. Resistance to the hypothalamic GHRH

2.1. Molecular and hormonal data

The Itabaianinha GHRHR mutation is a transversion (c.57 + 1G > A) in the consensus GT of the 5′ splice donor site of intron 1, preventing the correct splicing of intron 1 from RNA transcripts, as subsequently proven in a different mutation in the same nucleotide [9]. It is the *GHRHR* mutation with the highest number of affected individuals, and chronologically the second of more than twenty inactivating mutations in this gene [10], following the first reported (E72Xc.214G > T) in 2 siblings from consanguineous marriage [11], later reported in eighteen IGHD subjects residing in the Pakistani province of Sindh [12,13].

IGHD subjects exhibit obvious anterior pituitary hypoplasia [14], also described in the mouse model of GHRHR gene mutation (*little* mouse) [15], caused by the lack of the GHRH effect in somatotroph cells expansion. They also show marked reductions of serum concentrations of IGF-I, IGF-II and IGF binding protein type 3 (IGFBP-3) throughout the life [16]. Although, both IGF-I and IGF-II are marked below and completed separated from normal controls, IGF-I reduction is more accentuated with most undetectable levels in all ages [16]. In an attempt to measure the bioavailability of IGF-I and IGF-II, we calculated their molar ratios to IGFBP-3. We found a profound reduction in the ratio of IGF-I to IGFBP-3, accompanied by increase in the IGF-II/IGFBP3 ratio, so that the combined IGF-I plus IGF-II/IGFBP-3 ratio was almost doubled in IGHD adults as compared to controls. This indicates an increase in IGF-II relative to IGFBP-3 in IGHD, to compensate for the diminished IGF-I concentration [16,17]. It is noteworthy that the IGF-I-deficient child with an IGF-I gene deletion described by Woods et al. had IGF-II concentrations that, when expressed as a molar quantity, were 2-fold greater than the concentration of IGFBP-3 [18]. Individuals with Laron syndrome (GH receptor deficiency) are congenitally deficient in IGF-I and have IGF-II concentrations 25% of normal [19]. Conversely, individuals with GHD usually have reduced total and free IGF-II levels [20].

The severity of GHD in this kindred was confirmed by GH peak values consistently lower than 1 ng/ml to a variety of stimulatory tests [2,21]. The low but detectable serum GH response classifies this IGHD model at type 1B (autosomal recessive with low but measurable serum GH) [22]. This model differs from the IGHD type 1A (also autosomal recessive) caused by deletion or nonsense mutations in the GH-encoding gene (*GH1*), causing no detectable GH secretion, and from the GH insensitivity syndrome (Laron syndrome) with similar profound IGF-I deficiency, and high GH levels, but without any GH action [23,24,25].

Affected IGHD subjects from Itabaianinha have higher basal cortisol levels than control individuals, likely due to the increased activity of the enzyme 11 beta-hydroxysteroid dehydrogenase, which converts cortisone to cortisol [26], and modestly higher basal levels of serum TSH [27], possibly reflecting the reduced effect of IGF-I on hypothalamic somatostatin. They also exhibit a reduced serum total T3 and increased serum freeT4, due to a reduction in the function of the GH-dependent deiodinase system [27]. Serum prolactin and gonadotropins

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