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Impact of *Taenia solium* neurocysticercosis upon endocrine status and its relation with immuno-inflammatory parameters

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ABSTRACT

Neurocysticercosis (NC) is a parasitic disease caused by the infiltration of the larval stage of *Taenia solium* in the central nervous system. Clinical presentations are heterogeneous and particularly depend, on the age and gender of the host. We designed a clinical study to evaluate the hormonal changes associated with neurocysticercosis and the relationships between disease heterogeneity, endocrine and immunological status. A total of 50 patients and 22 healthy subjects were included. A precise clinical and radiological description of disease for each patient was recorded. A broad hormonal profile was assessed for each participant and, in a sub-group of patients, immunological features were also evaluated. Compared with controls, all patients had lower dehydroepiandrosterone (DHEA) concentration; male patients also had lower concentrations of 17β-estradiol and higher concentrations of luteinising hormone (LH). In the clinically severe patients, lower concentrations of progesterone and androstenedione were found in women. Higher concentrations of follicle stimulating hormone (FSH) and lower concentrations of testosterone were found in men when compared with the less clinically severe patients. Significant correlations were found between estradiol and IL-10 in male patients, and between dehydroepiandrosterone (DHEA) and IL-1β, and androstenedione and IL-17 in female patients. To our knowledge the present study constitutes the first demonstration that the presence of *T. solium* larvae in the central nervous system can modify the host environment by the induction of endocrine and immunological changes. These results provide a stimulating background to analyse the repercussions of these changes on the course of the disease and on patient reproductive health.

1. Introduction

Human neurocysticercosis (NC) is a parasitic disease caused by the installation of the larval stage of *Taenia solium* in the CNS. NC exhibits a clinically heterogeneous picture ranging from asymptomatic to a severe neurological syndrome (Sciutto et al., 2000; Garcia et al., 2003).

Cysticerci localization in the CNS and the intensity of the inflammatory reaction are two factors clearly related to the clinical severity of the disease (Fleury et al., 2004; Chavarría et al., 2005). Inflammatory reaction intensity is influenced by the host's sex and age; compared with men, women exhibit a higher inflammatory reaction (Del Brutto et al., 1998; Fleury et al., 2004). Young women more frequently present a severe clinical presentation caused by multiple degenerating cysticerci in the parenchyma (Rangel et al., 1987). The prevalence of damaged cysticerci is significantly higher in women than in men (Romero et al., 2007). Children present a lower NC frequency and a lower frequency of severe forms of the disease (Sáenz et al., 2006). Also, vesicular parasites are more frequent in elderly hosts (Fleury et al., 2004).

Cysticercosis prevalence can be affected by the hormonal status of the host. Castration and pregnancy in pigs increase cysticercosis prevalence (Morales et al., 2002). Once infected, cysticercosis modifies the hormonal levels of pigs with increased concentrations of testosterone and 17β-estradiol (E2) (Peña et al., 2007). Moreover, in vitro studies have shown that human chorionic gonadotropin (hCG) effectively promotes cysticercal evagination and *T. solium* tapeworm elongation (Díaz-Orea et al., 2007). The finding that

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T. solium is also able to synthesise sex steroid hormones adds complexity to the host-parasite interactions (Jiménez et al., 2006; Valdez et al., 2006; Fernández Presas et al., 2008; Romano et al., 2008).

The present study investigated whether hormones involved in reproduction and stress are affected by the presence of parasites in the human brain. Immunological changes accompanying different clinical and radiological forms of human NC were also explored.

2. Materials and methods

2.1. Patients

Fifty NC patients attending the Instituto Nacional de Neurología y Neurocirugía (INNN) in Mexico City, Mexico and 22 healthy subjects (controls) were recruited between August 2005 and October 2007. The controls were employees of the INNN who did not suffer from any diseases and had not taken any medication.

None of the NC patients had previously received any specific cysticidal treatment or anti-inflammatory drugs (corticosteroids). A venous sample was taken between 7:00 and 10:00 am from each participant. A sample of CSF was also collected from patients who required a lumbar puncture for medical reasons. Cysticercus number, stage and localisation were radiologically defined and the clinical manifestations of all patients were retrieved.

Patients were clinically classified regarding the presence or absence of intracranial hypertension (headache, nausea or vomit and papilledema upon fundoscopic examination), one of the most severe clinical NC presentations. Although other symptoms (for example uncontrolled generalised seizures or chronic meningitis) can also be clinically severe, in this study none of the patients presented such symptoms. For this study, patients with intracranial hypertension were considered as "clinically severe". Radiologically, patients were classified regarding the presence or absence of multiple vesicular parasites localised in the subarachnoid space at the base of the skull, which represents one of the most severe radiological presentations.

2.2. Ethical considerations

This study fulfilled the research regulations for human beings required by Mexican laws and International regulations as well as ethical aspects considered in the General Rules of Health for Clinical Investigation. The protocol was approved by the INNN Ethical Committee. Patients were instructed on the aims of the study and gave informed consent.

2.3. Hormonal profiles

Shortly after blood collection, serum was separated and maintained at −20 °C until required. The concentration of the following hormones was measured by radioimmunoanalysis (RIA) using ^{125}I tracers kits: testosterone (TESTO-CT2), 17β-estradiol (E2, ESTR-CTRIA), luteinising hormone (LH) (RIA-gnost hLH), follicle stimulating hormone (FSH) (RIA-gnost hFSH), prolactin (RIA-gnost PROL), cortisol (CORT-CT2), all from CIS-bio International (Gif sur Yvette, France) and dehydroepiandrosterone sulphate (DHEA-S, "coat-a-count" kit, Diagnostic Products Corp., Los Angeles, USA) which were measured in men. E2, progesterone (PROG-CTRIA, CIS-bio International), DHEA-S, LH, FSH, prolactin, androstenedione (A4) (RIAZENco Zentech, Liege Science Park, Belgium) and cortisol concentrations were measured in women. The detection limits were: E2, 8 pg/mL; progesterone, 0.05 ng/mL; cortisol, 4.6 nmol/L; A4, 0.05 ng/mL; testosterone, 0.1 nmol/L; DHEA-S, 5 ug/dL; LH 0.15 mUI/mL; FSH, 0.10 mUI/mL and prolactin, 5 uU/mL.

2.4. In vitro cytokine titration

A total of 2.5×10^6 of peripheral blood mononuclear cells (PBMC) per mL per well were stimulated with 30 μg/mL of *T. solium* antigen and plated in 12 cluster plates (Costar), and incubated at 37 °C in a 5% CO_2 humidified atmosphere. After 48 h (for IL6, IL10, TGFβ, TNFα) and 120 h (for IL1β, IL17, IFNγ), the culture supernatants (SN) were harvested and stored at -80 °C until required for cytokine quantification.

Cytokine titration in SN and CSF was determined using a commercial sandwich ELISA kit (BD Pharmingen Cytokine Sets, CA, USA; eBioscience; R&D Duo-Set, UK). Sensitivity levels were 9.4 pg/mL for all cytokines.

2.5. Statistical analysis

All data were recorded in Excel software and analysed using SPSS version 10 software. Quantitative variables were expressed as mean and S.D., or median and 25th–75th percentile values, and compared using the two-tailed Student's *t*, ANOVA, Mann–Whitney or the Kruskal–Wallis tests. Qualitative variables were expressed in percentages and compared using χ^2. Parametric or non-parametric statistics were employed according to the size of the sample and data distribution. Differences were considered statistically significant at $P < 0.05$.

3. Results

3.1. General characteristics of patients and controls

Fifty patients participated in this study; 21 women (18–61 years, mean: 37.3 ± 11.8 years) and 29 men (21–65 years, mean: 41 ± 12.5 years). Twenty-two healthy non-NC subjects were also included as controls, 13 women (mean: 35.5 ± 10.1ranging from 25–52 years) and nine men (mean: 37.1 ± 9.8 ranging from 30–60 years). Age was not significantly different between patients and controls ($P = 0.33$ for men and $P = 0.67$ for women).

Eight women (six patients and two controls) were considered as potentially menopausal based on their clinical story and hormone profiles, and were not considered for the female analysis of LH, FSH, E2 and progesterone. Thereafter, for sex steroid hormone analysis the mean age of female patients was 31.2 ± 7, while the mean age of female controls was of 32.9 ± 8.8 ($P = 0.58$).

3.2. Clinical and radiological presentation of patients

As shown in Table 1, intracranial hypertension was not present in 31 of the 50 (62%) patients included in this study. Severe radiological presentation with multiple vesicular parasites located in the basal cisterns or in the ventricular space was demonstrated by 27 of the 50 (54%) NC patients. No significant differences between men and women were found regarding clinical or radiological criteria. In addition, clinically severe forms occurred at an age significantly older than the non-severe presentations (mean: 43.9 ± 14.1 versus 36.7 ± 10.3, $P = 0.04$).

3.3. Differences in hormonal status between patients and controls

As shown in Table 2, male NC patients exhibited significantly lower concentrations of E2 (mean 21 ± 10 versus 30.4 ± 8.2, $P = 0.02$) and DHEA (mean 132.4 ± 107 versus 251.6 ± 102, $P = 0.006$), and higher LH concentrations (mean 6.5 ± 11 versus 2.2 ± 2.2, $P = 0.02$) than healthy controls.

Table 1
Clinical and radiological descriptions of neurocysticercosis (NC) patients included in this study.

	Women (n = 21)	Men (n = 29)	P
Age (years)	7.3 ± 11.8[a]	41 ± 12.5	0.29
Clinical presentation			
Not severe	12 (57.1)[b]	19 (65.5)	0.57
Severe	9 (42.9)	10 (34.5)	
Radiological presentation			
Not severe	7 (33.3)	16 (55.2)	0.16
Severe	14 (66.7)	13 (44.8)	
Number of cells/mm^3 in the CSF	25.8 ± 38.6	34.9 ± 40.9	0.44

[a] Mean ± S.D.
[b] Number of patients (percentage of patients).

Table 2
Hormonal differences between neurocysticercosis (NC) patients and healthy controls.

Hormones	Men			Women		
	Patients	Controls	P	Patients	Controls	P
LH (mUI/mL)[b]	6.5 ± 11[a]	2.2 ± 2.2	**0.02**	4.6 ± 6.4	7.5 ± 6.7	0.28
FSH (mUI/mL) [b]	7.8 ± 15	4 ± 1.9	0.13	3.6 ± 2.8	3.4 ± 2.3	0.86
Prolactin (uU/mL)	370.5 ± 373	182 ± 107	0.15	407.6 ± 483	381.1 ± 372	0.87
DHEA (ug/dL)	132.4 ± 107	251.6 ± 102	**0.006**	95.4 ± 99	158.3 ± 69	**0.05**
Cortisol (nmol/L)	221.7 ± 208	257 ± 83	0.47	304.6 ± 252	432.4 ± 191	0.13
Estradiol (pg/mL) [b]	21 ± 10.5	30.4 ± 8.2	**0.02**	46.3 ± 54.2	85.7 ± 78.6	0.15
Progesterone (ng/mL)[b]	ND	ND		1.8 ± 5.7	6 ± 11.7	0.15
Testosterone (nmol/L)	16.4 ± 9.5	17.2 ± 4.9	0.78	ND	ND	
Androstenedione (ng/mL)	ND	ND		0.45 ± 1.3	1.5 ± 2.5	0.19

LH, luteinising hormone; FSH follicle stimulating hormone; ND: not determined.
Bold indicates significant differences ($P \leqslant 0.05$).
[a] Mean ± S.D.
[b] Hormones levels in pre-menopausal women only.

In women, DHEA concentrations were significantly lower in NC patients than in healthy controls (P = 0.05). No significant differences were found in the other measured hormones.

3.4. Differences in hormonal concentrations between clinically and radiologically severe and non-severe NC patients

In clinically severe male patients, significantly decreased serum testosterone concentrations (9.7 ± 6 nmol/L versus 19.6 ± 9 nmol/L, P = 0.007) and significantly increased FSH concentrations (14.5 ± 26 mUI/mL versus 4.7 ± 2 mUI/mL, P = 0.05) were observed compared with non-severe patients (Table 3). Moreover, lower E2 concentrations were detected in severe (16.3 ± 9 pg/mL) than in non-severe patients (23.4 ± 10 pg/mL) albeit non-statistically significant (P = 0.09). No significant differences in other hormonal concentrations were found between radiologically severe and non-severe male patients (Table 3).

In women, clinically severe patients exhibited significantly lower progesterone (0.07 ± 0.1 ng/mL) and A_4 concentrations (0.08 ± 0.09 ng/mL) than non-severe patients (3.5 ± 7.9 ng/mL, P = 0.03, and 0.74 ± 1.7 ng/mL respectively, P = 0.01).

Different hormone concentrations were also found when comparing healthy controls with severe and non-severe patients of both sexes, classified both clinically and radiologically. As shown in Fig. 1, male patients displayed a significant decrease in DHEA and E2 concentrations as clinical severity increased (P = 0.018 and P = 0.015 compared with controls, respectively). Increased radiological severity in men was also accompanied by a significant increase in LH (P = 0.038) and a nearly significant decrease in E2 (P = 0.07). In women, a significant decrease in progesterone concentrations was observed as clinical severity increased compared with controls (P = 0.027).

No significant correlation was found between CSF cellularity and the studied hormones regardless of patient classification according to sex or disease severity.

3.5. Relation between cytokine profile and NC presentations

As Table 4 shows, radiologically severe NC patients (multiple vesicular parasites located in basal cisterns or ventricles) presented higher IL-1β concentrations in SN (50–127 pg/mL) with respect to non-severe patients (23.4–23.4 pg/mL, P = 0.003). Radiologically severe patients also exhibited higher IL-10 concentrations in CSF (34–225 pg/mL versus 9.4–41 pg/mL; P = 0.004). No statistically significant differences in the other cytokines were found between severe and non-severe patients.

3.6. Correlations between hormones and cytokines

Correlations between the serum hormonal and cytokine concentrations in SN or CSF were assessed. A significant negative correlation between E2 and IL-10 in CSF was detected in male patients (n = 14, r = −0.53, P = 0.049). Among women, significant positive correlations were observed between DHEA and IL-1β in SN (n = 7, r = 0.77; P = 0.04) and between A4 and IL-17 in SN (n = 8, r = 0.86; P = 0.006).

No significant correlations were found between other pairwise tested hormones and cytokines.

4. Discussion

In this study, differences between the hormonal profiles (sex-steroid hormones, gonadotropins, prolactin and cortisol) that accompany NC of different clinical and radiological severity were assessed. It is relevant to examine this aspect of NC as the disease

Table 3
Differences in the hormonal levels between clinical and radiological severe and non-severe neurocysticercosis (NC) patients.

Hormones	Radiological			Clinical		
	Severe	Non-severe	*P*	Severe	Non-severe	*P*
Men						
LH (mUI/mL)	10 ± 15.8[a]	3.8 ± 2.4	0.17	9.4 ± 17.3	5 ± 5.7	0.48
FSH (mUI/mL)	11.5 ± 23	5.1 ± 2.4	0.8	14.5 ± 25.9	4.7 ± 2.4	**0.05**
Prolactin (uU/mL)	360 ± 151	379 ± 490	0.9	256 ± 172	428 ± 434	0.27
DHEA (ug/dL)	148 ± 128	121 ± 91	0.66	110.4 ± 88	143 ± 116	0.47
Cortisol (nmol/L)	220 ± 198	223 ± 221	0.98	205 ± 190	229 ± 220	0.78
Estradiol (pg/mL)	20.7 ± 13.7	21.2 ± 8	0.89	16.3 ± 9	23.4 ± 10	0.09
Testosterone (nmol/L)	14 ± 11.7	18.3 ± 7	0.25	9.7 ± 5.7	19.6 ± 9	**0.007**
Women						
LH (mUI/mL)[b]	3.6 ± 6.1	7.8 ± 7	0.11	4.6 ± 6.7	4.4 ± 6.6	1
FSH (mUI/mL)[b]	3.2 ± 2.8	5.4 ± 2	0.2	4.2 ± 2.6	3.0 ± 3.1	0.38
Prolactin (uU/mL)	360 ± 381	494 ± 664	0.6	582 ± 638	252 ± 229	0.37
DHEA (ug/dL)	104 ± 106	78.9 ± 87	0.6	92.1 ± 109	97.9 ± 96	0.92
Cortisol (nmol/L)	267 ± 250	386 ± 258	0.28	222 ± 269	379 ± 222	0.28
Estradiol (pg/mL)[b]	50.4 ± 69	36 ± 23.8	0.66	50.0 ± 79.4	43 ± 21.1	0.23
Progesterone (ng/mL)[b]	2.7 ± 7	0.1 ± 0.09	0.49	0.07 ± 0.1	3.5 ± 7.9	**0.03**
Androstenedione(ng/mL)	0.6 ± 1.5	0.1 ± 0.07	0.45	0.08 ± 0.09	0.74 ± 1.7	**0.01**

LH, luteinising hormone; FSH, follicle stimulating hormone; DHEA, Dehydroepiandrosterone.
Bold indicates significant differences ($P \leqslant 0.05$).
[a] Mean ± S.D.
[b] Hormones levels determined only in pre-menopausal women.

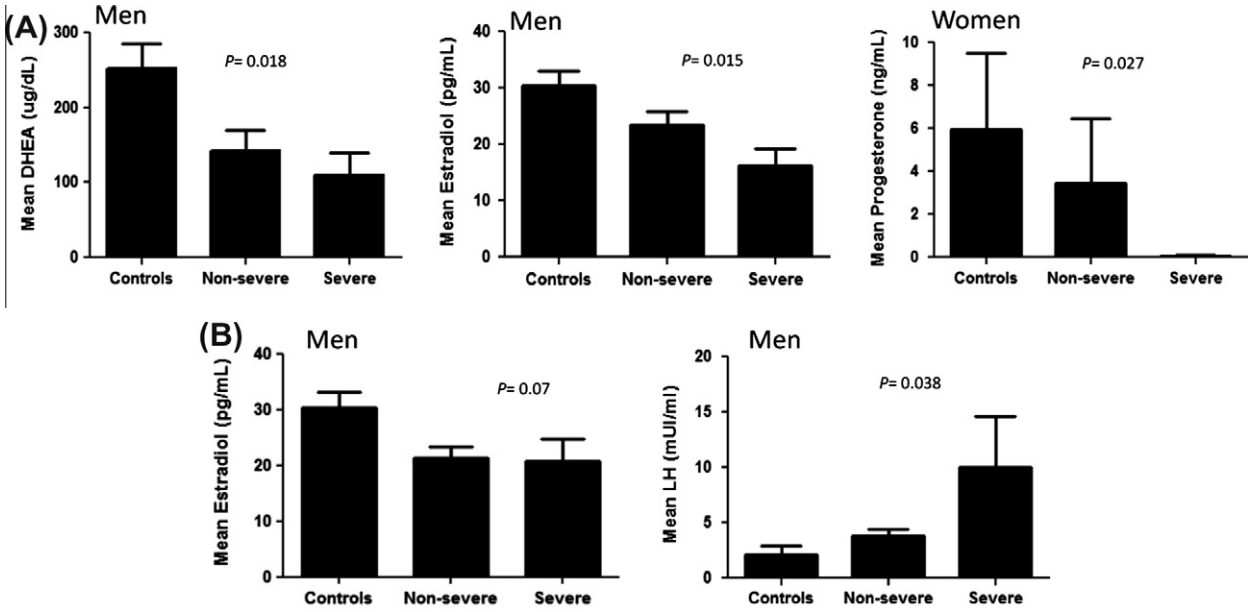

Fig. 1. Dehydroepiandrosterone (DHEA), 17β-estradiol, progesterone and luteinizing hormone (LH) concentrations in controls and in neurocysticercosis (NC) patients classified by (A) clinical and (B) radiological criteria according to disease severity. Data indicate media ± S.E.M.

affects the CNS, co-exists with clear immune-inflammatory changes, and presents gender- and age-associated differences both in clinical and radiological terms.

Alterations of the hormonal status during infections are not rare. Among the factors that may account for those are stress and infection-associated cytokine release (Papadimitriou and Priftis, 2009; Pérez et al., 2009).The stress response is mediated by the stress system that involves the CNS and peripheral organs (Chrousos, 2009). Due to the presence of inflammation, pain and other severe symptoms, neurological diseases cause chronic stress that result in the impaired function of several systems. Disruption of gonadal functions by chronic stress has been described and is the result of central and peripheral actions of hormones, proinflammatory cytokines and adipokines that inhibit the hypothalamus–pituitary–gonadal (HPG) axis at various levels (Kyrou and Tsigos, 2008; Chrousos, 2009). On the other hand, it is also known that chronic stress can have a major impact on different neurological diseases, for example neurodegenerative and mental disorders, and plays a significant role in susceptibility, progress and outcome of these diseases. The hypersecretion of glucocorticoids occurring in these diseases is probably one of the mechanisms involved (Chrousos, 2009; Sotiropoulos et al., 2011). Moreover, in infectious and neurological diseases, alterations of the hypothalamus–pituitary–adrenal (HPA) axis, the HPG axis, or a direct involvement of gonads or adrenal glands may occur.

Alterations in gonadal steroid production have been described in several parasitic infections and diverse hosts. Changes in E2 concentration have been shown in mice challenged with *Taenia crassi-*

Table 4
Cytokine profile in neurocysticercosis (NC) patients with severe and non-severe clinical and radiological presentation.

Cytokine	Radiological			Clinical		
(pg/mL)	Severe	Non-severe	*P*	Severe	Non-severe	*P*
IL-1 SN	88.5 (50–127)(*9*)[a]	23.4 (23.4–23.4)(*4*)	**0.003**	51.2 (31–93)(*7*)	55.9 (23–676)(*6*)	0.94
CSF	35.6 (23–49) (*14*)	23.4 (23.4–23.4) (*12*)	0.14	35.6 (23–49)(*10*)	23.4 (23–25) (*16*)	0.34
IL-6 SN	252 (56–692) (*18*)	117.8 (21–579)(*13*)	0.49	98.5 (34–429)(*13*)	379.9 (51–748) (*18*)	0.13
CSF	124 (9–243) (*14*)	14 (9–177)(*12*)	0.41	38.2 (9–184)(*9*)	92.0(9–272) (*17*)	0.44
IL-10 SN	59.6 (9–569)(*18*)	9.4 (9.4–353)(*13*)	0.39	9.4 (9.4–592) (*13*)	36.8 (9–207)(*18*)	0.77
CSF	69 (34–225) (*14*)	9.4 (9.4–41) (*13*)	**0.004**	54.3 (19–69) (*9*)	112 ± 158 (*18*)	0.67
IL-17 SN	19.7 (9–31) (*11*)	15.8 (10–25)(*4*)	1	15.7 (10–29) (*8*)	19.9 (9–26) (*7*)	0.87
CSF	35.6 (9–85) (*13*)	9.4 (9.4–9.4)(*7*)	0.22	13.3 (9–21) (*8*)	9.4 (9–13) (*12*)	0.38
IFN-γ SN	45.8 (23–78) (*9*)	167.4 (58–193)(*4*)	0.15	48.2 (39–93) (*7*)	92.8 (23–178)(*6*)	0.94
CSF	175 (23–207) *14*)	23.4 (23–146)(*12*)	0.23	181.6 (23–207)(*10*)	23.5 (23–182)(*16*)	0.45
TGF-β SN	37.6 (9–85) (*11*)	9.4 (9.4–212)(*4*)	0.18	20.5 (9–71)(*8*)	77.5 (9–280) (*7*)	0.46
CSF	9.4 (9.4–9.4) (*13*)	9.4 (9.4–9.4) (*7*)	1	9.4 (9.4–9.4)(*8*)	9.4 (9.4–9.4) (*12*)	0.68
TNF-α SN	9.4 (9.4–9.4) (*11*)	9.4 (9.4–9.4) (*4*)	0.85	9.4 (9.4–9.4) (*8*)	9.4 (9.4–9.4) (*7*)	0.71
CSF	9.4 (9.4–9.4) (*13*)	9.4 (9.4–9.4) (*7*)	0.82	9.4 (9.4–9.4) (*8*)	9.4 (9.4–9.4) (*12*)	0.77

SN, culture supernatants after specific stimulation of mononuclear cells with *Taenia solium* antigens.
Bold indicates significant differences ($P \leqslant 0.05$).
[a] Median (25–75% percentile values) (*number of samples tested*).

ceps (Larralde et al., 1995), as well as in *Plasmodium vinckei petteri* infections induced in mice (Barthelemy et al., 2003), in *Ligula intestinalis* infections induced in fish (Trubiroha et al., 2010), and in human filariasis (Mavoungou et al., 2005). Variations in testosterone concentrations have been described in infections with *Plasmodium chabaudi chabaudi* in mice, *Mycobacterium leprae* and *Mycobacterium tuberculosis* in humans (Barthelemy et al., 2004; Leal et al., 2006; Rey et al., 2007). In addition, ovarian dysfunction was reported in a woman diagnosed with NC (Choudhry S, Mejía J, Bahtiyar G, Mejía J, Sacerdote A., 2009. Endocrine Disruptor Effects of Central Nervous System Cysticercosis; Induction of Polycystic Ovarian Syndrome. Presented at the Endocrine Society 91st Annual Meeting, June 2009, Washington D.C., USA).

The data found in this study point to the involvement of the HPG axis and to a probably primary gonadal failure in NC patients. This latter alteration seems to predominate in men, who showed a decrease in E2 with an increase in LH, together with decreased testosterone and E2 levels, and the increase in FSH detected in severe patients. These alterations may be the result of an inhibitory effect of some molecules participating in the inflammatory reaction that accompanies progression of the disease (Kalyani et al., 2007). For example, significantly higher IL-1 levels in the SN of severe patients can act negatively on testicular function (Tsigos et al., 1999; Garcia et al., 2006). No significant negative correlation between IL-1 and testosterone was found in this study, but this may be due to the small number of patients (six) in which both features were measured. Also, it is possible that the lack of correlation between this cytokine and testosterone may be in part attributed to the fact that cytokines were measured in vitro, when blood immune cells are no longer in their natural environment where they are exposed to steroid concentration changes caused by the disease. On the other hand, decreased testosterone concentrations may be participating in the maintenance of the inflammatory reaction since testosterone is considered an anti-inflammatory hormone, as it reduces co-stimulatory factors expressed by antigen-presenting cells, induces the suppression of inflammatory cytokines (Klein, 2004), and increases the anti-inflammatory cytokine IL-10 (Liva and Voskuhl, 2001). This is an important result since inflammation is the most critical sign of NC severity. The findings of the present study present new prospects to manage and control the inflammatory response in NC. Decreased E2 levels found in the entire group of male patients in the presence of preserved levels of testosterone may be the consequence of diminished testosterone aromatisation to E2 by the P-450 aromatase enzyme, as aromatisation is influenced by different cytokines (Lambard et al., 2005).

In women, clear involvement of ovarian function (decrease of progesterone and A4 concentrations) was found in severe patients. Considering our results, it could not be ascertained whether NC directly affects the ovarian functions or the HPG axis. However, some findings argue in favour of an HPG axis engagement since changes in ovarian hormones did not correlate with changes in pituitary hormones. Mediators involved in the patients' inflammatory reaction, either local or systemic, may account for suppression of the HPG axis. Support for this premise comes from the correlation of A4-IL-17 found in female patients, and the raised IL-1β and IL-10 levels registered in SN and CSF, respectively, in the entire group of severe patients. On the other hand, evidence of a direct effect on ovaries is supported by the normal prolactin levels, which suggest that at least part of the pituitary gland was working properly. Additionally, the lack of significant gonadotropin differences between patients and controls may be due to the natural cyclic hormonal variations in women, which introduced a large dispersion in the results. The significant variations in progesterone levels suggest that most NC patients, particularly the severe cases, could present ovulation failure and thus probably be infertile during the active infection.

Regarding the adrenal function, significantly decreased DHEA concentrations were found in both male and female patients together with no significant changes in cortisol levels. Such findings are partly in line with data from patients with leprosy (Leal et al., 2003) and tuberculosis (Botasso et al., 2007). Serum cortisol concentrations found in patients and controls in the present study cannot be considered as basal because non-invasive methods should be employed to obtain these measurements (Romano et al., 2010). However, cortisol levels showed no differences between patients and controls, which at least discard the premise of a profound compromise of the glomerular layer of the adrenal gland. DHEA production may have been affected by cytokines released by immunocompetent cells that can act on the hypothalamus, on the pituitary or even directly on the adrenal glands. A shift in adrenal steroid synthesis, away from adrenal androgens and toward the essential cortisol pathway may occur, as enzymes involved in steroidogenesis are modulated by different cytokines (Herrmann et al., 2002). The link between cytokine and hormone synthesis is illustrated by the positive correlation between IL-1 and DHEA found in women. It is also possible that the normal levels of cortisol are related to the chronicity of the clinical distress experienced by patients (Van den Berghe, 2002). Although information on duration of symptoms before inclusion of the patients in this study was not available, the time between the onset of symptoms and hospital consultation is usually long.

One point deserving attention is the poor association between the hormonal profile and radiological criteria. Instead, results indicate that the clinical criteria of severity are more clearly related to hormonal changes. The poor correlation between clinical and radiological features is striking upon patient examination. In fact, it is common to see patients with a large parasite burden and few symptoms, and patients with a small parasite load but with significant clinical distress when critical cerebral areas are affected. This result could indicate that the ailment caused by the neurological affliction may be more important than the parasitosis itself in the genesis of hormonal alterations.

It is also interesting to note that the most salient differences were recorded in men. Data obtained on female menstrual phases were not consistent enough. However, the clear differences in progesterone concentrations found in the study strongly suggest that the reproductive cycle was altered.

To the best of our knowledge, the present study constitutes the first known demonstration of immuno-endocrine alterations in NC patients. Results of this study show the complex immune-endocrinological relationships that underlie NC pathogenesis, and provide a stimulating background to analyse the repercussion of these changes on the course of the disease and in patient reproductive health.

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