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Transient hypogonadotrophic hypogonadism in males with acute toxoplasmosis: suppressive effect of interleukin-1β on the secretion of GnRH

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BACKGROUND: In September 2002, an outbreak of toxoplasmosis was noted in a male boarding high school on the Aegean coast of Turkey. We have focused our efforts to investigate the sex hormones in this population. METHODS: Blood samples were collected from 40 male patients, 17–18 years old, who also had positive titres of antibody to *Toxoplasma gondii*. Serum FSH, LH, free testosterone (FT), total testosterone (TT), interferon-γ (IFN-γ), interleukin-1β (IL-1β) and macrophage-inflammatory protein-1α (MIP-1α) concentrations were measured in all patients and 20 control subjects. Initially, the patients were divided on the basis of the levels of sex hormones into the following groups: patients who had normal sex hormone levels (*n* = 31) as group A and patients with low sex hormone levels (*n* = 9) as group B. RESULTS: IL-1β levels were found to be higher in group B patients than group A. The levels of IL-1β correlated significantly in a negative manner with FSH, LH, FT and TT in all patients with acute toxoplasmosis (*n* = 40). CONCLUSIONS: Acute toxoplasma infection may cause temporary hypogonadotrophic gonadal insufficiency regardless of the course of the disease.

Key words: hypogonadotrophic hypogonadism/interferon-γ/interleukin-1β/macrophage-inflammatory protein-1α/toxoplasmosis

Introduction

Toxoplasmosis, a worldwide infection caused by the obligatory intracellular coccidian *Toxoplasma gondii*, is usually acquired through the ingestion of raw or undercooked meat or by contamination by oocysts present in the faeces of cats infected with the parasite (Bowie *et al*., 1997). During the acute stage of the infection, tachyzoites quickly proliferate within a variety of nucleated cells and spread throughout host tissues (Suzuki, 2002). The acute infection/disease is caused by this form of the parasite. The clinical manifestations of toxoplasmosis results from direct tissue destruction by the parasite, but inflammatory cytokine-mediated immunopathological changes may also contribute to disease progression (Sarciron and Gherardi, 2000).

In immunocompetent individuals, the immune system controls multiplication of the parasites and stops its dissemination, and the severity of disease closely correlates with the immune status of the infected person (Beaman *et al*., 1992). Therefore, immunocompetent adults and adolescents with primary infection are usually either asymptomatic or paucisymptomatic. Symptoms may include mild malaise, fatique, fever, and lymphadenopathy (Krick and Remington, 1978). Symptoms, if present, usually resolve within a few months and rarely persist beyond 12 months. These symptoms are also self-limited, and specific treatment for non-pregnant adults and adolescents is not required unless they are immunodeficient. Outbreaks of toxoplasmosis involving more than a single family or small group are infrequent (Kean *et al*., 1969; Teutsch *et al*., 1979; Benenson *et al*., 1982).

Toxoplasmosis is one of the classical conditions known to have a profound adverse effect on human reproductive functions (Zighelboim *et al*., 1968; Pal *et al*., 1975). Experimental evidence has established that mice undergo acquired hypogonadotrophic hypogonadism secondary to hypothalamic dysfunction after chronic infection with *T. gondii* (Stahl *et al*., 1985, 1994; Antonios *et al*., 2000). In addition to this, a male patient was previously reported with transient hypogonadotrophic hypogonadism due to toxoplasma infection from our centre (Oktenli *et al*., 2001). Furthermore, it has been recently reported that children with congenital toxoplasmosis have a high frequency of precocious puberty (Setian *et al*., 2002). Although previous reports suggest that toxoplasma infection may cause transient hypogonadotrophic hypogonadism, no detailed analysis has been conducted in

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humans. In September 2002, an ongoing outbreak of toxoplasmosis was noted in a male boarding high school. This population offers a unique opportunity to study any likely adverse effects of toxoplasmosis infection on male reproductive function.

Materials and methods

Case selection and description

Initially, 171 of 1797 male students (5/428 freshmen, 9/427 sophomores, 148/516 juniors, and 9/426 senior students) in a male boarding high school were found to be positive for mild symptoms of acute toxoplasma infection, in September 2002. As immunocompetent adults and adolescents with primary infection are generally asymptomatic, and these cases largely go unrecognized, the exact date of onset of the infection remains unknown. However, exposure probably took in place in late Summer of 2002. Symptomatic students presented with mostly flu-like complaints (subfebrile fever, myalgia, dizziness, headache) with lympadenopathy. No ocular lesion was visualized upon fundoscopic examination by ophthalmologist in these patients. All subjects were followed as outpatients; none was hospitalized. Because all cases of acquired acute toxoplasmosis in immunocompetent cases are self-limiting, specific drug therapy was not required.

Blood samples were collected from 40 of 171 symptomatic patients (who had all undergone age-appropriate normal puberty) aged 17–18 years old with a significant positive titre of antibody (IgM and IgG, and strongly indicative IgG avidity) to *T. gondii*. None of the patients had hyposmia, anosmia, or a family history of hypogonadism. They were of normal height for age. There was no significant history of any drug use. The control group ($n = 20$) consisted of age-matched male students, who had been living in the same school, and were ultimately shown to have no remarkable IgM antibody or IgG avidity to *T. gondii*. All control subjects had a spontaneous pubertal development and their physical and biochemical findings were within the normal limits. All subjects were informed about the study and they gave their written consent.

Design of the study

Initial fasting blood samples were collected from patients and controls between 0800 and 0830 h after an overnight fast in September 2002, additional samples were collected over a 9 month period. Sera were stored at –80°C until parameters were measured. Serum FSH, LH, free testosterone (FT), total testosterone (TT), sex hormone-binding globulin (SHBG), interferon-γ (IFN-γ), interleukin-1β (IL-1β) and macrophage-inflammatory protein-1α (MIP-1α) concentrations were measured in all patients and control subjects.

In the beginning of the study, patients with acute toxoplasmosis were divided based on the levels of sex hormones into the following groups: patients who had normal sex hormone levels ($n = 31$) as group A or patients with low sex hormone levels ($n = 9$) as group B. In group B, the major complaint at presentation was impaired sexual performance in three (33%) patients. Initially, each of these patients had low FSH, LH and testosterone levels. Development of the penis and scrotum, voice, musculature, and secondary sex hair were all normal in these patients. The follow-up visits to the school were on a periodic basis for serological, immunological and endocrinological work-up. All symptomatic patients with lympadenopathy and fever received no treatment for toxoplasmosis and their signs and symptoms resolved spontaneously by the end of the year 2002.

In nine patients with low sex hormone levels initially, these parameters were serially determined after 1 and 3 months of the study period. After the 3 months, five patients had normal sex hormone levels, the remaining four patients who still had low sex hormone levels were re-assessed in the 6th month. Gonadotrophin and testosterone levels were also found to be low in the 6th month. Furthermore, because hypogonadotrophic hypogonadism may be caused by pituitary insufficiency or abnormalities within the hypothalamus or higher brain centres, traditional dynamic test of a bolus i.v. injection of 100 μg GnRH (GnRH bolus test) was applied to these four patients in the 6th month. Cranial magnetic resonance imaging (MRI) and hypophysis MRI were also performed. Finally, sex hormone levels were determined in the 9th month and found to be within normal limits.

Serological tests

Detection of specific IgG and IgM antibodies

IgG antibodies to *T. gondii* were detected by enzyme-linked immunosorbent assay (ELISA) IgG (Equipar, Italy); specific IgM titres were measured by an automatic assay (VIDAS TOXO IgM; VITEK system, bioMérieux, Marcy-l'Ëtolie, France) and ELISA IgM (Equipar, Italy).

Toxoplasma-specific IgG avidity test

IgG avidity was determined with the *T. gondii* IgG avidity (Bouty Beia, Italy). Values <15% indicated low avidity; values 15–25% were considered borderline avidity; and values >25% were considered high avidity.

Measurement of serum hormone concentrations

Serum LH, FSH and TT levels were determined by chemiluminescence method using an automated hormone analyser Advia Centaur (Bayer Corporation, USA). The intra- and inter-assay CV were 2.6 and 2.3% for LH, 2.3 and 1.4% for FSH, 3.9 and 3.7% for TT. Serum SHBG levels were determined by chemiluminescence method using an automated hormone analyser Immulite 1000 (DPC, UK). The intra- and inter-assay CV were 6.4 and 8.7% for SHBG. Serum free testosterone was determined by analogue radioimmunoassay method (Diagnostic Systems Laboratories, USA). The normal ranges in our laboratory are 1.4–18.1 IU/l for FSH, 1.5–9.3 IU/l for LH, 8.4–28.7 nmol/l for TT, 39.9–147.5 pmol/l for FT, 13–71 nmol/l for SHBG.

Measurement of serum cytokine and chemokine concentrations

The levels of MIP-1α (Accucyte Human MIP-1α), IFN-γ (Cytelisa, Human IFN-γ), and IL-1β (Cytelisa, Human IL-1β) in sera of patients were measured by using enzyme immunoassay (EIA). All kits were from Cytimmune Sciences Inc. (USA). The range of detection was 0.195–50.0 ng/ml for MIP-1α and 8–500 pg/ml for both IFN-γ and IL-1β.

Statistical analysis

All of the statistical analyses were performed by SPSS 10.0 (SPSS Inc., USA). Descriptive statistics are shown as arithmetic mean ± SD. After the tests of normality, the differences between the groups were investigated with analysis of variance or Kruskal–Wallis test. We used Tukey's *b* or Mann–Whitney *U*-test for multiple comparisons. Correlations between the sex hormones and immunological parameters were investigated by Spearman's ρ-test. $P \leqslant 0.05$ was considered statistically significant (Zar, 1996; Tabachnick and Fidell, 2001).

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Table I. The mean levels and comparisons of parameters in patients (group A and group B) and controls (mean ± SD)

Parameters	Group A	Group B	Controls	Group A versus control		Group B versus control		Group A versus group B	
	(n = 31)	(n = 9)	(n = 20)	z	P	z	P	z	P
Age (years)	17.19 ± 0.40	17.44 ± 0.53	17.25 ± 0.44	0.245	NS	0.358	NS	0.399	NS
BMI (kg/m^2)*	22.48 ± 1.12	22.33 ± 1.00	22.65 ± 1.09		NS		NS		NS
Toxoplasma IgM[a]	3.88 ± 1.14	4.00 ± 1.03	0.53 ± 0.13	5.996	< 0.001	4.301	< 0.001	0.308	NS
Toxoplasma IgG[b]	4.95 ± 0.91	4.50 ± 1.08	0.43 ± 0.14	5.992	< 0.001	4.276	< 0.001	1.022	NS
IFN-γ (pg/ml)*	10.37 ± 1.48	10.01 ± 1.58	3.55 ± 0.85		< 0.001		< 0.001		NS
IL-1β (pg/ml)	13.37 ± 4.46	34.51 ± 9.74	3.53 ± 0.79	5.984	< 0.001	4.249	< 0.001	4.326	< 0.001
MIP-1α (ng/ml)*	11.89 ± 1.35	11.50 ± 1.33	3.82 ± 1.16		< 0.001		< 0.001		NS
FSH (IU/l)	8.21 ± 1.31	0.71 ± 0.11	8.19 ± 1.38	0.222	NS	4.251	< 0.001	4.522	< 0.001
LH (IU/l)	5.59 ± 0.73	0.53 ± 0.07	5.58 ± 0.67	0.251	NS	4.256	< 0.001	4.531	< 0.001
FT (pmol/l)	71.39 ± 10.06	19.16 ± 1.52	69.93 ± 9.61	0.405	NS	4.244	< 0.001	4.518	< 0.001
TT (nmol/l)	17.29 ± 1.38	4.57 ± 0.56	17.11 ± 1.01	0.406	NS	4.248	< 0.001	4.522	< 0.001
SHBG (nmol/l)*	25.40 ± 4.48	28.94 ± 6.44	25.36 ± 5.34		NS		NS		NS

In the beginning of the study, patients with acute toxoplasmosis were divided based on the levels of sex hormones into the following groups: patients who had normal sex hormone levels (n = 31) as group A or patients with low sex hormone levels (n = 9) as group B.
[a]Positive >1; [b]positive >1.
*Analysis of variance with Tukey's b as post-hoc test was used.
BMI = body mass index; SHBG = sex hormone-binding globulin; IFN-γ = interferon-γ; IL-1β = interleukin-1β; MIP-1α = macrophage inflammatory protein-1α; FT = free testosterone; TT = total testosterone; NS = not significant.

Results

Acute toxoplasmosis outbreak was confirmed by the presence of anti-*T. gondii* antibodies by serological tests (ELISA IgG/IgM) and significant IgG avidity results. Initially, all subjects had lymphadenopathy in cervical/submandibular/retroauricular/suboccipital regions, ~1×1.5 cm in size. Four patients in group A and two patients in group B had subfebrile fever.

The mean levels and comparisons of parameters in the patient and control groups are shown in Table I. Age and body mass index did not significantly differ between the groups. Based on serological tests, all patients were seropositive for *T. gondii* antibodies by ELISA IgG/IgM, whereas negative results in both tests for IgM antibodies and IgG avidity virtually ruled out the diagnosis of acute toxoplasmosis in control subjects. Compared with control subjects, patients in both group A and group B had elevated plasma concentrations of IFN-γ, IL-1β and MIP-1α. The mean concentrations of MIP-1α and IFN-γ were similar in group A and group B patients, while IL-1β levels were found to be higher in group B patients than group A. The mean levels of FSH, LH, FT and TT were significantly lower in group B patients than both controls and group A. SHBG levels did not differ significantly between the groups.

The levels of IL-1β correlated significantly in a negative manner with FSH (Figure 1a), LH (Figure 1b), FT (Figure 1c) and TT (Figure 1d) in all patients (n = 40) with acute toxoplasmosis ($\rho = -0.505$, $P = 0.001$; $\rho = -0.534$, $P < 0.001$; $\rho = -0.538$, $P < 0.001$ and $\rho = -0.476$, $P = 0.002$ respectively).

Initially, nine of 40 patients (22.5%) had lower levels of sex hormones than normal. Chief symptom of these patients at presentation was diminished sex drive and erection. After 1 month, sex hormone levels were still low in all patients in group B. In the 3rd month, sex hormone levels reached normal levels in five patients, while four patients still had low sex hormone levels (Figures 2 and 3). In the 6th month, these patients still had low levels (Figure 4). The pituitary secretion of LH and FSH were normal in response to GnRH test at this time (data not shown). Cranial magnetic resonance imaging (MRI) and hypophysis MRI revealed no abnormal change in these patients. We were also unable to identify any factors typically known to impair GnRH secretion transiently in these men, e.g. stress, strenuous exercise, or malnutrition.

In four students with prolonged suppression of sex hormone levels, decreased libido and decreased frequency of shaving were the only complaint so far. Both sexual function and sex hormone concentrations have returned to normal in the 9th month without any treatment (Figure 4).

Discussion

In the current study, we report several observations that further our understanding of the abrupt effect of *T. gondii* infection on human reproductive function. First, we demonstrate for the first time that transient hypogonadotrophic hypogonadism in men is not rare in *Toxoplasma* infection. This observation is in line with previous results of experimental studies in animals (Stahl *et al*., 1985, 1994; Antonios *et al*., 2000). In this context, Stahl et al. demonstrated that Nya:NYLAR female mice undergo acquired hypogonadotrophic hypogonadism secondary to hypothalamic dysfunction within a few weeks after infection with *T. gondii* (Stahl *et al*., 1985, 1994). They also suggested that the edematous changes, particularly within the thalamus and hypothalamus, may have caused malfunctioning of the supra- and intrahypothalamic centres regulating the pulsatility and the release of GnRH. Additionally, in a further experimental study, the integrity of the pituitary–ovarian axis of female mice chronically infected with *T. gondii* was evaluated by administering GnRH to stimulate the release of gonadotrophins from the pituitary, then monitoring the secondary effects on the ovary (Stahl *et al*., 1995). The atrophied ovaries of the infected mice were found to be responsive to single injections of GnRH, thereby confirming the release of

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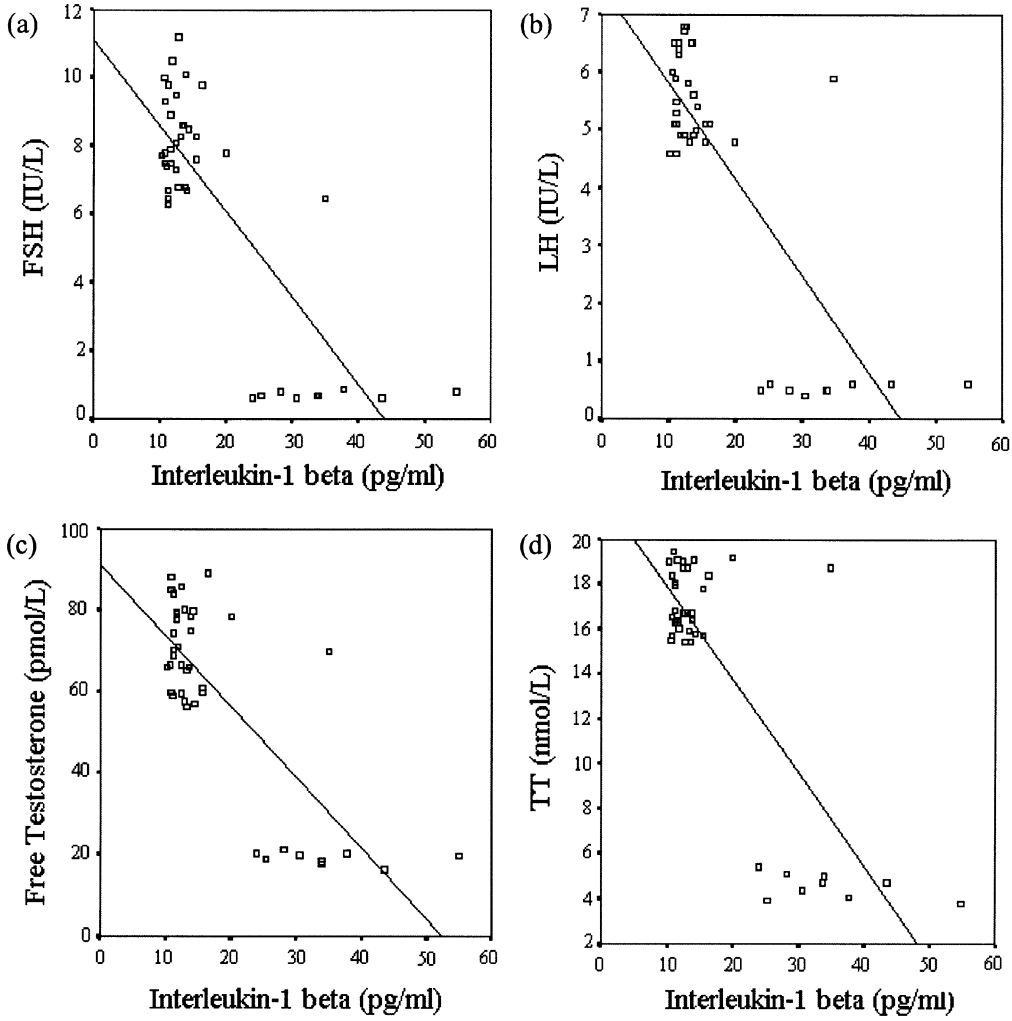


Figure 1. Correlations between interleukin-1β and (**a**) FSH; (**b**) LH; (**c**) free testosterone; (**d**) total testosterone (TT) in all patients with acute toxoplasmosis (n = 40).

endogenous gonadotrophins from the pituitary. The authors proposed that inadequate levels of the readily releasable pool of pituitary gonadotrophins, indicated to result from a hypothalamic inhibition of the pulsatile release of GnRH, are responsible for the weak ovarian responses (Stahl *et al*., 1995). Similar to these experimental studies, GnRH test indicated that the primary defect in the patients with prolonged hypoandrogenaemia was at the level of the hypothalamus rather than the pituitary in the present study. Second, patients with toxoplasmosis had significantly higher levels of IL-1β, IFN-γ and MIP-1α than did the control subjects, a finding that is in accordance with previous reports (Suzuki *et al*., 1988; Subauste and Remington, 1991; Bliss *et al*., 1999). There is an extremely complex interplay between *T. gondii* and cells of the immune system, cascades of cytokines and numerous other less defined factors (Sarciron and Gherardi, 2000; Stahl *et al*., 2002). Classically, infection with *T. gondii* triggers production of proinflammatory cytokines, including IFN-γ and IL-1β (Burke *et al*., 1994; Gazzinelli *et al*., 1994; Alexander and Hunter, 1998; Nguyen *et al*., 2003). Likewise, up-regulated expression of MIP-1α and MIP-1β gene transcripts is induced (Bliss *et al*., 1999). Thus, it seems that *T. gondii* possesses the ability to induce neutrophil proinflammatory cytokine production and that parasite-induced MIP-1α and MIP-1β partly result from autocrine stimulation through TNF-α (Bliss *et al*., 1999). In the current study, however, at the recovery period, the levels of IL-1β, but not MIP-1α and IFN-γ, are still high in patients with hypogonadism. This may indicate the efficiency of immune mechanisms and an induction of IL-1β not linked to parasitic elements but instead to a cytokine network dysregulation. Third, the increased levels of IL-1β in the patients with hypogonadism, together with the correlation between IL-1β and sex hormones, led us to hypothesize a relevant pathophysiological role of IL-1β in the development of transient hypogonadotrophic hypogonadism. Cytokines have a number of endocrine effects influencing the release of anterior pituitary hormones (Jones and Kennedy, 1993; Ray and Melmed, 1997; McCann *et al*., 1998). Moreover, cytokines are known to suppress the hypothalamic–pituitary–gonadal (HPG) axis, directly or indirectly through increased corticotrophin-releasing hormone (CRH) and/or cortisol (Rivier *et al*., 1986). Determining whether or not increased CRH and/or cortisol contribute in part to HPG axis changes in our patients was not an aim of the present study. In this context, acute administra-

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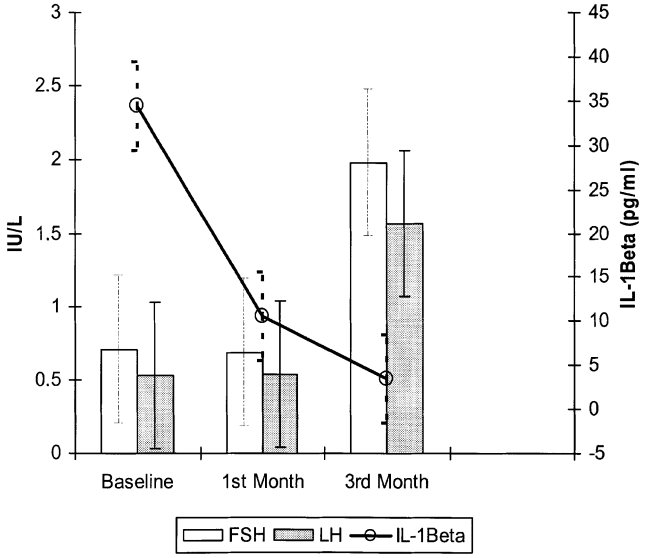


Figure 2. Effect of interleukin-1β on FSH and LH in group B patients (n = 9).

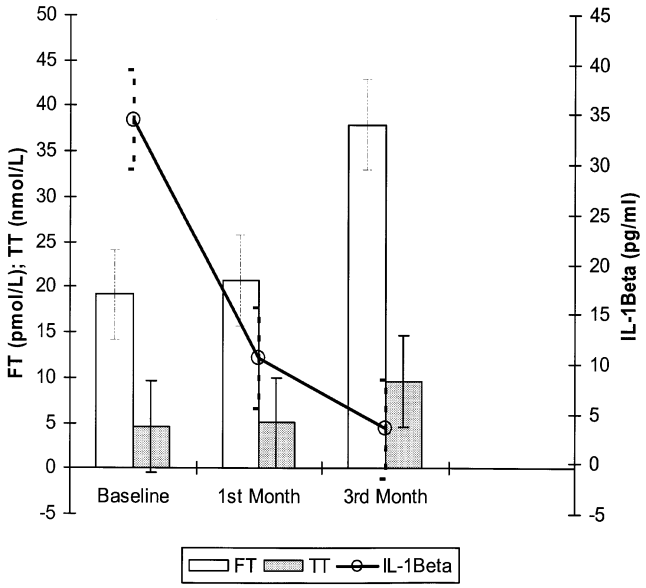


Figure 3. Effect of interleukin-1β on free testosterone (FT) and total testosterone (TT) in group B patients (n = 9).

tion of IL-1β into the lateral ventricle of castrated rats selectively depressed serum LH concentrations (Kang *et al*., 2000). This assumption was also supported by the fact that microinfusion of IL-1β into the lateral ventricle of proestrus rats reduces *in vivo* GnRH release from the median eminence (Rivest and Rivier, 1993). Furthermore, IL-1β injected into a lateral ventricle of 3 week-castrated female rats resulted in the expected decrease in serum levels of LH and FSH, accompanied by a decrease in the number of GnRH receptors (Dondi *et al*., 1998). These results may indicate that the inhibition of gonadotrophin release may result from a decrease in the number of GnRH pituitary receptors either through a direct effect on the pituitary or by modulating the release of GnRH from hypothalamic neurons able to induce a reduction in pituitary GnRH receptors (Dondi *et al*., 1998). In summary, IL-1β-induced modulation of hypothalamic GnRH release, and probably synthesis, is mediated by augmented release of the neurotransmitters, norepinephrine and dopamine from neurons in the brain stem and hypothalamus that are inhibitory to GnRH (Shintani *et al*., 1993; Kalra *et al*., 1998).

Encephalitis is the most important complication of toxoplasmosis in immunosuppressed patients as it causes the most severe damage to the patient (Renold *et al*., 1992; Luft *et al*., 1993). In addition, direct pituitary or hypothalamic destruction by *T. gondii* was reported in such patients (Milligan *et al*., 1984). Interestingly, symptomatic central nervous system toxoplasmosis and the involvement of the pituitary are not rare during primary infection in immunocompetent hosts (Townsend *et al*., 1975; Bach and Armstrong, 1983; Grant and Klein, 1987; Zhang *et al*., 2002). The clinical syndrome of toxoplasmic encephalitis is non-specific and may include both focal and non-focal signs and symptoms of central nervous system dysfunction (Hunter and Remington, 1994). However, our patients had neither symptoms of toxoplasma encephalitis such as headache, disorientation, drowsiness, reflex changes, seizures, altered mental status, visual disturbances, loss of consciousness or hemiparesis nor had MRI finding of any lesion.

Acute illness of any cause has profound and abrupt effects on the HPG axis. First, acute injury primarily leads to an immediate and direct Leydig cell suppression (Van den Berghe *et al*., 1998). Indeed, low serum testosterone concentrations despite elevated LH levels have been documented during the acute stress of surgery or myocardial infarction, whereas FSH and inhibin levels remain normal (Wang *et al*., 1978; Dong *et al*., 1992). Likewise, Spratt *et al*. (1992) suggested that primary hypogonadism occurs in acute illness. Second, hypogonadism in men with critical ilness (Wang *et al*., 1978; Vogel *et al*., 1985; Woolf *et al*., 1985; Semple *et al*., 1987; Christeff *et al*., 1988), surgery (Aono and Hurachi, 1972) or respiratory failure (Semple *et al*., 1981) is attributed to hypogonadotrophism. Furthermore, hypogonadotrophic hypogonadism is usually reversible and presumably has a mechanism involving hypothalamic control of GnRH secretion (Semple *et al*., 1987). Reproductive axis suppression in acute illness is related to disease severity (Dong *et al*., 1992; Spratt *et al*., 1993). In addition to the stress of the illness or injury itself, accompanying factors such as medication, malnutrition, weight loss and fever accentuate the decrease in gonadal function. However, the patients with hypogonadism we studied were not severely ill, and none had any drug known to suppress the HPG axis. Additionally, in the present study, the degree of impairment of reproductive function was not related to the severity of disease based on clinical findings.

HPG dysfunction due to infectious agents such as *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, the causative agents of human African trypanosomiasis also known as sleeping sickness, were reported previously (Hublart *et al*., 1988; Boersma *et al*., 1989; Reincke *et al*., 1998). It is proposed that the dysfunction may be of central origin (Hublart *et al*., 1988; Reincke *et al*., 1998).

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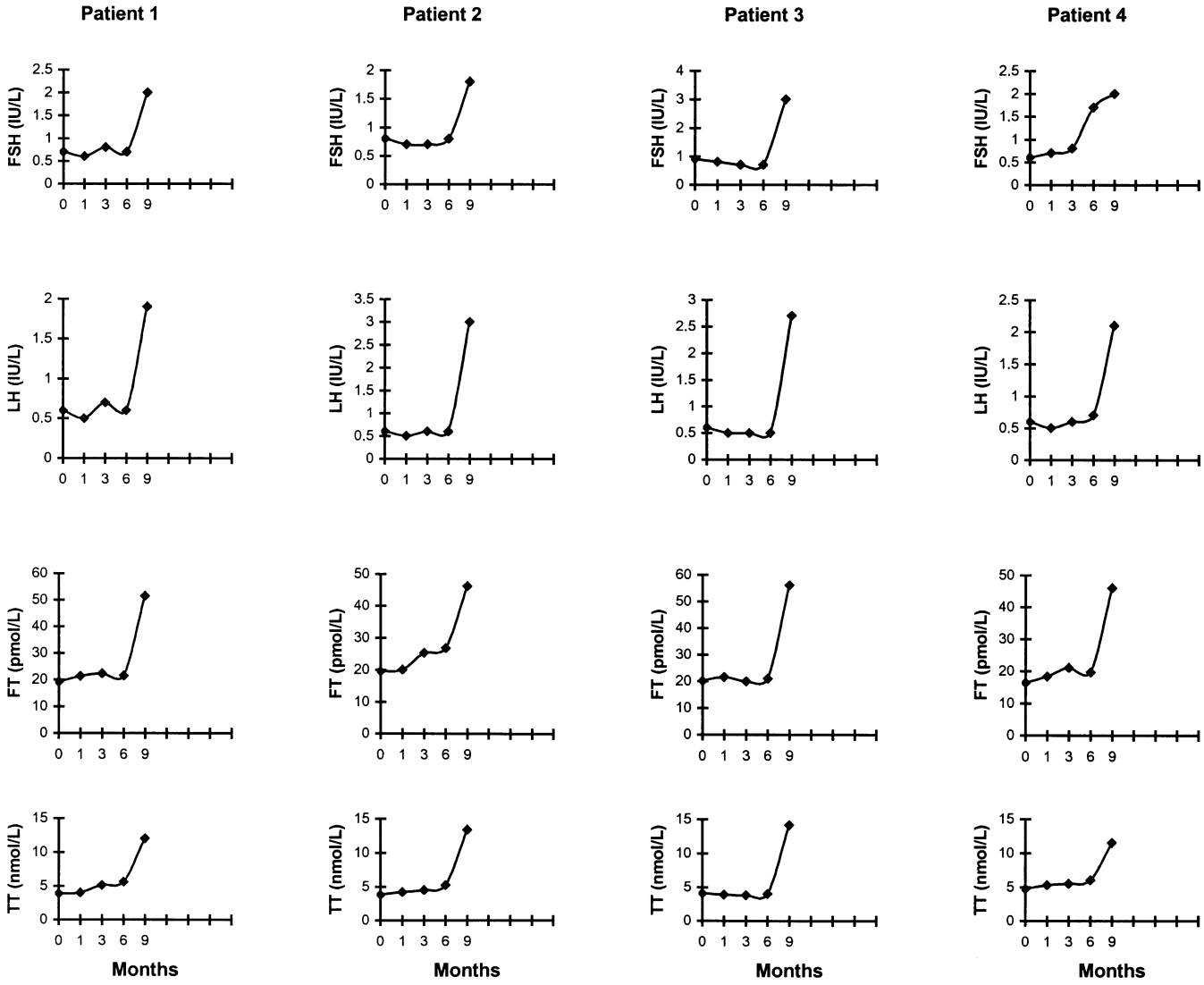


Figure 4. Serum sex hormone levels of patients with prolonged hypoandrogenaemia.

Despite the specific therapy, hypogonadism persisted for years in a substantial portion of patients (Reincke *et al*., 1998). This is only in part reversible after cure and most likely due to direct parasitic infiltration and/or secondary inflammation causing necrosis and/or fibrosis at the pituitary and gonadal levels (Petzke *et al*., 1996). Furthermore, the presence of hypopituitarism correlated with high cytokine concentrations (TNF-α, IL-6) which are involved in the pathogenesis of sleeping sickness-associated endocrine dysfunction (Reincke *et al*., 1998). In contrast to toxoplasmosis, sleeping sickness can rapidly become life-threatening, and patients may have a severe presentation (Lejon *et al*., 2003).

In the current study, hypogonadal patients present with the classic signs and symptoms of androgen deficiency, complaining of decreased libido or decreased frequency of shaving. Theoretically, low testosterone levels cause loss of libido, reduced beard and body hair growth. On the one hand, if the onset of reproductive failure occurs before puberty, sexual maturation will not occur, and the individual will acquire the clinical features termed eunuchoidism, including an increased length of the arms and legs relative to the trunk because of delayed epiphyseal fusion, and underdevelopment of the penis and scrotum, voice, musculature, and secondary sex hair (Oktenli *et al*., 2003). In the current study, however, the patients with hypogonadism had normal spontaneous sexual maturation and no evidence of eunuchoidism. On the other hand, boys presenting with delayed puberty (failure to enter puberty by age 14 years) are frequently hampered by a lack of external signs of virilization as well as short stature (Sedlmeyer and Palmert, 2002). Conversely, our hypogonadal patients are of normal height for age. The previous initiation of shaving in group B patients was also against this diagnosis. Furthermore, sexual functions and sex hormone concentrations have been restored to normal, without the need for any treatment. Therefore, in the light of these findings, it appears that the defect is acquired in our patients. Interestingly, some patients with hypogonadism showed prolonged hypoandrogenaemia. Recent studies have suggested that a variety of parasitic and

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host factors, as well as unrecognized cofactors, may influence disease presentations in toxoplasmosis (Boothroyd and Grigg, 2002; Araujo and Slifer, 2003). Strain virulence, the size of inoculum, the life cycle stage, duration exposure, and the route of infection are important parasitic variables. Host variables include competence of the immune response, integrity of mucosal and epithelial barriers, and age at time of infection. Meanwhile, differences in susceptibility based on genetic background in men need further elucidation. Consequently, cytokine-induced inflammatory reactions and edema in the hypothalamic region seem to be the factors most responsible for GnRH deficiency: central disruption of the pulsatile release of hypothalamic GnRH, leading to inadequate pituitary priming, depletion of gonadotrophin reserves, and perturbation of the release of gonadotrophins from the pituitary. This was followed by gonadal insufficiency and the decline in serum testosterone levels, and by the normal gonadotrophin responses to exogenous GnRH.

In conclusion, acute toxoplasma infection may cause temporary hypogonadotrophic gonadal insufficiency regardless of the course of the disease. It seems likely that the influence of IL-1β on hypothalamic–pituitary function plays an important role in the development of transient hypogonadotrophic hypogonadism. Furthermore, the observations presented here support the previous clinical and experimental data that cytokines, besides their prominent actions on immune functions, can also be implicated in the normal and pathological functioning of the endocrine system. However, at present, the following needs to be further clarified: the other cytokines involved, and their mechanism of action.

References

Alexander J and Hunter CA (1998) Immunoregulation during toxoplasmosis. Chem Immunol 70,81–102.

Antonios SN, Ismail HI and Essa T (2000) Hypothalamic origin of reproductive failure in chronic experimental toxoplasmosis. J Egypt Soc Parasitol 30,593–599.

Aono T and Hurachi K (1972) Influence of major surgical stress on plasma levels of testosterone, luteinizing hormone, and follicle-stimulating hormone in male patients. J Clin Endocrinol Metab 35,535–538.

Araujo FG and Slifer T (2003) Different strains of Toxoplasma gondii induce different cytokine responses in CBA/Ca mice. Infect Immun 71,4171–4174.

Bach MC and Armstrong RM (1983) Acute toxoplasmic encephalitis in a normal adult. Arch Neurol 40,596–597.

Beaman MH, Wong SY and Remington JS (1992) Cytokines, Toxoplasma and intracellular parasitism. Immunol Rev 127,97–117.

Benenson MW, Takafuji ET, Lemon SM, Greenup RL and Sulzer AJ (1982) Oocyst-transmitted toxoplasmosis associated with ingestion of contaminated water. N Engl J Med 307,666–669.

Bliss SK, Marshall AJ, Zhang Y and Denkers EY (1999) Human polymorphonuclear leukocytes produce IL-12, TNF-alpha, and the chemokines macrophage-inflammatory protein-1 alpha and -1 beta in response to Toxoplasma gondii antigens. J Immunol 162,7369–7375.

Boersma A, Noireaus F, Hublart M, Boutignon F, Lemesre JL, Racadot A and Degand P (1989) Gonadotropic axis and Trypanosoma brucei gambiense infection. Ann Soc Belg Med Trop 69,127–135 (Abstract).

Boothroyd JC and Grigg ME (2002) Population biology of Toxoplasma gondii and its relevance to human infection: do different strains cause different disease? Curr Opin Microbiol 5,438–442.

Bowie WR, King AS, Werker DH, Isaac-Renton JL, Bell A, Eng SB and Marion AS (1997) Outbreak of toxoplasmosis associated with municipal drinking water. Lancet 350,173–177.

Burke JM, Roberts CW, Hunter CA, Murray M and Alexander J (1994) Temporal differences in the expression of mRNA for IL-10 and IFN-gamma in the brains and spleens of C57BL/10 mice infected with Toxoplasma gondii. Parasite Immunol 16,305–314.

Christeff N, Benassayag C, Carli-Vielle C, Carli A and Nunez EA (1988) Elevated estrogen and reduced testosterone levels in the serum of male septic shock patients. J Steroid Biochem 29,435–440.

Dondi D, Limonta P, Montagnani Marelli M and Piva F (1998) Mechanism of action of interleukin-1 in modulating gonadotropin secretion. In vivo and in vitro studies. Biol Signals Recept 7,55–60.

Dong Q, Hawker F, McWilliam D, Bangah M, Burger H and Handelsman DJ (1992) Circulating immunoreactive inhibin and testosterone level in men with critical illness. Clin Endocrinol 36,399–404.

Gazzinelli RT, Wysocka M, Hayashi S, Denkers EY, Hieny S, Caspar P, Trinchieri G and Sher A (1994) Parasite-induced IL-12 stimulates early IFN-gamma synthesis and resistance during acute infection with Toxoplasma gondii. J Immunol 153,2533–2543.

Grant SC and Klein C (1987) Toxoplasma gondii encephalitis in an immunocompetent adult: a case report. S Afr Med J 71,585–587.

Hublart M, Lagouche L, Racadot A, Boersma A, Degand P, Noireau F, Lemesre JL and Toudic A (1988) Endocrine function and African trypanosomiasis. Evaluation of 79 cases. Bull Soc Pathol Exot Filiales 81,468–476 (Abstract).

Hunter CA and Remington JS (1994) Immunopathogenesis of toxoplasmic encephalitis. J Infect Dis 170,1057–1067.

Jones TH and Kennedy RL (1993) Cytokines and hypothalamic–pituitary function. Cytokine 5, 531–538.

Kalra PS, Edwards TG, Xu B, Jain M and Kalra SP (1998) The anti-gonadotropic effects of cytokines: the role of neuropeptides. Domest Anim Endocrinol 15,321–332.

Kang SS, Kim SR, Leonhardt S, Jarry H, Wuttke W and Kim K (2000) Effect of interleukin-1β on gonadropin-releasing hormone (GnRH) and GnRH receptor gene expression in castrated male rats. J Neuroendocrinol 12,421–429.

Kean BH, Kimbal AC and Christenson WN (1969) An epidemic of acute toxoplasmosis. J Am Med Assoc 208,1002–1004.

Krick JA and Remington JS (1978) Toxoplasmosis in the adult—an overview. N Engl J Med 298,550–553.

Lejon V, Reiber H, Legros D, Dje N, Magnus E, Wouters I, Sindic CJM and Büscher P (2003) Intrathecal immune response pattern for improved diagnosis of central nervous system involvement in trypanosomiasis. J Infect Dis 187,1475–1483.

Luft BJ, Hafner R, Korzun AH, Leport C, Antoniskis D, Bosler EM, Bourland DD and Uttamchandani R, Fuhrer J, Jacobson J et al (1993) Toxoplasmic encephalitis in patients with the Acquired Immunodefiency Syndrome. N Engl J Med 329,995–1000.

McCann SM, Kimura M, Walezewska A, Karanth S, Rettori V and Yu WH (1998) Hypothalamic control of gonadotropin secretion by LHRH, FSHRF, NO, cytokines, and leptin. Domest Anim Endocrinol 15,333–344.

Milligan SA, Katz MS, Craven PC, Strandberg DA, Russel IJ and Becker RA (1984) Toxoplasmosis presenting as panhypopituitarism in a patient with the acquired immune deficiency syndrome. Am J Med 77,760–764.

Nguyen TD, Bigaignon G, Markine-Goriaynoff D, Heremans H, Nguyen TN, Warnier G, Delmee M, Warny M, Wolf SF, Uyttenhove C et al (2003) Virulent Toxoplasma gondii strain RH promotes T-cell-independent overproduction of proinflammatory cytokines IL-12 and γ-interferon. J Med Microbiol 52,869–876.

Oktenli C, Koc B, Alis M, Tasar M and Doganci L (2001) Unilateral renal agenesis and hypogonadotropic hypogonadism: an interesting coincidence. Clin Nephrol 55,340–342

Oktenli C, Yesilova Z, Ozata M, Yaman H, Tuzun A, Dundar S, Sanisoglu SY, Musabak U, Erbil MK and Dagalp K (2003) Gonadotropin treatment increases homocysteine levels in idiopathic hypogonadotropic hypogonadism: an indirect effect mediated by changes in body composition. J Endocrinol 179,35–39.

Pal MN, Bhatia VN, Kotwani BG and Agarwal DS (1975) Toxoplasmosis in relation to reproductive disorders. Ind J Med Res 63,11–16 (Abstract).

Petzke F, Heppner C, Mbulamberi D, Winkelmann W, Chrousos GP, Allolio B and Reincke M (1996) Hypogonadism in Rhodesian sleeping sickness: evidence for acute and chronic dysfunction of the hypothalamic–pituitary–gonadal axis. Fertil Steril 65,68–75.

Ray D and Melmed S (1997) Pituitary cytokine and growth factor expression and action. Endocr Rev 18,206–228.

Reincke M, Arlt W, Heppner C, Petzke F, Chrousos GP and Allolio B (1998) Neuroendocrine dysfunction in African trypanosomiasis. The role of cytokines. Ann NY Acad Sci 840,809–821.

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Renold C, Sugar A, Chave JP, Perrin L, Delavelle J, Pizzolato G, Burkhard P, Gabriel V and Hirschel B (1992) Toxoplasma encephalitis in patients with the acquired immunodeficiency syndrome. Medicine 71,224–239.

Rivier C, Rivier J and Vale W (1986) Stress-induced inhibition of reproductive functions: role of endogenous corticotropin-releasing factor. Science 231,607–609.

Rivest S and Rivier C (1993) Interleukin-1 inhibits the endogenous expression of the early gene c-fos located within the nucleus of LH-RH neurons and interferes with hypothalamic LH-RH release during proestrus in the rat. Brain Res 613,132–142.

Sarciron ME and Gherardi A (2000) Cytokines involved in Toxoplasmic encephalitis. Scand J Immunol 52,534–543.

Sedlmeyer I and Palmert MR (2002) Delayed puberty: analysis of a large case series from an academic center. J Clin Endocrinol Metab 87,1613–1620.

Semple PD, Beastall GH, Watson WS and Hume R (1981) Hypothalamic–pituitary dysfunction in respiratory hypoxia. Thorax 36,605–609.

Semple CG, Robertson WR, Mitchell R, Gordon D, Gray CE, Beastall GH and Reid WH (1987) Mechanisms leading to hypogonadism in men with burns injuries. Br Med J 295,403–407.

Setian N, Andrade RS, Kuperman H, Manna TD, Dichtchekenian V and Damiani D (2002) Precocious puberty: an endocrine manifestation in congenital toxoplasmosis. J Pediatr Endocrinol Metab 15,1487–1490.

Shintani F, Kanba S, Nakaki T, Nibuya M, Kinoshita N, Suzuki E, Yagi G, Kato R and Asai M (1993) IL-1β augments release of norepineprine, dopamine and serotonin in the rat anterior hypothalamus. J Neurosci 13,3574–3581.

Spratt DI, Bigos ST, Beitins I, Cox P, Longcope C and Orav J (1992) Both hyper- and hypogonadotropic hypogonadism occur transiently in acute illness: bio- and immunoactive gonadotropins. J Clin Endocrinol Metab 75,1562–1570.

Spratt DI, Cox P, Orav J, Moloney J and Bigos T (1993) Reproductive axis suppression in acute illness is related to disease severity. J Clin Endocrinol Metab 76,1548–1554.

Stahl W, Dias JA and Turek G (1985) Hypothalamic–adenohypophyseal origin of reproductive failure in mice following chronic infection with Toxoplasma gondii. Proc Soc Exp Biol Med 178,246–249.

Stahl W, Kaneda Y and Noguchi T (1994) Reproductive failure in mice chronically infected with Toxoplasma gondii. Parasitol Res 80,22–28.

Stahl W, Dias JA, Turek G and Kaneda Y (1995) Etiology of ovarian dysfunction in chronic murine toxoplasmosis. Parasitol Res 81,114–120.

Stahl W, Sekiguchi M and Kaneda Y (2002) Cerebral anomalies in congenital murine toxoplasmosis. Parasitol Res 88,507–512.

Subauste CS and Remington JS (1991) Role of gamma interferon in Toxoplasma gondii infection. Eur J Clin Microbial Infect Dis 10,58–67.

Suzuki Y (2002) Host resistance in the brain against Toxoplasma gondii. J Infect Dis 185,S58–S65.

Suzuki Y, Orellana MA, Schreiber RD and Remington JS (1988) Interferon-gamma: the major mediator of resistance against Toxoplasma gondii. Science 240,516–518.

Tabachnick BG and Fidell LS (2001) Using Multivariate Statistics. 4th edn, Allyn and Bacon, MA, USA.

Teutsch SM, Juranek DD, Sulzer A, Dubey JP and Sikes RK (1979) Epidemic toxoplasmosis associated with infected cats. N Engl J Med 300,695–699.

Townsend JJ, Wolinsky JS, Baringer JR and Johnson PC (1975) Acquired toxoplasmosis: a neglected cause of treatable nervous system disease. Arch Neurol 32,335–343.

VandenBerghe G, de Zegher F and Bouillon R (1998) Acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab 83,1827–1834.

Vogel AV, Peake GT and Rada RT (1985) Pituitary–testicular axis dysfunction in burned men. J Clin Endocrinol Metab 60,658–665.

Wang C, Chan V and Yeung RTT (1978) Effect of surgical stress on pituitary–testicular function. Clin Endocrinol (Oxf) 9,255–266.

Woolf PD, Hamill RW, McDonald JV, Lee LA and Kelly M (1985) Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab 60,444–450.

Zar JH (1996) Biostatistical Analysis. Prentice Hall, NJ, USA.

Zhang X, Li Q, Hu P, Cheng H and Huang G (2002) Two case reports of pituitary adenoma associated with Toxoplasma gondii infection. J Clin Pathol 55, 965–966.

Zighelboim I, Maekelt GA, Teppa P, Perera JR, Garran de Teppa D and Maneiro P (1968) Reproductive wastage and toxoplasma antibodies. Am J Obstet Gynecol 101, 839–843 (Abstract).

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