Clinical research

Potential role of gender specific effect of leptin receptor deficiency in an extended consanguineous family with severe early-onset obesity

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ABSTRACT

Congenital leptin receptor (LEPR) deficiency is a rare genetic cause of early-onset morbid obesity characterised by severe early-onset obesity, major hyperphagia, hypogonadotropic hypogonadism and immune and neuroendocrine/metabolic dysfunction. We identified a homozygous loss-of-function mutation, NM_002303.5:c.464 T > G; p.(Tyr155*), in the LEPR in an extended consanguineous family with multiple affected individuals influenced by early-onset severe obesity and hyperphagia. Interestingly, the LEPR-deficient adult females have extremely high body mass index (BMI) with hypogonadal infertility, the BMI of the affected males began to decline around the onset of puberty (13–15 years) with fertility being preserved. These findings lead to the speculation that LEPR deficiency may have a gender-specific effect on the regulation of body weight. In order to elucidate gender-specific effects of LEPR deficiency on reproduction further investigations are needed. The limitations of this study are that our conclusion is based on observations of two males and two females. Further LEPR deficient males and females are required for comparison in order to support this finding more confidently.

1 Introduction

Congenital deficiency of the leptin receptor (LEPR) is a rare cause of severe early-onset obesity caused by bi-allelic mutations in the LEPR gene (Dubern and Clement, 2012). LEPR is the most commonly mutated gene in monogenic obesity within consanguineous families (Dubern and Clement, 2012). The LEPR is involved in the regulation of fat metabolism and energy homeostasis, in addition to a wide variety of other neuroendocrine functions (Farooqi et al., 2007; Dubern and Clement, 2012). The clinical presentation of LEPR deficiency is characterised by extreme early-onset obesity occurring soon after birth, marked by hyperphagia with ravenous hunger, as well as increased susceptibility to infection, in particular recurrent respiratory tract infections, which is associated with a deficiency in T-cell number and function. Failure of pubertal development and a lack of secondary sexual characteristics as a consequence of hypogonadotropic hypogonadism and thyrotropic insufficiency of central origin is also frequently seen in these patients (Farooqi et al., 2007; Wasim et al., 2016). Although, there is evidence in the literature of spontaneous pubertal development and improvement in endocrine function over time (Ozata et al., 1999; Nizard et al., 2012).

In this study, we present a large kindred with a novel homozygous loss-of-function mutation in the LEPR. Whilst all affected members have a history of severe hyperphagia and rapid weight gain from birth with severe obesity, interestingly however, unlike the females, the body mass index (BMI) of the affected males began to decrease around the
time of puberty (13–15 years) with subsequent development of normal sexual and reproductive function.

2. Materials and methods

Members of an extended Iranian family comprising nine affected individuals aged three to 36 years-old with severe early-onset obesity across six interlinked nuclear families were enrolled in this study. The family’s pedigree demonstrates an autosomal recessive pattern of inheritance (Fig. 1A). Informed consent was obtained from all participants in accordance with research protocols approved by the institutional review boards of Shahid Sadoughi University of Medical Sciences in Yazd, Iran. Blood samples were collected from the participating individuals and genomic DNA was extracted from peripheral blood using standard methods. Clinical examination, anthropometric, medical and family history particularly obesity-related information was recorded.

To identify the genomic location of the underlying disease gene defect, genome-wide SNP genotyping was performed on DNA samples from affected individuals using the Illumina Human CytoSNP-12 array (Illumina, Santa Clara, CA, USA) containing ∼330,000 markers. The array was processed according to the manufacturer’s protocol. Mutation screening of the entire coding region of LEPR (NM_002303.5) and its exon–intron boundaries was performed by means of bidirectional PCR-amplified Sanger sequencing in the proband of the family.

3. Results and discussion

All the affected members of the family were within the range of normal deciles for head circumference and weight at birth, weight gain occurred rapidly shortly after birth leading to severe obesity in early infancy. There were no abnormalities detected on clinical examination, developmental milestones were reached at the appropriate times with height being within the normal range. The cases presented had marked hyperphagia and demonstrated aggressive constant food-seeking behaviours. Additionally, it was reported that the affected individuals had an increased rate of intestinal and respiratory tract infections compared to their unaffected relatives, this suggests an increased susceptibility to infectious diseases. Furthermore, the parents of these individuals reported that the period of recovery was generally longer in those affected individuals (IV:1, V:1, III:10, III:9, III:7) revealed a single g.464 T > G transition in exon three resulting in a tyrosine (Tyr155*) to stop codon (NM_002303.5:c.464 T > G; p.(Tyr155*) (Fig. 1B). The mutation affects the extracellular N-terminus of the LEPR protein, thus impacting all transcripts, and is predicted to result in nonsense-mediated decay due to the introduction of a premature stop codon, this leads to a complete loss of LEPR. The mutation segregated with the disorder in the family and was not found in the dbSNP, 1000Genome project, genome Aggregation Database (gnomAD) The Greater Middle East (GME) Variome Project and Iranome.

Anecdotally, the BMI of the two affected males aged 36 (III:10) and 32 (III:9) began to reduce from the onset of puberty at the age of 13–15 years-old (Fig. 2), i.e. at the onset of their secondary sexual characteristics. Furthermore, both males have produced three offspring each. On the contrary, the BMI of the two females aged 34 (III:7) and 25 (IV:1) increased over time (Figs. 1C and 2). IV:1 had delayed puberty and developed menstrual ‘like’ bleeding once started on Yasmin (drospirenone/ethinyl estradiol) at the age of 18 years-old. These bleedings were initially irregular, but eventually became monthly bleedings. IV:1 was also diagnosed with an underdeveloped uterus at the age of 18 via sonography. No pubertal development was observed in III:7 and she reached a BMI > 160 at the age of 26 years-old. However, with an
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