




CASE REPORT

Case Report: The first familial hCG syndrome in a Chinese family [version 1; peer review: 2 approved]

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Abstract

Familial hCG syndrome is a rare and benign cause of elevated serum beta human chorionic gonadotropin (hCG). We present here a case of familial hCG syndrome diagnosed in a Hong Kong Chinese family, which we believe to be the first reported in Chinese. A 38-year-old woman presented with incidental finding of persistently elevated hCG, analytically confirmed both in urine and blood. Extensive radiological and biochemical work-up were performed but were negative for pregnancy and malignancy. Testing of another asymptomatic family member revealed unexplained elevation of serum hCG, confirming the diagnosis of familial hCG syndrome. Knowledge and awareness of this entity among clinicians are important to avoid unnecessary investigations and treatment in affected families.

Keywords

familial hCG syndrome, hCG, human chorionic gonadotropin, gestational trophoblastic disease, ectopic pregnancy, tumour marker, autosomal inheritance

Open Peer Review

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Invited Reviewers

1

2

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report



report

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Familial hCG syndrome is a rare but benign cause of elevated serum/urine hCG. To date, fewer than 20 families have been reported worldwide in the literature¹⁻³. Patients present with an otherwise unexplained elevation in serum/urine hCG, and diagnosis is established by exclusion of other causes of elevated hCG and testing of family members. An autosomal dominant pattern of inheritance was observed, although the molecular mechanism has been poorly defined. We present here a case of familial hCG syndrome diagnosed in Hong Kong, which we believe to be the first reported family in Chinese.

Case presentation

A 38-year-old Chinese woman, a veterinary surgeon, was referred for investigation of persistent unexplained elevation in serum beta human chorionic gonadotropin (hCG) levels first revealed in a positive urine pregnancy test for the investigation

of abdominal pain in August 2020. Apart from a history of menorrhagia and iron deficiency anaemia, the patient had unremarkable past health. She was not on any drugs or supplement and had never been sexually active. Family history was unremarkable. Blood tests showed stable elevation of total beta-hCG ranging from 93–112 IU/L by Roche Elecsys HCG+ β assay over the subsequent five months. Transabdominal ultrasound of the pelvis showed no intrauterine sac, and no abnormality was detected in the uterus and ovaries. Pituitary hormones, including serum thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin levels were normal. Biochemical findings of the patient are summarized in [Table 1](#).

Due to the discordant clinical and biochemical findings, analytical interference of hCG assay was suspected and a series of interference studies were performed ([Table 2](#)). Serial dilution

Table 1. Summary of biochemical results of the patient.

Assay	Result	Reference intervals
Serum results		
hCG		
Roche Elecsys hCG+ β	98 IU/L	≤ 6 IU/L
Abbott Architect Total β -hCG	30 IU/L	< 5 IU/L
Siemens Immulite 2000 total β -hCG	424 IU/L	< 5 IU/L
Beckman DxI total β -hCG	37 IU/L	< 5 IU/L
Hyperglycosylated hCG (hCG-H)	< 0.5 μ g/L	< 1.0 μ g/L
LH	3.6 IU/L	Follicular 2.4 – 12.6 Ovulation 14.0 – 95.6 Luteal 7.7 – 58.5
FSH	2.1 IU/L	Follicular 3.5 – 12.5 Ovulation 4.7 – 21.5 Luteal 1.7 – 7.7
Prolactin	251 mIU/L	102 – 496 mIU/L
TSH	3.08 mIU/L	0.27 – 4.20 mIU/L
CEA	< 1.8 μ g/L	≤ 4.7 μ g/L
CA125	11 U/mL	≤ 35 U/mL
AFP	< 2 IU/mL	≤ 6 IU/mL
Urine results		
Roche Elecsys hCG+ β	168 IU/L	NA

hCG: human chorionic gonadotropin

LH: Luteinizing hormone

FSH: Follicle stimulating hormone

TSH: Thyroid stimulating hormone

CEA: Carcinoembryonic antigen

CA125: Cancer antigen 125

AFP: Alpha fetoprotein

Table 2. Results of interference studies performed on patient's serum specimen.

Dilution recovery	hCG in neat sample: 112 IU/L hCG with x5 dilution: 106 IU/L (Recovery: 95%) hCG with x10 dilution: 103 IU/L (Recovery: 92%)
Heterophilic blocking tube	hCG in neat sample: 112 IU/L hCG post blocking tube treatment: 107 IU/L (Recovery: 96%)
PEG precipitation	hCG in neat sample: 105 IU/L hCG in supernatant after 1:1 PEG treatment: 100 IU/L (Recovery: 95%)

hCG: human chorionic gonadotropin

PEG: Polyethylene glycol (PEG 6000)

study was performed on the Roche Elecsys HCG+ β assay with manufacturer diluent in 1:4 and 1:9 dilutions, which showed linear recovery. Satisfactory recovery was observed in serum hCG level on the Roche assay after treatment with heterophilic blocking tube (Scantibodies Laboratory, Inc). Polyethylene glycol (PEG) precipitation study was performed by mixing 200 μ L of patient sample with 200 μ L of 25% (w/v) PEG 6000 (Sigma Aldrich). The sample was then incubated at room temperature for 10 minutes and centrifuged at 9500 \times g for 10 minutes. hCG levels were assayed by the Roche Elecsys HCG+ β assay in the supernatant. Recovery was satisfactory compared to the hCG result in the neat untreated serum sample. Aliquots of serum were sent to three local laboratories for analyses using different analytical platforms (Abbott Architect, Beckman DxI and Siemens Immulite 2000), all confirming elevation in beta-hCG but to variable extents, with the highest hCG result obtained using Siemens Immulite 2000 (Table 1). Spot urine total beta-hCG was checked by the Roche Elecsys HCG+ β assay and measured 168 IU/L.

To look for underlying tumours, tumour markers including carcinoembryonic antigen, cancer antigen 125 and alpha fetoprotein were checked but were not elevated. Hyperglycosylated hCG (hCG-H) was undetectable (<0.5 μ g/L) using the Nichols Advantage hCG-H assay (Nichols Institute Diagnostics, San Clemente, California). Whole body positron emission tomography-computed tomography, magnetic resonance imaging of the pituitary, abdomen and pelvis were unrevealing. Oesophagogastroduodenoscopy was negative.

As biochemical and radiological work-up could not explain the persistently elevated hCG, familial hCG syndrome was considered in this otherwise asymptomatic patient. Blood hCG test was arranged for one female sibling who also had never been sexually active, and the level was elevated (37 IU/L). There were no other family members available for testing. The diagnosis of familial hCG syndrome was thus established. This is to the best of our knowledge the first case of familial hCG syndrome reported in Chinese.

Discussion

Human chorionic gonadotropin is a heterodimeric glycoprotein hormone produced by placental syncytiotrophoblast during

pregnancy⁴. It comprises of a common alpha subunit shared between LH, FSH and TSH, and a unique beta subunit that has been shown to be encoded by at least seven genes^{4,5}. In blood circulation, hCG exists in various forms arising from post-translational glycosylation and its degradation in the liver and kidneys⁴. Apart from pregnancy, increased levels may be seen in gestational trophoblastic diseases, and a number of tumours including germ cell tumours, non-small cell lung cancer⁶, as well as squamous cell carcinoma of the head and neck region^{7,8}, in which other hCG forms such as free beta-subunit or hyperglycosylated form may predominate⁹. In postmenopausal women or patients with gonadal insufficiency, sulfated hCG secreted from the pituitary is a frequent cause of mildly elevated hCG. Occasionally, elevated hCG may arise from exogenous administration in doping athletes or as a dietary supplement. In a patient who has otherwise unexplained elevation of hCG discordant with clinical findings, analytical interferences, such as heterophilic antibody interference, are important causes that should be excluded. According to data from USA, hCG Reference Service, among 424 cases of positive hCG with no history of gestational trophoblastic disease or malignancy and pregnancy excluded, the commonest aetiologies were quiescent gestational trophoblastic disease (32%), analytical interference (25%) and pituitary hCG (23%), followed by other malignant conditions (15%) and exogenous intake (1%)¹.

The above differentials were, however, unlikely in our patient based on the extensive negative biochemical and radiological work-up. Intrauterine and extrauterine pregnancies were unlikely given the negative pelvic imaging. Active gestational trophoblastic disease and occult malignancies were less likely with the negative findings on extensive whole-body imaging and undetectable hyperglycosylated hCG. The normal LH and FSH ruled out pituitary hCG. Analytical interferences were less likely although not entirely excluded by the normal recovery on serial dilution, treatment with heterophilic antibody blocking tube and PEG precipitation. The detection of hCG in the urine provides further evidence for a genuine increase in endogenous hCG levels. The negative work-up and persistent elevation in hCG led to the suspicion of familial hCG syndrome, which was subsequently confirmed with testing of hCG level in an asymptomatic family member.

Familial hCG syndrome is a rare but benign cause of elevated hCG. Serum hCG from reported cases in literature ranged from <1.0 – 216 IU/L, and levels showed fluctuation with time on serial testing². Antibody profiling by Cole demonstrated the predominance of free β -subunit and β -subunit missing the C-terminal peptide in affected patients¹. Both forms are biologically inactive, thus explaining the unaffected fertility in these patients. The presence of these uncommon hCG variants may account for the difference in hCG results across different analytical platforms. Studies comparing the reactivity of available international standards and international reference preparations with sandwich immunoassays on major analyzers have shown vastly different recoveries towards different hCG variants^{9–11}. For instance, the Siemens Immulite 2000 total β -hCG assay, which was shown to have equimolar detection of β -subunit missing C-terminal peptide and nicked hCG β , consistently returned the highest hCG result among the four platforms tested in our patient. The incongruent results across multiple immunoassay platforms may provide additional support to the diagnosis of familial hCG syndrome, as direct measurements of the various hCG subtypes are not readily available in routine clinical practice. Knowledge of the assay reactivity towards the different variants may aid in the interpretation of discordant results.

Reliable markers or diagnostic tests specific to familial hCG syndrome are lacking. Diagnosis relies on careful exclusion of

common causes and testing of family members, the former often includes performing a number of costly diagnostic imaging. Of note, a lack of response to a trial of methotrexate therapy has been proposed as one of the diagnostic criteria for familial hCG syndrome in female patients of reproductive age to exclude ectopic pregnancy¹, which, however, is not without risk. Further research into the underlying molecular mechanisms and structural characterization of the variants may identify better means of establishing a diagnosis, and may allow detection of concurrent physiological or pathological hCG elevations in diagnosed patients.

In conclusion, we report here the first case of familial hCG syndrome in a Chinese family. Given the rarity of the entity and the lack of readily available biochemical markers, familial hCG syndrome remains a diagnosis by exclusion. Knowledge and awareness of this disorder among clinicians are important to avoid over investigations and unnecessary treatment, and in offering reassurance to affected patients and family members.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of clinical and laboratory details was obtained from the patient.

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Ravi Krishna Cheemakurthi

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I appreciate authors for their effort in presenting the case report with clinical findings and proper diagnostic parameters. My suggestion is it would have been more exciting if authors would have tried to find the genetic cause behind the clinical condition, because in many rare disorders it is very difficult to find a family member with similar clinical condition. As of now it is just a case with familial hCG syndrome which was first case in a Chinese family.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My area of research is in the field of reproductive genetics especially in the pharmacogenomic aspects of LH and FSH supplementation in COS protocols

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 16 June 2021

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Weldon Chiu

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A very well written and worked-up case report on this rare but clinically important condition to avoid over-investigation or worse still, potentially invasive and harmful treatments offered for a benign condition. Though there is no gold standard test, the arguments in favour of this diagnosis are scientifically sound. My only suggestion is that especially with the rarity of this condition, if there are any additional information including serial hCG results and/or any free beta HCG results e.g. from Autodelfia or Johnson and Johnson free beta-hCG platform (designed mainly for maternal serum screening), they would be worth mentioning in the report too.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Gastrointestinal and liver related clinical biochemistry; General chemical pathology. Had encountered 2 families with familial hCG syndrome.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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