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Familial hCG Syndrome

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ABSTRACT

An explanation is needed for why some men and women show positive in hCG screening tests when they are not pregnant, do not have cancer and are otherwise asymptomatic. In this study, a total of 10 families comprising 30 persons with a history of positive hCG tests were investigated. Total hCG was measured in serum and urine samples using the Siemens Immulite hCG test. Total hCG, C-terminal peptide determinant, and hCGβ were measured in 96 well plate assays. Twenty-four of 30 family members produced only hCGβ, and hCG or hCGβ missing the β-subunit C-terminal peptide, two rarely detected hCG degradation products as the only source of hCG immunoreactivity. In every one of the 10 families, hCG related molecules were detected first in one member and then later detected in other family members. In 8 of 10 families, all members produced comparable hCG concentration (Cases 1–8). All of the 10 original family members investigated were otherwise asymptomatic, and tested negative in ordered head and pelvis MRI scans and CT chest cancer tests. None had been administered hCG for dietary, anabolic or fertility reasons. Therefore Familial hCG Syndrome, a genetic defect, was indicated in each of the 10 families. In these cases of Familial hCG Syndrome only biologically inactive variants of hCG were detected. It is inferred that in Familial hCG Syndrome, hCG gene expression does not interfere with fertility.

1. Introduction

Today, all women are screened by hCG test for pregnancy prior to surgery, and prior to the commencement of major radiographic and chemotoxic procedures. This testing has identified multiple women producing hCG outside of pregnancy. Men are also tested for hCG for detection of testicular cancer, and for control of hCG doping in sport. In the last 12 years the USA hCG Reference Service has been referred 425 cases of men and women with positive hCG tests after pregnancy has been excluded (no fetal sac) and ectopic pregnancy has been excluded (Table 1). The most common cause for positive hCG test has been quiescent gestational trophoblastic disease ($n = 137$) following ectopic pregnancy and spontaneous abortion. In these cases the cause is inactive gestational trophoblastic disease (Table 1). Other causes include false positive serum hCG ($n = 108$), pituitary sulfated hCG ($n = 96$), non-trophoblastic neoplasm or placental site trophoblastic tumor (PSTT) ($n = 65$), gestational trophoblastic neoplasm ($n = 10$), sportsmen with hCG doping ($n = 4$), Munchausen's syndrome ($n = 3$), and women using hCG as a dietary aid ($n = 2$).

The USA hCG Reference Service has specific tests and protocols for each of these diagnoses (Cole et al., 2010). One diagnosis remains somewhat of a problem. When serum total hCG contains more than 30% hCGβ, non-trophoblastic neoplasm is suggested (Cole et al., 2008). As shown in 2008, this criterion suggests non-trophoblastic neoplasm or PSTT. Upon Reference Service recommendation, physicians use MRI scan and CT scans to test these individuals for malignancy. As shown in Table 1, of the 65 cases indicated by the service, 25 were confirmed as non-trophoblastic neoplasm and 29 were shown to have PSTT. Ten were found to Familial hCG Syndrome by showing the presence of multiple familial hCG occurrence, and 1 cases remained unexplained.

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Table 1
Data from the USA hCG Reference Service, summarizing 424 cases of positive hCG, with no history of gestational trophoblastic disease or cancer, and pregnancy excluded. History date is August 1, 2011. PSTT is placental site trophoblastic tumor.

USA hCG Reference Service Diagnosis from multiple testing	Number of cases	Total hCG median (range), mIU/ml
1. Quiescent gestational trophoblastic disease	137	13.8 (1–207)
A. History of ectopic pregnancy	10	43 (6–82)
B. History of spontaneous abortion	127	13.4 (1–207)
2. False positive serum hCG	108	38 (5.6–1010)
3. Pituitary sulfated hCG	96	7.7 (1–39)
A. Pre-menopause	38	7.2 (1.8–29)
B. Post menopause	49	8.0 (2.5–33)
C. Bilateral oophorectomy	9	6.3 (2.3–39)
4. Non-trophoblastic neoplasm or PSTT	65	39 (<1–564)
A. Then screened by MRI/CT, cancer found	25	31 (<1–249)
B. Then screened by MRI/CT, PSTT	29	94 (1–564)
C. Then screened by MRI/CT, no cancer/PSTT	11	29 (<1–216)
C1. Of the 10 no cancer/PSTT cases, cases shown to be Familial hCG Syndrome	10	21 (<1–216)
C2. Of the 10 no cancer/PSTT cases, cases still without diagnosis	1	
5. Gestational trophoblastic neoplasm	10	740 (27–11,700)
6. Sportsmen, positive in doping test	4	42 (15–230)
7. Munchausen's syndrome	3	44,150 (7900–80,400)
8. Women using hCG as a diet aid	2	227 (106–333)

In 2004, serum and urine were obtained from a woman in Utah who was screened in a hospital for hCG. Prior to surgery at a hospital she tested positive for pregnancy, with a serum hCG of 45 mIU/ml. Ultrasound showed the absence of a fetal sac, excluding clinical pregnancy. The physician then suspected an ectopic pregnancy and the patient was treated with methotrexate to terminate an ectopic pregnancy. However serum hCG remained elevated, showing that the hCG was not due to ectopic pregnancy. The physician then referred the patient to an oncologist, who proposed a choriocarcinoma case and administered actinomycin D chemotherapy. After the chemotherapy had no effect of the patient's hCG level, the physician then referred the case to the USA hCG Reference Service. The USA hCG Reference Service thoroughly examined her samples and her medical records. Her total serum hCG was 43, there was no evidence of hyperglycosylated hCG, or reason for pituitary hCG. She had no recent history of ectopic pregnancy or spontaneous abortion, excluding quiescent gestational trophoblastic disease. She had notably high hCGβ (79%), suggesting the possibility of non-trophoblastic neoplasm. As recommended by the USA hCG Reference Service, her physician then ran an MRI of her head and pelvis and CT of her chest. Neither showed any evidence of cancer. Further investigation revealed that the patient had not taken hCG for dietary or other reason, and that the patient's sister and mother had also both tested positive for hCG. After Reference Service testing of her mother's and sister's serum and urine, it was confirmed that levels were quite similar to those of the patient (Table 2, Case 1). A report was written suggesting that she had some form of genetic abnormality. This case history is summarized in Table 3.

The concept of Familial hCG Syndrome came to light in 2008. A 28 year old college sportsman proved positive for hCG in urine at 6.8 mIU/ml hCG. Over the 8 weeks that followed, his urine hCG did not significantly change, proving that there was an endogenous source of hCG production and that hCG had not been taken for doping (urine hCG levels should at least half every 2 days). The USA hCG Reference Service first investigated his serum, but no hCG was detected. In urine, no hCG was detected by the hyperglycosylated hCG assay suggesting that this was not a testicular germ cell malignancy. It was later shown that 83% of the total hCG was hCGβ (Table 2). A non-trophoblastic malignancy was suggested, but no cancer was found by head and pelvis MRI and chest CT scan. His hCG continued to be positive 3 months later. On the basis of the 2004 Utah case, serum and urine were requested from his mother and father and tested by the Reference Service. Like the sportsman, both were negative in the serum (<1 mIU/ml), but the father was positive in urine at 10 mIU/ml. It was concluded that he had a genetic disorder and the name Familial hCG Syndrome was born. The case history is summarized in Table 3.

In this publication, 10 cases of Familial hCG Syndrome are now described, along with the characteristic pattern of hCG degradation products produced. Familial hCG Syndrome is a genetic hCG-producing syndrome affecting both men and women. Including all relatives, a total of 24 cases are identified.

2. Methods

The USA hCG Reference Service is an independent CLIA certified (32D0972561) clinical laboratory that is part of the College of American Pathologists Excel consistency program (7176750-01). All cases described in this report were independently referred to the USA hCG Reference Service. This study is considered a CLIA-Certified Clinical Laboratory confidential synopsis of referred patient results and does not require Internal Review Board or ethics committee monitoring.

When the USA hCG Reference Service is presented with a case of persistent low hCG levels outside or pregnancy, 6 hCG-related tests on serum and urine are performed. Total hCG is measured in serum and urine using the Siemens (New York, NY) Immulite 1000 automated test. As previously published (Cole et al., 2004), this test detects with equal reactivity regular hCG, hyperglycosylated hCG, nicked hCG, nicked hCG missing β-subunit C-terminal

Table 2
Data from the USA hCG Reference Service on cases with Familial hCG Syndrome. CTP is β-subunit C-terminal peptide. The concentration of molecules missing the CTP is determined as Serum hCG less Serum hCG CTP. All values are in mIU/ml hCG molar equivalents.

Case	Sex	Age	Serum hCG, mIU/ml	Serum hCGβ Molar, mIU/ml	Serum hCG CTP, mIU/ml	Molecules missing CTP calculated, mIU/ml	Total biologically inactive hCG in serum	Total Urine hCG, mIU/ml
Case 1	F	32	43	34 (79%)	12	(43–12) or 31	43 total, 31 −CTP + 34 β	3.0
Sister	F	34	34	17	12	(34–12) or 22	34 total, 22 −CTP + 17 β	2.0
Mother	F	54	54	16	15	(54–15) or 39	54 total, 39 −CTP + 16 β	2.0
Father	M	56	<1.0	No hCG-related molecules detected				<1.0
Case 2	M	28	<1.0	<0.3	0.5	(<1.0–0.5) or <0.5	<1 total, <0.5 −CTP + <0.3 β	6.8
Father	M	52	<1.0	<0.3	<0.3	(<1–<0.3) or <0.5	<1 total, <0.5 −CTP + <0.3 β	10
Mother	F	49	<1.0	No hCG-related molecules detected				<1.0
Case 3	M	32	2.0	1.3 (65%)	0.4	(2.0–0.4) or 1.6	2.9 total, 1.6 −CTP + 1.3 β	26
Brother	M	28	1.1	<0.3	<0.3	(<1–<0.3) or <0.5	<1 total, <0.5 −CTP + <0.3 β	4.0
Father	M	50	1.3	<0.3	<0.3	(1.3–<0.3) or 1.3	<1 total, <0.5 −CTP + <0.3 β	1.6
Mother	F	50	<1.0	No hCG-related molecules detected				<1.0
Case 4	M	22	2.8	1.7 (61%)	<0.3	(2.8–<0.3) or 2.8	4.5 total, 2.8 −CTP + 1.3 β	54
Father	M	45	3.3	1.4	0.5	(3.3–0.5) or 2.8	3.3 total, 2.8 −CTP + 1.4 β	27
Mother	F	44	<1.0	No hCG-related molecules detected				<1.0
Case 5	F	28	201	113 (56%)	29	(201–29) or 172	201 total, 172 −CTP + 113 β	83
Sister	F	27	153	113	41	(153–41) or 112	153 total, 112 −CTP + 113 β	100
Father	M	53	142	129	30	(142–30) or 112	142 total, 112 −CTP + 129 β	670
Case 6	M	22	1.8	1.0 (55%)	0.7	(1.8–0.7) or 1.1	2.1 total, 1.1 −CTP + 1.0 β	2.9
Mother	F	55	2.5	1.2	1.6	(2.5–1.6) or 0.9	2.1 total, 0.9 −CTP + 1.2β	2.8
Father	M	55	<1.0	No hCG-related molecules detected				<1.0
Case 7	F	33	216	121 (56%)	24	(216–24) or 192	314 total, 192 is −CTP, 121 β	24
Father	M	56	201	119	20	(201–29) or 181	300 total, 181 is −CTP, 119 β	178
Mother	F	51	<1.0	No hCG-related molecules detected				
Case 8	F	28	32	17 (53%)	16	(32–16) or 16	32 total, 16 is −CTP, 16 β	27
Son	M	3	24	12	11	(24–11) or 13	25 total, 13 is −CTP, 12 β	12
Father	M	55	<1.0	No hCG-related molecules detected				<1.0
Case 9	F	58	9.4	7.6 (81%)	2.5	(9.4–2.5) or 6.9	9.4 total, 6.9 is −CTP, 7.6 β	1.5
Daughter	F	22	Only urine collected					2.5
Case 10	M	20	2.0	1.2 (60%)	0.8	(2.0–0.8) or 1.2	2.4 total, 1.2 is −CTP, 1.2 β	25
Father	M	46	Only urine collected					1.6
Brother	M	16	Only urine collected					4.0
Mother	F	47	Only urine collected					<1.0

peptide (βCTP), free β-subunit and free β-subunit missing the β-subunit CTP. It also detects the urinary terminal degradation product, β-core fragment with one quarter the molar sensitivity of regular hCG. As demonstrated previously (Cole and Khanlian, 2009), the Immulite test equally detects total hCG in serum and urine samples. Hyperglycosylated hCG is a marker of choriocarcinoma, gestational trophoblastic neoplasm, persistent hydatidiform mole, testicular germ cell malignancy and ovarian germ cell malignancy. Hyperglycosylated hCG is measured using the B152 antibody (Cole et al., 2006). hCGβ, a marker for non-trophoblastic neoplasm and PSTT (Cole et al., 2008), is measured using FBT11 antibody (Cole et al., 2008). This test detects hCGβ and hyperglycosylated hCGβ but does not detect hCGβ missing the C-terminal peptide. Another total hCG test uses an antibody to β-subunit C-terminal peptide. A test for urine β-core fragment, using antibody B210 is also found useful. All tests repeat the determination four times, and run determinations at 1:2 and 1:10 dilution to confirm results, and with heterophilic antibody blocking agent, HBR (Scantibodies, San Diego, CA), to exclude false positive hCG results.

Table 3
Histories of Familial hCG Syndrome Cases 1–10. U/S is ultrasound, hCG RS is USA hCG Reference Service.

Case 1
hCG detected pre-surgery at hospital
↓
U/S shows no fetal sac of pregnancy
↓
Methotrexate excludes ectopic pregnancy
↓
Choriocarcinoma suspect, give actinomycin D
↓
Chemotherapy hopeless, refer to hCG RS
↓
High free β, cancer indicated, give MRI/CT
↓
No cancer found, family positive for hCG
↓
Familial hCG Syndrome

Case 2
Played football for university team
↓
Random urine doping testing positive for hCG
↓
Denies taking hCG, refer to hCG RS
↓
High free β, cancer indicated, give MRI/CT
↓
No cancer found, family positive for hCG
↓
Familial hCG Syndrome

Case 3
hCG detected in a male at hospital
↓
Testicular germ cell cancer suspect, give VP16
↓
Chemotherapy hopeless, refer to hCG RS
↓
High free β, cancer indicated, give MRI/CT
↓
No cancer found, family positive for hCG
↓
Familial hCG Syndrome

Case 4
Tested for hCG in testicular cancer screening
↓
Denies taking hCG, refer to hCG RS
↓
High free β, cancer indicated, give MRI/CT
↓
No cancer found, family positive for hCG
↓
Familial hCG Syndrome

Case 5
hCG detected after physical examination
↓
U/S shows no fetal sac of pregnancy
↓
Methotrexate excludes ectopic pregnancy
↓
Cancer suspected, give hysterectomy
↓
Chemotherapy hopeless, refer to hCG RS
↓
High free β, cancer indicated, give MRI/CT
↓
No cancer found, family positive for hCG
↓
Familial hCG Syndrome

Case 6
Played football for NFL football team
↓
Random urine doping testing positive for hCG
↓
Denies taking hCG, refer to hCG RS
↓
High free β, cancer indicated, give MRI/CT
↓
No cancer found, family positive for hCG
↓
Familial hCG Syndrome

Case 7
hCG detected pre-surgery, no fetal sac
↓
Methotrexate excludes ectopic, refer to hCG RS
↓
High free β, cancer indicated, give MRI/CT
↓
No cancer found, family positive for hCG
↓
Familial hCG Syndrome

Case 8
Man with leukemia, found positive for hCG
↓
Denies taking hCG, refer to hCG RS
↓
High free β, cancer indicated, give MRI/CT
↓
No cancer found, family positive for hCG
↓
Familial hCG Syndrome

Case 9
hCG detected pre-surgery, no fetal sac
↓
Methotrexate excludes ectopic, refer to hCG RS
↓
High free β, cancer indicated, give MRI/CT
↓
No cancer found, family positive for hCG

Case 10
Man with leukemia, found positive for hCG
↓
Denies taking hCG, refer to hCG RS
↓
High free β, cancer indicated, give MRI/CT
↓
No cancer found, family positive for hCG
↓
Familial hCG Syndrome

The Siemens Immulite tests uses antibodies to β1 and β2 epitopes as indicated in Fig. 1. Serum and urine samples were tested with specific 96 well microtiter plate assays for total hCG with a β-subunit C-terminal peptide (CCF01 coating antibody) and H222-POD peroxidase tracer (Fig. 1, antibodies to β3 and β1 epitopes). This test does not detect hCG variants missing the β-subunit C-terminal peptide. Serum and urine samples were also tested for hCGβ using FBT11 hCGβ coating antibody and H222-POD peroxidase anti-core β tracer antibody (Fig. 1, antibodies to free β epitope and to β1 epitope). All assays involved two 2 h incubations with capture and tracer antibody. The ingredients were finally incubated with tetramethylbenzidine substrate, then measured using a computerized microtiterplate reader at 450 nm (Titertek Inc., Huntsville, AL; the Multiskan Ascent microtiterplate reader) (Cole et al., 2004; Cole and Khanlian, 2009). Serum and urine FSH and LH were measured on the Siemens Immulite 1000 machine using FSH and LH packs as needed.

As published previously (Cole et al., 2004; Cole and Khanlian, 2009; Cole, 2011), hCG and its free β subunit (hCGβ) were all measured in molar units, pmol/L. Result were then converted to mIU/ml, the units that all physicians are accustomed to. Results are presented in mIU/ml

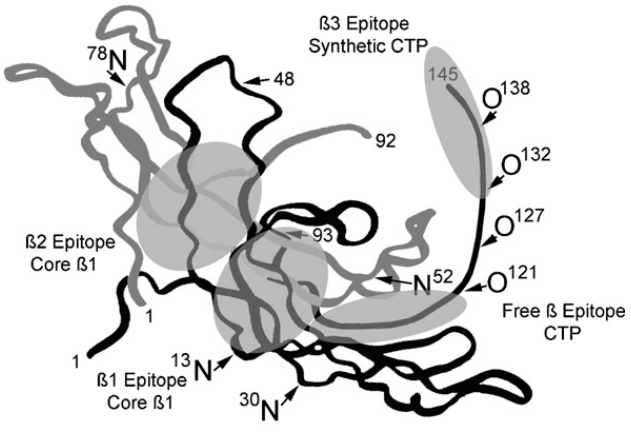

Fig. 1. Specificity of antibodies used in this study. Structure is the crystal structure of hCG (Lapthorn et al., 1994). Black lines represent the β-subunit of hCG and dark gray lines the α-subunit of hCG. Light gray shaded areas show pertinent epitopes. The Siemens Immulite total hCG assay uses β1 epitope as capture antibody and β2 epitope as tracer antibody. The free β assay used uses free β epitope on CTP as capture antibody and β1 epitope as tracer antibody, and the total hCG C-terminal peptide assay uses the β3 synthetic C-terminal peptide epitope (synthetic CTP) as capture antibody and β1 epitope as tracer antibody.

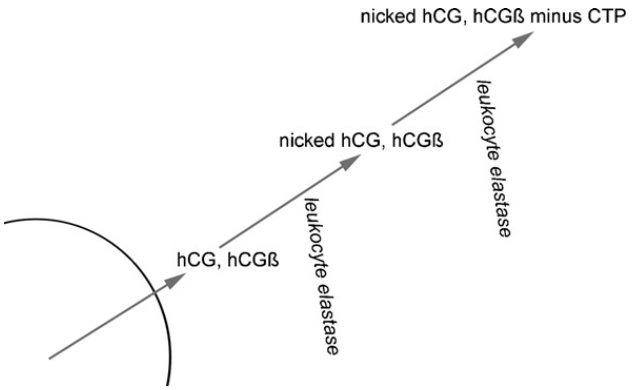

Fig. 2. Proposed degradation pathways in cases with Familial hCG Syndrome. The action of leukocyte elastase has been described previously (Cole et al., 1991). The distribution between liver and kidney degradation is that published for hCG metabolites (Nisula et al., 1989).

in this paper. All molar values were multiplied by 404 to achieve a value in hCG equivalents, mIU/ml. As shown using the Siemens Immunlite total hCG test, standards in pmol/L and in mIU/ml determined by multiplying by 404, gave identical results.

In this report 10 cases of Familial hCG Syndrome are described (Table 3), among the 425 cases of positive hCG outside of pregnancy referred to the USA hCG Reference Service 1999–2011 (Table 1). The USA hCG Reference Service was referred 10 cases, tested 32 family members including the 10 cases, and found that 24 family members were producing an hCG immunoreactive molecule. These are the cases described here.

3. Results

Ten cases were examined by the USA hCG Reference Service (Table 3). In each suspected case the Service tested as many first degree relatives as possible, including sisters, brothers, mothers, fathers and children. All cases were otherwise asymptomatic. A total of 22 first degree family members were examined. Of these, 14 were found to produce hCG. In 8 of the 10 cases, one of two parents were positive, suggesting that inheritance of this syndrome involved a dominant gene. In the two other cases, Cases 8 and 9, one or both parents had perished. Of those referred cases, 5 were female and 5 were male suggesting that the syndrome has no gender-specific disposition (Table 2). Inherited hCG production was indicated and this was designated “Familial hCG Syndrome”.

The serum samples were variably positive (range = <1.0–216 mIU/ml). Members of one of the 10 families (Case 2) were positive for hCG in urine but not serum. As demonstrated, the families were not positive in a hyperglycosylated hCG test, suggesting choriocarcinoma or testicular germ cell malignancy, and were not positive in urine for β-core fragment, the end-product of hCG degradation. All the samples only showed positive for hCGβ, and for either hCGβ or hCG missing the β-subunit C-terminal peptide. This was detected using two total hCG tests, one using two antibodies to core β-subunit (β1 and β2 epitope, Fig. 1), and one using an antibody to β3 (synthetic C-terminal peptide) and an antibody to β1 epitope (Fig. 1). Subtracting the β3 assay values from the core total hCG assay values yielded the concentration of molecules missing the C-terminal peptide (Table 2).

It is concluded that this mixture of hCG degradation products, hCGβ and hCG or hCGβ missing the C-terminal peptide, are characteristic of Familial hCG Syndrome. Both of these degradation products appear to be biologically inactive and are cleared rapidly from the circulation. As previously learned, all molecules missing the β-subunit C-terminal peptide are nicked or cleaved at β47–48 leading to biological deactivation (Cole et al., 1991). The biological deactivation explains why families are normally fertile while producing an hCG-related molecule. This rapid clearance would seemingly explain Case 2, with total hCG negative serum and total hCG positive urine. None of the 10 cases showed positively in the serum LH test.

Each of the 10 families had interesting case histories (Table 3). Two cases needlessly received chemotherapy, for assumed cancer (Table 3, Cases 1 and 3), and one case received a hysterectomy for assumed malignancy. All 10 were resolved by the finding that first degree family members were producing similar forms of hCG.

4. Discussion

The USA hCG Reference Service has identified a new genetic disorder, Familial hCG Syndrome. Ten cases are identified and the genetic nature of the disorder is confirmed by the finding of similar hCG profiles in index cases and in 24 first degree relatives (including the 10 cases). Interestingly, all cases and relatives produced a unique combination of hCG degradation products, hCGβ and either hCG dimer or hCGβ missing the β-subunit C-terminal peptide. No other hCG-related variants were detected Fig. 2.

The USA hCG Reference Service considered the possibility that the low level positive hCG results were erroneous or false positive hCG results. It was noticed that samples were positive in 4 assays, serum total hCG and parallel urine total hCG (automated Siemens Immulite test), and serum hCGβ, serum hCGβ C-terminal peptide antibody test (microtiter plate immunometric assay). The USA hCG Reference Service had archived samples from 130 cycling (non-pregnant) women, including parallel serum and urine samples like those tested in the current study. Considering the samples described in this article (see Table 2), 19 of 21 parallel samples were positive in all 4 assays (the serum total hCG, hCGβ C-terminal peptide, hCGβ and urine total hCG). When the 130 menstrual cycle urine and serum samples were tested with the same 4 assays, none of the 130 parallel samples were positive in all 4 assays at maximum sensitivity. Six of 130 samples were sporadically low level positive, but only in one or two assays. It is inferred that the serum and urine samples tested here are true positive and not erroneous or false positive.

The major question raised by these data is the identity of the tissue producing hCG in this syndrome. hCG is normally produced by trophoblast tissues during pregnancy. No pregnancy is involved in Familial hCG Syndrome. It is known that the pituitary gland can produce hCG, under the stimulation of gonadotropin releasing hormone (GnRH) (Odell and Griffin, 1987, 1989). Pituitary hCG production is

normally very low, at <1 mIU/ml in serum and urine (Odell and Griffin, 1987, 1989). The pituitary could be responsible for the hCG levels reported here, but only in the event that GnRH reverted to an amenorrhea-like state. This is not the case because all cases were normally fertile, having children and normal menstrual periods suggesting normal hypothalamic GnRH production, and in all cases the FSH was <30 mIU/ml (Gronowski et al., 2008). Furthermore, the pituitary does not produce hCGβ (Cole et al., 2010), as was detected in these cases. The possibility of pituitary-derived hCG was considered. One remote explanation is that pituitary cells express a gain of function mutation in the GnRH receptor, which might result expression of hCG despite low levels of GnRH.

What tissue can be expressing the hCGβ gene in Familial hCG Syndrome? Interestingly, hCGβ and hCGβ missing the C-terminal peptide are sometimes detected in serum and urine in non-trophoblastic cancer cases. It appears that non-trophoblastic cancer cases tissues are unable to combine hCG subunits (Cole et al., 2008).

The 10 cases had quite eventful histories as indicated in Table 3. Two had undergone needless chemotherapy and one had an unnecessary hysterectomy for assumed cancer. Two were sportsmen. Data indicated that the hCG forms were biologically inactive, consistent with the cases having normal reproductive histories. Indeed the 10 cases were all seemingly asymptomatic other than production of hCG-related molecules. Cases exist in multiple members of each family suggesting dominant gene expression. The identification of 5 male and 5 female cases suggest that Familial hCG Syndrome does not exert gender preference. What is this genetic abnormality leading to solely hCGβ gene expression, without aberrant production of any other protein and a lack of symptoms? Speculative explanations include a genetic abnormality in GnRH expression, an inherited promoter of hCGβ leading to a liver or kidney expression of hCGβ, an abnormality in the hCGβ gene, or in an inducing agent such as interferon-α, the apparent promoter of hCGβ in cancer cells (Iles and Chard, 1989).

It is difficult to estimate the occurrence of Familial hCG Syndrome. As a vague indication, the USA hCG Reference Service is currently referred 110 cases each year, this includes 50 cases of gestational trophoblastic disease and 60 cases of individuals positive for hCG outside of pregnancy. The 50 cases of gestational trophoblastic disease are generally complex or complicated cases. In general, approximately 1 in 10 cases of gestational trophoblastic disease have chemotherapy resistance and other complications. There are approximately 50,000 cases of gestational trophoblastic disease in the USA in any one year. If one considers that 1 in 10 cases are complicated, this suggests 5000 cases a year in the USA. The USA hCG Reference Service consults on 50 cases each year (or 1 in 100) of these cases. Based on the fact that the USA hCG Reference Service has identified 10 families with Familial hCG Syndrome, it is estimated that there may be 100 × 10 or 1000 families in the USA with this syndrome. There are approximately 60 million families in the USA, suggesting an approximate incidence of 1 in 60,000 families affected with Familial hCG Syndrome. It should be noted that this is a very approximate estimate of the incidence of Familial hCG Syndrome.

It is concluded that Familial hCG Syndrome is a rare explanation for men and women found to have positive hCG tests outside of pregnancy. As examples, the USA hCG Reference Service has observed 10 cases of Familial hCG Syndrome among 425 male and female cases positive for hCG due to multiple reasons. It appears to the USA hCG Reference Service that Familial hCG Syndrome is a 'last resort' answer, applicable when somebody shows positive on a hospital pregnancy test and is not pregnant. To diagnose Familial hCG Syndrome, first clinical pregnancy must be excluded by ultrasound, then ectopic pregnancy must be excluded by methotrexate. If hCGβ is detected (>30% of total hCG), then cancer or PSTT is suggested. After MRI and CT scans to exclude cancer, relatives should be investigated for production of hCG and when found to be positive, Familial hCG Syndrome is indicated. Familial hCG Syndrome should be viewed as a remote explanation for men found to be hCG positive by sports anti-doping testing. The World Anti-Doping Agency is now using an intact hCG assay to test for doping to avoid detection of Familial hCG Syndrome.

Conflict of interest

The USA hCG Reference Service receives money and patent royalties from Church and Dwight Co. Inc., a manufacturer of home pregnancy tests, and Quest Diagnostics Inc., the largest clinical laboratory in the US. These financial associations played no role in the described research.

References

Cole, L.A., Kardana, A., Andrade-Gordon, P., Gawinowicz, M.A., Morris, J.C., Bergert, E.R., O'Connor, J., Birken, S., 1991. The heterogeneity of hCG: III. The occurrence, biological and immunological activities of nicked hCG. Endocrinology 129, 1559–1567.

Cole, L.A., Sutton, J.M., Higgins, T.N., Cembrowski, G.S., 2004. Between-method variation in hCG test results. Clin. Chem. 50, 874–882.

Cole, L.A., Butler, S.A., Khanlian, S.A., Giddings, A., Muller, C.Y., Seckl, M.J., Kohorn, E.I., 2006. Gestational trophoblastic diseases: 2. Hyperglycosylated hCG as a reliable marker of active neoplasia. Gynecol. Oncol. 102, 150–158.

Cole, L.A., Khanlian, S.A., Muller, C.Y., 2008. Blood test for placental site trophoblastic tumor (PSTT) and for non-trophoblastic malignancy for evaluating patients with low positive hCG results. J. Reprod. Med. 53, 457–464.

Cole, L.A., Khanlian, S.A., 2009. The need for a quantitative urine hCG assay. Clin. Biochem. 42, 676–683.

Cole, L.A., Laidler, L., Muller, C., 2010. USA hCG Reference Service, 10 year report. Clin. Biochem. 43, 1013–1022.

Cole, L.A., 2011. The utility of 6 over-the-counter (home) pregnancy tests. Clin. Chem. Lab. Med. 49, 1317–1322.

Gronowski, A.M., Fantz, C.R., Parvin, C.A., Sokoll, L.J., Wiley, C.L., Wener, M.H., Grenache, D.G., 2008. Use of serum FSH to identify perimenopausal women with pituitary hCG. Clin. Chem. 54, 652–656.

Iles, R.K., Chard, T., 1989. Enhancement of ectopic β hCG expression by interferon-α. J. Endocrinol. 123, 501–507.

Lapthorn, A.J., Harris, D.C., Littlejohn, A., Lustbader, J.W., Canfield, R.E., Machin, K.J., 1994. Crystal structure of hCG. Nature 369, 455–461.

Nisula, B.C., Blithe, D.L., Akar, A., Lefort, G., Wehmann, R.E., 1989. Metabolic fate of human chorionic gonadotropin. J. Steroid Biochem. 33, 733–737.

Odell, W.D., Griffin, J., 1987. Pulsatile secretion of human chorionic gonadotropin in normal adults. N. Engl. J. Med. 317, 1688–1691.

Odell, W.D., Griffin, J., 1989. Pulsatile secretion of chorionic gonadotropin during the normal menstrual cycle. J. Clin. Endocrinol. Metab. 69, 528–532.