Novel treatment (new drug/intervention; established drug/procedure in new situation)

Effect of raloxifene in human neurocysticercosis

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Summary

The authors report a patient whose polycystic ovarian syndrome (PCOS) and increased calcitriol level were associated with neurocysticercosis (NCC), for which she refused standard therapy. Based upon a report on treatment with tamoxifen in murine cysticercosis,¹ she was offered raloxifene. She began raloxifene 60 mg/day on 21 January 2010. On 17 March 2010 she was pregnant, and was terminated on 14 April 2010. MRI 26 April 2010 showed diminution in size, shrinkage and loss of viability in a number of the cysts. Total lesions fell from 37 to 33, 10 lesions shrunk, 5 resolved, 18 were unchanged, 4 enlarged and 1 new lesion developed. Concomitantly serum calcitriol fell from 81 to 41 pg/ml while 25-OH-vitamin D level fell from 34 to 30 ng/ml. Alteration of the hormonal milieu may reduce cestode burden in human NCC. The pregnancy on raloxifene, though unfortunate, supports the concept that NCC caused the PCOS. Serum calcitriol may be a useful biomarker for assessing disease activity in NCC.

BACKGROUND

To our knowledge this is the first report of:

- ▶ An endocrine disrupter effect of neurocysticercosis (NCC) in a human host
- ▶ Reduction of NCC burden by alteration of the hormonal milieu
- ▶ Enhanced 1- α -hydroxylation of 25-OH-Vitamin D either by the encysted parasite or by surrounding host macrophages
- ▶ Normalisation of 1,25-(OH)₂-vitamin D₃ level concomitant with reduction of cestode burden.

CASE PRESENTATION

A 33-year-old Mexican lady, G3P2O12, with extensive NCC presented with secondary oligomenorrhea, acne and hirsutism. Although logical signs, none of her cysts involved the hypothalamus or pituitary. There was no family history of polycystic ovarian syndrome (PCOS). She had previously conceived two children without difficulty, followed by normal pregnancies and deliveries and one elective abortion. Body mass index (BMI)=28.34 kg/m² (almost unchanged from 2003).

On metformin 500 mg 2x/day monthly menses resumed, lasting 2 days. On metformin 850 mg twice daily, menstrual periods lengthened to 4 days; acne and hirsutism noticeably diminished, however, she did not conceive despite having regular unprotected intercourse.

Our patient, at the age of 34 years, repeatedly refused standard treatment with albendazole and dexamethasone for her extensive NCC due to her concern about possible side effects experienced by other people she knew. After giving her fully informed consent and verbalising the importance of avoiding pregnancy while on treatment she commenced treatment with the selective oestrogen

receptor modulator (SERM), raloxifene 60 mg orally daily. Common disorders leading to a hypercoagulable state were excluded before commencing treatment on 21 January 2011. Raloxifene was chosen, rather than tamoxifen, as used in a report by Vargas-Villavicencio *et al*,¹ because of the lack of an association of the former with endometrial carcinoma and because raloxifene is known to exacerbate vasomotor symptoms in early premenopausal women, suggesting that it crosses the blood/brain barrier acting as an oestrogen receptor antagonist in the central nervous system (CNS).

She returned to endocrine clinic on 17 March 2010, reporting apologetically that, according to a home pregnancy test, she was pregnant. Pregnancy was confirmed in our laboratory and she was referred to Family Planning Clinic for termination because raloxifene is FDA Class X (should not be used) in pregnancy. Raloxifene was stopped.

INVESTIGATIONS

Endovaginal ultrasound was normal. Leutenising hormone (LH) and follicle stimulating hormone (FSH) by chemiluminescence were 12.21 IU/l and 4.67 mIU/l, respectively, ratio=2.6, while sex hormone binding globulin (SHBG)=23 nmol/l by chemiluminescence (17–120). In 6/07 LH/FSH=0.7, almost quadrupling in 1 year with nearly constant BMI.

On metformin 500 mg 2x/day LH/FSH=2.6 and SHBG=21.00. Serum insulin by chemiluminescence=18.7 mIU/L (2.6–24.9) (table 1). 25-OH-vitamin D₃ (25OHD) and 1,25 (OH)₂-vitamin D₃ by immunoextraction=34 ng/ml (20–100) and 81 pg/ml (19–67), respectively. On metformin 850 mg 2x/day the LH/FSH normalised, SHBG rose slightly and serum insulin declined (table 1).

Table 1 Parameters related to polycystic ovarian syndrome

Date	LH	FSH	LH/FSH	SHBG	BMI	Insulin
June 2007	4.9	6.9	0.7		26.31	
June 2008	12.2	4.7	2.6	23	27.66	
October 2008 on metformin 500 mg twice daily pc	9.7	3.8	2.6	21	28.34	18.7
January 2009 on metformin 850 mg twice daily pc	7.6	7.9	1.0	24	27.48	9.1

Units and reference ranges for the parameters given in the table: BMI, body mass index kg/m² (20–25); FSH, follicle stimulating hormone mIU/l (1.37–17.20); Insulin mIU/l (<17.0); LH, luteinising hormone IU/l (1.9–76.3); LH/FSH (≤1.0); SHBG, sex hormone binding globulin nmol/l (17–120).

Figure 1 Effect of raloxifene on neurocytotoxic lesions.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for a patient presenting with hirsutism, acne and oligomenorrhea, include PCOS, non-classical adrenal hyperplasia, hyperprolactinemia, virilising tumours and Cushing syndrome. She fulfilled the Rotterdam criteria for PCOS by having oligoovulation and evidence of end organ hyperandrogenic effect, for example, hirsutism and acne. In addition, she met the diagnostic

criteria of The Androgen Excess PCOS Society in meeting the Rotterdam criteria and, in addition, excluding the other virilising disorders listed above by virtue of normal basal and cosyntropin-stimulated levels of 17-OH-progesterone, 17-OH-pregnenolone, 11-deoxycortisol, deoxycorticosterone, corticosterone and 18-OH-corticosterone, normal serum prolactin and normal 24 h urine free cortisol. Also supporting the diagnosis of PCOS was the very high LH/

Figure 2 Effect of treatment of neurocysticercosis with raloxifene followed by albendazole/dexamethasone on patient's 1,25(OH)₂-vitamin D₃ level (pg/ml).

FSH ratio (2.6) and the low, normal level of SHBG as well as the resolution of her oligomenorrhea and diminution of her hirsutism and acne on metformin.

TREATMENT

Treatment is included in the case presentation and investigations above to provide a smoother flow.

OUTCOME AND FOLLOW-UP

Repeat brain MRI on 26 April 2010 showed diminution in number, size and viability of encysted lesions. (see accompanying representative pre, post-treatment MRI images, figure 1). The total number of lesions fell from 37 to 33, 10 lesions shrank, 5 lesions resolved, 18 lesions appeared unchanged, 4 enlarged and only one new lesion was detected. Concomitantly, her serum calcitriol level by immunoextraction fell from 81 to 41 pg/ml while her 25-OH-vitamin D level by immunoextraction only fell from 34 to 30 ng/ml. (figures 2 and 3). On 5 May 2010, she began a 2 week course of standard treatment with albendazole and dexamethasone, which she tolerated well.

She had her pregnancy terminated at 8 weeks gestation, not because of any known problem in the course of her pregnancy up to that point, but only because raloxifene is US FDA Class X (should not be used in pregnancy) and we could not assure her that she would have a healthy baby.

We continued to follow the patient after pregnancy termination on metformin 850 mg twice daily and spironolactone 25 mg daily until family concerns prompted her permanent return to Mexico in August 2011. She continued to have normal menses and good cosmetic control of her hirsutism and acne. On her last visit on 9 August 2011 it was noted that her BMI was 24.71, however, her non-preovulatory LH had risen to 13.76 IU/l with an FSH=4.99 mIU/l for an LH/FSH=2.8 (the highest since we had been following her).

SHBG had fallen from her previous level of 31 nmol/l to 25. Her 1,25-OH₂-vitamin D₃ level had again risen to

71 pg/ml. The rise in both the LH/FSH and calcitriol levels coupled with the fall in her SHBG, strongly suggested a reactivation of her NCC and associated PCOS. After reviewing treatment options with the patient again and re-emphasising the importance of effective contraception, she elected to resume treatment with raloxifene 60 mg daily. She continued spironolactone 25 mg daily and her metformin dosage was raised to 1000 mg twice daily. A case summary, copies of results and contact information was prepared for her physician in Mexico.

DISCUSSION

Cysticercosis is a parasitic infection that results from ingestion of eggs from the adult tapeworm, *Taenia solium* (*T solium*).^{2,3} NCC is the most common parasitic infection of the brain and a leading cause of epilepsy in the developing world, especially Latin America, India, Africa and China. Peak incidence is between ages 30 and 40 years, as in our patient. Many patients experience few or no symptoms, while others report vague sensations of headache and dizziness. Still others have major neurologic findings including seizures. NCC is a pleomorphic disease. This is due to the variation in the locations of the lesions, the number of parasites present, the strength of the host's immune response, the host's gender and endocrine disruption by the parasite.

NCC is an endocrine disrupter parasite which may induce PCOS via the endogenous biosynthesis of androstenedione, testosterone and 17-hydroxyprogesterone; the latter has been reported *in vitro* by Gomez,⁴ Jimenez,⁵ Diaz Orea,⁶ Valdez,⁷ Romano,⁸ Morales-Montor⁹ and Fernandez-Presas.¹⁰

This is the first report to characterise endocrine disrupter effects of NCC in a human host. It is the first report to examine Vitamin D metabolism in an NCC patient. Both PCOS and cysticercosis are common disorders in the Mexican population, however, she had no family history of PCOS; she had a normal menstrual and reproductive

Figure 3 Effect of treatment of neurocysticercosis with raloxifene followed by albendazole/dexamethasone on patient's 25(OH)-vitamin D level (ng/ml).

history until a year before presentation and no history of hirsutism or acne until after her diagnosis of NCC. Furthermore, she did not conceive again, despite having frequent, unprotected relations, until her treatment with the SERM, raloxifene.

This patient had enhanced 1- α -hydroxylation of 25-OH-vitamin D, which declined with raloxifene. This may represent an endocrine disrupter effect of the parasite itself or a host reaction to the parasite similar to the enhanced production of calcitriol by alveolar macrophages in pulmonary sarcoidosis. A recent case report by Kallas *et al*¹¹ and literature review of increased 1- α -hydroxylation by non-alveolar macrophages in other granulomatous disorders lends support to this possibility.

The absence of elevated serum androgens as well as basal or cosyntropin-stimulated steroid metabolites in this patient may be due to most of the parasites' steroid secretion being paracrine (into the surrounding CNS) rather than endocrine (into the circulation).

Intermediate dose metformin (500 mg twice daily) ameliorated the secondary amenorrhea in our patient without normalising the LH/FSH ratio or raising the SHBG, possibly because her BMI did not decline on this dose. Higher dose metformin (850 mg twice daily) lowered the BMI, normalised the LH/FSH ratio and increased the SHBG level. The addition of spironolactone 25 mg daily lengthened her menstrual periods from 2 to 5 days and further improved her hirsutism.

Morales-Montor⁹ has reviewed the subject of host gender in mammalian parasitoses, reporting that *Taenia* sp, as well as other mammalian parasites, display a distinct female host preference and even more readily infect and reproduce in pregnant hosts. This group's findings consistently corroborate a female host preference in cysticercosis with the hyperestrogenic female host being even more attractive, whether hyperestrogenic naturally (eg, pregnancy) or due to estradiol supplementation. Infected males typically become feminised with a decrease in free

and total testosterone and an increase in oestradiol. Given this background it may seem counterintuitive that NCC would induce PCOS, a hyperandrogenic state, until one considers that PCOS is also an unopposed oestrogen state characterised by clinical findings such as: superficial cell predominant vaginal cytology, cervical mucus ferning and spinbarkeit. PCOS is, after pregnancy, the most oestrogenic milieu for *Taenia* sp.

Vargas-Villavencio *et al*¹ have reported that treatment of mice infected with *T crassiceps* with the SERM tamoxifen resulted in a very rapid 80% reduction in parasite burden in infected females and a 50% reduction in infected males. Tamoxifen also produced an increase in the Th1/Th2 ratio favoring increased cellular immunity as well as a change in cytokine levels consistent with Th1 expression. They have also reported that cultured *T crassiceps* cestodes exposed *in vitro* to concentrations of tamoxifen comparable with those achieved in human treatment died rapidly.

Our patient showed enhanced 1- α -hydroxylation of 25OHD. Treatment with raloxifene caused dramatic reduction in her 1,25 (OH)₂-vitamin D₃ levels paralleling the reduction of her CNS cestode burden.

Although fibroblast growth factor 23 (FGF-23) upregulates 1- α -hydroxylation, there are no published data on FGF-23 levels in either experimental or clinical cysticercosis.

Our report is limited by the fact that we have only studied one patient. Both PCOS and cysticercosis are common disorders among Mexicans, however, PCOS generally has an onset in much younger patients, often presenting as premature adrenarche,¹² while this patient had a normal menstrual and reproductive history and no hirsutism before her diagnosis of cysticercosis. She only conceived again after beginning treatment with raloxifene with reduction in her NCC. Our patient had enhanced 1- α -hydroxylation of 25OH-vitamin D; her calcitriol level declined promptly on raloxifene, despite the fact that the dexamethasone which she took as part of her standard anticysticercosis treatment would be expected to further increase her calcitriol level.¹³

Since invitro 1- α -hydroxylation of 25OHD by *Taenia* cestodes has not yet been reported it is possible that this represents a host reaction to *Taenia* infection.

We recommend that cysticercosis patients be screened for steroidogenic disorders and that patients with steroidogenic disorders who originate in endemic areas be screened for cysticercosis. We further suggest that screening patients with 25-OH-vitamin D levels alone (as recommended by current guidelines and enforced by government and private insurers in the US as well as by health maintenance organisations), may be insufficient to uncover abnormalities in vitamin D metabolism in patients with granulomatous disorders. As in pulmonary sarcoidosis, calcitriol levels may be a useful, relatively low cost parameter, to assess response to treatment of cysticercosis.

Learning points

- ▶ Alteration of the hormonal milieu may be an effective primary or adjunctive treatment for human cysticercosis, possibly signalling a paradigm shift in the therapy of this disorder.
- ▶ The pregnancy which occurred while taking raloxifene, though accidental and unfortunate, provides further proof of concept that this patient's PCOS was indeed an endocrine disrupter effect of NCC, since even though metformin normalised the patient's previously, oligomenorrheic menstrual pattern conception did not place until raloxifene was added with a concomitant decrease in the parasite burden.
- ▶ Patients of reproductive age should exercise extreme caution not to conceive while on SERMs.
- ▶ We suggest that 1,25-(OH)-vitamin D3 may prove to be a useful biomarker for parasite burden in NCC, which, if further corroborated, may replace a portion of the expensive imaging required for therapeutic follow-up.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Sacerdote AS, Mejía JO, Bahtiyar G, Salamon O. Effect of raloxifene in human neurocysticercosis. *BMJ Case Reports* 2012; 10.1136/bcr.06.2011.4417, Published XXX

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