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CASE REPORT

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A clinical case of identical twins with hypogonadotropic hypogonadism, primary empty sella syndrome and identified rare *CHD7* gene variant

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Key Clinical Message

Empty sella syndrome is a complex syndrome with a diverse clinical presentation. The combination with functional hypogonadotropic hypogonadism is a real challenge for the clinician. Mutations in the CHD7 gene could be a possible, yet unproven, cause of "empty sella" syndrome. Patients with hypogonadotropic hypogonadism should be examined for possible CHD7 mutations, even if they do not have any CHARGE syndrome characteristics.

Abstract

Empty sella is an anatomo-radiological finding characterized by arachnoid herniation into the sellar fossa with reduction of pituitary volume and/or pituitary stalk compression). We report a clinical case of 35-year-old identical male twins, admitted to the clinic of endocrinology and metabolic diseases with history of infertility, hormonal constellation of hyposomatotropism and hypogonadotropic hypogonadism. The patients presented with hyposmia. Magnetic resonance imaging (MRI) of the hypothalamic–pituitary region revealed the presence of partial empty sella. *CHD7* gene variant was observed on genetic testing. *CHD7* gene mutation was considered as a possible reason for the presence of central hypogonadism and yet unproven genetic cause of "empty sella" syndrome.

KEYWORDS

CHARGE syndrome, *CHD7* gene, empty sella, growth hormone deficiency, hypogonadotropic hypogonadism, Kallmann syndrome

1 | INTRODUCTION

Empty sella syndrome (ESS) or "arachnoidocele" is defined as herniation of the subarachnoid space into the sella turcica. A diagnosis of partial empty sella is made when less than 50% of the sella is filled with cerebrospinal fluid.[1] ESS is divided into primary (PES) and secondary (SES), depending on the presence or absence of previous pituitary pathology. The cause of PES is not entirely understood.

Sharavii et al. studied all candidate genes related to the development of ESS in humans and divided them

into four groups: Group 1—genes, related to the development of ESS (the most significant are the *PRL gene* coding for prolactin, the *GH1 gene* coding for growth hormone, the *POMC gene* coding for proopiomelanocortin, the *TRH gene* coding for thyrotropin releasing hormone, the *IGF1 gene* coding for insulin like growth factor 1); Group 2—candidate genes related to pathways of ESS (*TRH, PRL, POMC, NPY, GNRH1, GH1 genes* coding for peptide-ligand building receptors); Group 3—candidate genes related to cellular components of ESS (*PRL, POMC, NPY, IGFBP3, IGF1*); Group 4—candidate genes related to biological processes of ESS (*TRH, POMC, NPY, INS, GNRH1)* which participate in the regulation of biological processes associated with the G protein-coupled receptors signaling pathway.[2]

Only a few cases of familial ESS are described in the literature. White et al. reported a case of three sisters, born of a consanguineous marriage. Short stature enlarged pituitary fossa, progressive failure of anterior pituitary hormone function and an empty sella were observed. GH and TSH deficiencies were registered. They considered it as a possible new syndrome of familial hypopituitarism.[3]

Gorar et al. performed genetic analysis of *PROP1* (homeobox protein prophet of Pit-1) gene in a Turkish pedigree with three siblings who presented with short stature. Parents were first-degree cousins. The index case, a boy, had growth hormone, gonadotropin, thyroid-stimulating and adrenocorticotropic hormone deficiency. Two elder sisters had hyposomatotropism, hypogonadism, hypothyroidism. On pituitary magnetic resonance, partial empty sella was detected in all siblings. In genetic analysis, they found a gross deletion involving *PROP1* coding region. *PROP1* mutations represent the most common known genetic defect of both familial and sporadic combined pituitary hormone deficiency. The deletion of *PROP1* in mice causes severe pituitary hypoplasia with failure of the entire PIT1 lineage and delayed gonadotrope development.[4]

Headache, menstrual irregularities, galactorrhea, hirsutism, and infertility are the most common clinical manifestation in PES syndrome. Insufficient glandular secretion can be caused by the compression of the pituitary parenchyma against the sellar cavity walls. Growth hormone deficiency represents the most frequent pituitary deficit, both in adults and pediatric population.[5] Empty sella can be confirmed through magnetic resonance (MRI) study of the sellar and supra-sellar region. Typical findings are intra-sellar cerebrospinal fluid filling in continuity with overlying subarachnoid spaces, residual pituitary gland with a semilunate morphology, flattened against the sellar floor and, often, enlarged sella turcica. Pituitary stalk is usually thinned, located on midline.[5]

2 | CLINICAL CASE

35-year-old monozygotic male twins (history data) presented to the clinic with history of reproductive disorders. One of the patients had a history of primary infertility. The other one had a child and two prior pregnancies with the same partner that ended up with spontaneous abortion. In the past they were registered with low levels of serum testosterone, gonadotropic hormones, and growth hormone deficiency. Testosterone replacement treatment was used in the past. As comorbidities they had primary hypothyroidism—chronic autoimmune thyroiditis and prediabetes. On admission, patients' therapy included a central estrogen blocker (clomiphene citrate 50 mg/daily), recombinant growth hormone (Genotropin 0.6 mg/daily), metformin (Glucophage XR 1000 mg/daily), and L-thyroxin (100 mcg/daily).

The patients presented with normosthenic habitus, BMI—26.7 kg/m^2, pale skin. No visible dysmorphic features were observed. Well-developed primary and secondary sex characteristics were present. Physical examination of other organs and systems was unremarkable.

Hormonal tests on admission (Table 1) showed suppressed levels of growth hormone (GH). Normoprolactinemia was observed.

The estrogen blocker and somatotropin hormone were discontinued to reevaluate hypothalamic–pituitary-gonadal axis and growth hormone endogenous production. Hormonal assessment on the first and the second months after, showed a reduction of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone levels, which confirmed the presence of secondary hypogonadism and the positive effect of clomiphene citrate due to the preserved, although reduced hormonal production capacity of the residual pituitary parenchyma (Figure 1).

Suppressed levels of endogenous somatotropic hormone were registered. IGF-1 was evaluated, and the result was within normal limits. Latent adrenal insufficiency as a part of autoimmune polyendocrine

TABLE 1 Hormonal tests on admission.

Parameter (reference range)	Values of Patient 1	Values of Patient 2
ACTH (5–47 pg/mL)	52.35	41.7
Cortisol 8 h (154–624 nmol/l)	357.4	433.16
GH (0.05–8 ng/mL)	0.027	0.027
FSH (1.27–19.26 mIU/mL)	3.08	2.99
LH (1.24–8.62 IU/L)	7.12	8.67
Testosterone (1.75–7.81 ng/mL)	5.57	5.95
Prolactin (58–415 mU/l)	192.23	177.5

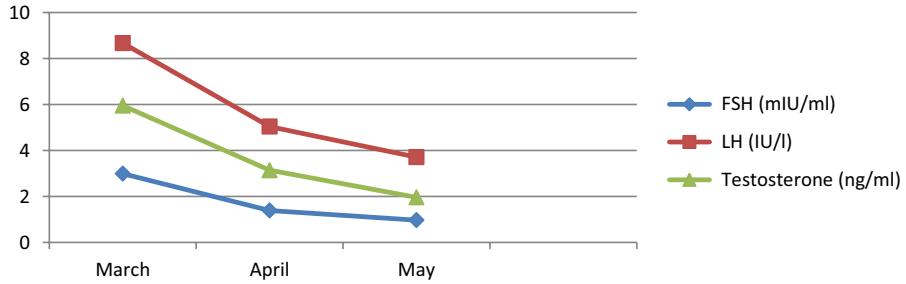
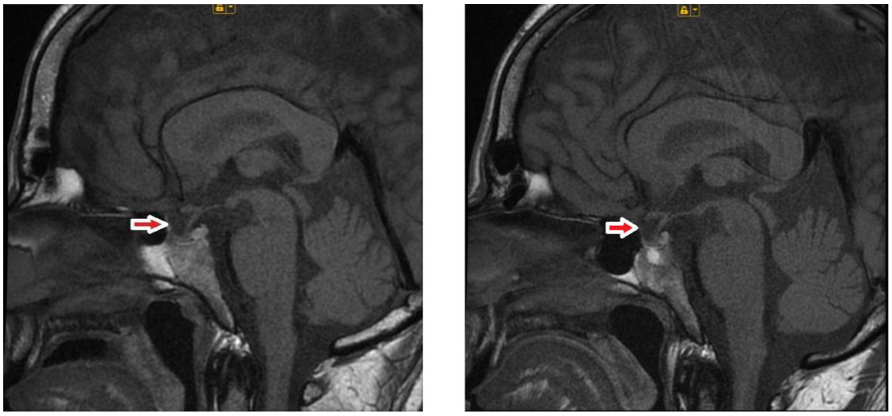


FIGURE 1 FSH, LH, and testosterone levels obtained during the first and second month after discontinuing the treatment with clomiphene citrate. We showed the dynamics of hormones for both siblings like an average.

FIGURE 2 Magnetic resonance imaging (MRI) of the hypothalamic–pituitary region revealed the presence of partial empty sella. Sagittal projection T1 of Patient 1 and Patient 2.



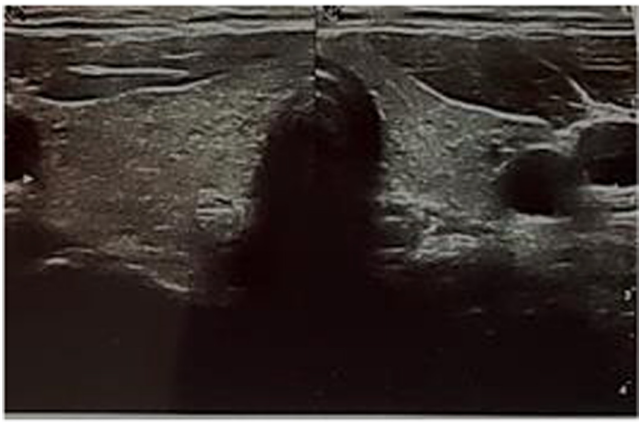


FIGURE 3 Ultrasound of the thyroid gland.

syndrome type 2 was observed due to the upper limit values of ACTH and the presence of chronic autoimmune thyroiditis. The levels of ACTH and morning cortisol obtained during the second hospitalization were within normal limits. Follow-up and performing a corticotropin stimulating test 250 μg, if any clinical and biochemical suspicion of adrenal insufficiency is present were recommended. Spermogram was performed and it showed teratozoospermia with 1% normal morphology according to Kruger's strict criteria. Infection with Chlamydia trachomatis and urogenital mycoplasms was excluded. Negative results for Candida spp., T.vaginalis were obtained. Magnetic resonance imaging (MRI) of the hypothalamic–pituitary region was performed and it revealed a partial "empty sella", probably due to insufficiency of the sellar diaphragm (Figure 2).

Ultrasound of the thyroid gland showed diffuse structural changes suggestive of chronic autoimmune thyroiditis (Figure 3).

Olfactory testing was performed and hyposmia was registered. Genetic testing showed normal karyotype, no Y-chromosome deletion. A target gene panel for hypogonadotropic hypogonadism was performed on Patient 1. A variant of uncertain significance, *c.2615T>C (p.Ile872Thr)* was identified in *CHD7* gene.

Given the history of maintaining sufficient levels of endogenous serum testosterone while using estrogen blocker in the past, the reduction in FSH, LH, and serum testosterone levels after discontinuing the treatment for 2 months and future plans for reproduction, the patients were started on clomiphene citrate 50 mg/daily. Clomiphene citrate (CC) is a weak selective estrogen receptor modulator (SERM) antagonist at the level of the hypothalamus. It attaches to the receiver for an extended period, reducing the availability of these receptors. As estradiol exerts negative feedback on the hypothalamus, downregulating the production and the release of gonadotropin-releasing hormone (GnRH), CC increases hormone levels

TABLE 2 Comparison between the patients of cited case and literature review with identified with *CHD7 c.2615 T > C (p. Ile872Thr)* variant.

Diagnosis	Sex	Age of dignosis	Olfactory MRI	Basal testicular size, left/right	LH (basal)	FSH (basal)	T (basal)
Patient 1	M	35	ESS	14/15 (mL.)	7.12 (IU/L)	3.08 (mIU/L)	5.57 (ng/mL)
Patient 2	M	35	ESS	15/17 (mL.)	8.67 (IU/L)	2.99 (mIU/L)	5.95 (ng/mL)
Kalman Syndrome 1	M	14	Absence of olfactory bulb and tract	2/2 cm	0.06 (mIU/L)	1.5 (mIU/L)	1.36 nmoL/L
Kalman Syndrome 2	M	N/A	Olfactory bulb and tract dysplasia in magnetic resonance	2 Basal mean testicle size (ml)	0.1 (IU/L)	0.5 (IU/L)	40 (ng/dL)

and consequently increases the stimulus on the pituitary gland. The usual dose is 25–50 mg per day.[6]

3 | DISCUSSION

At least 15%–30% of male infertility may be caused by genetic factors. Chromodomain helicase DNA-binding protein 7 (*CHD7*) gene is one of the nine members of the CHD protein family, which have the common function of hydrolyzing ATP and changing the structure of the nucleosome. *CHD7* gene is located on chromosome *8q12*.[7] CHD protein function is critical for the ontogeny of GnRH neurons and olfactory neurons development.[8] Its structure is highly conserved, and it is expressed ubiquitously in the human body. Pathogenic variants of *CHD7* exist in about 10% of congenital hypogonadotropic hypogonadism patients, and they are also the major pathogenic cause (detection rate is more than 90%) for another autosomal dominant disease, CHARGE (coloboma, heart defect, atresia choanae, growth and developmental retardation, genital hypoplasia, ear anomalies/deafness) syndrome *CHD7* (*OMIM, 214800*).[9] Growth retardation and genital abnormalities are potential overlapping symptoms between CHARGE and congenital hypogonadotropic hypogonadism. Missense *CHD7* variants are more common in congenital hypogonadotropic hypogonadism patients, whereas null variants (e.g., nonsense, frameshift) are more common in CHARGE syndrome.[10] Milder allelic variants in *CHD7* have been linked to a non-syndromic presentation of isolated gonadotropin-releasing hormone (GnRH) deficiency (IGD)—both Kallmann syndrome (KS) and idiopathic hypogonadotropic hypogonadism. IGD patients with *CHD7* mutations may also have additional CHARGE-related features, such as hearing loss.[11]

Following ACMG criteria the variant *c.2615 T > C* p.Ile872Thr is classified as variant of uncertain significance (PS4; PP3). This variant is present in population databases (*rs751181139, gnomAD* 0.05%). There is one submission for this variant in ClinVar (1899993). This missense change has been observed in two individuals with Kallman syndrome.[12,13] We present the cited cases in a table together with the data of our patients (Table 2).

The *c.2615 T > C (p.Ile872Thr)* variant is classified as variant of uncertain significance but reclassification may be required with additional global evidence obtained through studies in the future.

Gonçalves et al screened for mutations in *CHD7* gene. Fifty Portuguese patients with congenital hypogonadotropic hypogonadism. Eight (16%) patients had *CHD7* rare sequence variants that consisted of six missense (*p. Gly388Glu, p.His903Pro, p.Thr1082Ile, p.Val1452Leu, p.Asp1854Gly, and p.Arg2065His*), and two synonymous (*p. Ser559Ser, and p.Ala2785Ala*) mutations.[14]

Empty sella is not a frequent finding regarding idiopathic hypogonadotropic hypogonadism. To our knowledge, such association has been reported only in three occasions. Takahashi et al. reported a case of Kallmann syndrome in a 28-year-old male with arachnoid cyst and empty sella. Quinton et al. reported a case of a female with Kallmann syndrome variant and empty sella. Zucchini et al. reviewed a series of 43 patients with hypothalamic–pituitary disorders and empty sella and mentioned one case of KS. In these previously reports, no molecular analysis was performed.[15]

4 | CONCLUSION

We presented a rare clinical case of identical twins with partial hypopituitarism—hypogonadotropic hypogonadism and hyposomatotropism based on familial partial "empty sella" and *CHD7* gene variant of uncertain significance. Although variants in *CHD7* are commonly sporadic, genetic counseling of these patients is important because of potential autosomal dominant inheritance and reports of incomplete penetrance.[7] Mutations in the *CHD7* gene could be a possible, yet unproven, cause of "empty

sella" syndrome. Patients with hypogonadotropic hypogonadism should be examined for possible *CHD7* mutations, even if they do not have any CHARGE syndrome characteristics. *CHD7* should be tested in the presence of clinical features, such as coloboma, abnormal ears, deafness, and/or semicircular canal hypoplasia/aplasia.[16]

AUTHOR CONTRIBUTIONS

Sava Petrov: Writing – review and editing. **Ekaterina Babadzhanova:** Writing – original draft. **Maria Orbetzova:** Methodology. **Hristo Ivanov:** Data curation.

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The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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