CLINICAL CASE SEMINAR

Adrenal and Gonadal Hormone Variations during a Febrile Attack in a Woman with Tumor Necrosis Factor Receptor-Associated Periodic Syndrome

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Context: TNF-receptor-associated periodic syndrome (TRAPS) is a hereditary fever syndrome that results from mutations in the TNF-receptor superfamily 1A gene (TNFRSF1A). It is characterized by periodic fever, arthralgia, abdominal pain, myalgia, headache, and skin lesions.

Objective: Because adrenal and gonadal hormone cascades are modulated by TNF, this study aimed to investigate specific hormones and enzyme steps during an attack phase in a woman with TRAPS.

Design: Morning blood samples were taken from a 38-yr-old woman before, during, and after the febrile episode in the late luteal, menstrual, and early follicular phase of the menstrual cycle, respectively.

Results: Serum cortisol levels were markedly increased throughout the entire observation period and demonstrated a dip during the attack phase. In contrast, serum levels of dehydroepiandrosterone and 17-hydroxyprogesterone demonstrated a sharp rise during the febrile episode. Dehydroepiandrosterone in relation to androstenedione or cortisol was increased. Indicative of aromatase activation, estrone and 17β-estradiol demonstrated a marked increase during the attack phase.

Conclusion: This study suggests that some important steroid hormone-conversion steps are activated (aromatase) and inhibited (second step of the P450c17 and the 3β-hydroxysteroid dehydrogenase) during the inflammatory attack phase in a TRAPS patient. These changes of enzyme pathways are typical on the basis of increased TNF signaling. (J Clin Endocrinol Metab 90: 5884–5887, 2005)

THE HEREDITARY TNF-receptor-associated periodic syndrome (TRAPS) is a multisystemic chronic inflammatory disorder with relapsing nature that is characterized by periodic fever, arthralgia, abdominal pain, myalgia, headache, and skin lesions (1). A portion of these patients develop systemic amyloidosis with nephropathy, which is potentially life threatening. TRAPS is the second most common inherited periodic fever syndrome, after familial Mediterranean fever (2). This disease entity is related to point mutations in the TNF-receptor superfamily 1A gene (TNFRSF1A). Many pathogenetic TNFRSF1A mutations have now been identified (3).

Impaired shedding of TNFRSF1A ectodomain upon cellular activation with reduced serum concentrations of soluble TNFRSF1A has been proposed as the underlying mechanism of the hyperinflammatory response in TRAPS (1). Altered cleavage of TNFRSF1A is possibly related to stronger TNF signaling and an increase of downstream proinflammatory cascades (2).

Because TNF and other cytokines are able to modulate different enzymes of steroid hormone cascades (Fig. 1, enzymes 3, 5, and 6) (4–8), altered TNF signaling in TRAPS patients may result in subsequent hormonal changes during febrile episodes. In patients with rheumatoid arthritis (RA), we have recently demonstrated that anti-TNF antibody therapy improves adrenal androgen secretion due, most probably, to increased conversion of 17-hydroxyprogesterone to androstenedione (ASD) (Fig. 1, enzyme 3) (9). This study demonstrated that TNF probably inhibits an important enzyme step (9). In this present study, the possible TNF-modulated changes of steroidogenesis were investigated in a woman with TRAPS (10). We studied a panel of important adrenal and gonadal hormones and their molar ratios during the febrile attack.

Subjects and Methods

Subject and blood samples

In this study, we included a 38-yr-old female patient with a known mutation in the TNFRSF1A gene [mutation: I199N (10)] after obtaining written consent for further evaluation of blood samples. We focused on this single patient because no other female patients with the same mutation and a similar menstrual cycle-dependent course of TRAPS are known. Since the age of 19, this woman has suffered from recurrent
Fig. 1. Influence of TNF on steroid hormone cascades. TNF inhibits the second step of the P450c17 (enzyme 3). In contrast, TNF stimulates the aromatase complex (enzyme 6) and the 17β-hydroxysteroid dehydrogenase (enzyme 5). Hormones in blue and large font increase relative to precursors during acute inflammatory episodes. Enzymes: 1, 3β-hydroxysteroid dehydrogenase; 2, P450c17 first step (17-hydroxylase); 3, P450c17 sec step (17,20-lyase); 4, the mixed reaction of the DHEA sulfatase and sulfotransferase; 5, 17β-hydroxysteroid dehydrogenase; 6, aromatase complex; 7, P450c21; 8, P450c11. DHEAS, DHEA sulfate; E1, estrone; E2, 17β-estradiol.

episodes of febrile attacks (up to 40 C) with arthralgia (particularly in the hip, knees, wrist, shoulder, and spine), morning stiffness in finger joints, myalgia in both shoulders, and intermittent diarrhea. Febrile attacks were often accompanied by pharyngitis and vaginal mycosis demanding antibiotic and antifungal therapy, respectively. Between attacks, symptoms remitted completely. Remarkably, during pregnancy and breast feeding, attacks vanished. Intermitent therapy with nonsteroidal antiinflammatory drugs or glucocorticoids improved attack symptoms. At the time of investigation, glucocorticoids had not been used for more than 6 months.

In the past, this particular woman showed febrile episodes during different phases of the menstrual cycle. Coincidentally, the present attack occurred during the time of menstruation. This allowed us to study the unaffected investigation of hormonal changes because, during this period, sex hormone levels are typically low. The menstrual cycle had a normal rhythm (28 ± 3 d), owing to the long-term use of the contraceptive pill (>5 yr; see below). The menstrual cycle was normal in terms of uterine contractions, pain, bleeding volume, bleeding patterns, and extrauterine symptoms (no dysmenorrhea). The patient was administered a contraceptive pill [drospirenone (3 mg) and ethinylestradiol (0.03 mg)]. The contraceptive pill was given because the patient did not want to become pregnant after two successful pregnancies. According to the normal therapy regimen, the contraceptive pill was discontinued 3 d before the attack and continued 1 d after the attack. Under normal therapy conditions, discontinuation of the contraceptive pill does not lead to observed hormonal changes because during long-term contraceptive therapy, hormone profiles are largely suppressed. We drew blood before, during, and after discontinuation of the contraceptive pill to ensure that the pill did not interfere with measurements. Blood was always drawn at 0800 h in the late luteal phase of the menstrual cycle (d 22), during the attack phase (period of menstruation during 4 d), and in the early follicular phase (d 5 and 8). We obtained written consent from the patient to carry out this particular study.

During the attack, the patient was administered amoxicillin to treat pharyngitis. The available literature does not indicate that amoxicillin interferes with hormone secretion or serum levels of hormones. This was particularly true for those hormones that were altered during the attack (11, 12).

For comparison, 11 age-matched premenopausal healthy women were included (mean age, 36 ± 2.4 yr), and health status was verified by means of a 33-item questionnaire (13). Blood of these healthy women was drawn between 0800 and 1000 h in the early follicular phase of the menstrual cycle (results given as broken line in Fig. 2). In addition, we investigated serum hormone levels of two healthy women (ages 36 and 38 yr) during the menstrual bleeding (d 1 and 3; open symbol in Fig. 2). The study was approved by the Ethics Committee of the University of Regensburg.

Laboratory parameters

Several adrenal hormones were considered to detect major adrenal pathways of steroidogenesis (Fig. 1). We used RIAs for the quantitative determination of serum levels of cortisol (Coulter Immunotech, Mar-seilles, France; detection limit, 10 nmol/liter). Serum levels of 17-hydroxyprogesterone (IBL, Hamburg, Germany; detection limit, 0.3 nmol/liter), dehydroepiandrosterone (DHEA) (Diagnostic Systems Laboratory, Webster, TX; detection limit, 0.13 nmol/liter), ASD (IBL, Hamburg, Germany; detection limit, 0.3 nmol/liter), and DHEA sulfate (IBL, Hamburg, Germany; detection limit, 130 nmol/liter) were measured by means of immunometric enzyme immunoassays. Serum levels of IL-6 and TNF (high sensitivity; Quantikine, R&D Systems, Minneapolis, MN; detection limit, 0.2 pg/ml) were measured using the same technique. Furthermore, we measured estrone (IBL, Hamburg, Germany; detection limit, 0.037 nmol/liter) and 17β-estradiol (IBL, Hamburg, Germany; detection limit, 0.017 nmol/liter) by ELISA. Intraassay and interassay coefficients of variation for all above-mentioned tests were less than 10%.

Results

Throughout the entire observation period, serum levels of IL-6 and TNF did not change significantly (TRAPS, range of IL-6, 1.2–3.2 pg/ml; TNF, 0.6–1.0 pg/ml), and serum levels of these cytokines were not significantly different from normal subjects (range of IL-6, 0.9–2.2 pg/ml; TNF, 0.9–3.2 pg/ml). No peaks or dips were observed during the febrile attack (data not shown). During the observation period, serum cortisol levels were markedly higher in the TRAPS patient compared with healthy women, but no marked change was observed during the febrile attack (Fig. 2A; 11 healthy women in the early follicular phase, broken line; two healthy women during menstrual bleeding, open symbols). In contrast, serum DHEA and serum 17-hydroxyprogesterone peaked in the attack phase (Fig. 2, B and C), whereas ASD did not markedly change (Fig. 2D). During the attack, serum DHEA was higher compared with controls (Fig. 2B; 11 healthy women in the early follicular phase, broken line; two healthy women during menstrual bleeding, open symbols), but serum ASD was similar (Fig. 2D; 11 healthy women in the early follicular phase, broken line; two healthy women during menstrual bleeding, open symbols). The relative increase of cortisol in relation to 17-hydroxyprogesterone is demonstrated as the molar ratio during the attack phase (Fig. 2E). The ratio of serum cortisol to serum DHEA dipped during the attack phase, which indicates that DHEA secretion is enhanced relative to cortisol (Fig. 2F). This relative predominance of DHEA is also reflected in the obvious peak of the molar ratio of serum DHEA to serum ASD (Fig. 2G), which was not observed in healthy women (Fig. 2G; 11 healthy women in...
In our TRAPS patient, serum ASD dipped relative to the precursor 17-hydroxyprogesterone (Fig. 2H). This is indicative of P450c17 inhibition in the attack phase. This was not observed in healthy women (Fig. 2H; 11 healthy women in the early follicular phase, broken line; two healthy women during menstrual bleeding, open symbols). ASD is an important precursor of estrogens, and aromatization of this steroid hormone is stimulated by TNF (Fig. 1). Both estrone and 17β-estradiol peaked in the attack phase (Fig. 2I and J), which was not observed in healthy women (Fig. 2I and J; 11 healthy women in the early follicular phase, broken line; two healthy women during menstrual bleeding, open symbols). Furthermore, 17β-estradiol peaked relative to estrone (Fig. 2K), which indicates an increased activity of the 17β-hydroxysteroid dehydrogenase (Fig. 1). The overall increase of aromatization of ASD is reflected in a relative increase of 17β-estradiol in relation to ASD (Fig. 2L), which was not observed in healthy women (Fig. 2L; 11 healthy women in the early follicular phase, broken line; two healthy women during menstrual bleeding, open symbols).

Discussion

This study on a female patient with TRAPS demonstrates hormonal changes that are typical for an increased signaling through the TNF-signaling pathway. We observed an increase of DHEA and 17β-estradiol relative to other hormones. This indicates that, in particular, these two steroid hormones are increased during an acute inflammatory attack. It is interesting that IL-6 and TNF did not markedly change during the febrile period, which demonstrates that the attack phase is not accompanied by a strong systemic proinflammatory response. Most probably, only subtle changes of local TNF-signaling pathways may cause the observed hormonal changes. This can happen locally in the adrenal and gonadal glands because TNF is present in the adrenal cortex of the normal adrenal gland (14, 15) and in the ovary (16).

TNF has been demonstrated to inhibit or stimulate important steroid hormone conversion steps in different cell types in vitro (Fig. 1, enzymes 3, 5, and 6) (4–8). It was demonstrated that TNF was associated with similar steroid alterations in acute inflammatory episodes in patients undergoing cardiovascular surgery (17). Similarly, patients
with early RA demonstrated an increase of DHEA (18), which is, however, followed by strong reduction of this hormone and the sulfated form (DHEA sulfate) in the chronic phase of the disease. Anti-TNF therapy in patients with RA is accompanied by an increase of the important adrenal androgen ASD relative to the precursor 17-hydroxyprogesterone (9), which indicates that TNF seems to inhibit the second step of the P450c17 (Fig. 1). In our TRAPS patient, we observed an inhibition of this particular enzyme step (Fig. 2H).

Estrogens are typically increased in RA synovial fluid, which was thought to depend on the influence of TNF (19, 20). In the TRAPS patient, increased activity of the aromatase and 17β-hydroxysteroid dehydrogenase seems to be obvious in the attack phase. Because TNF can stimulate the aromatase complex (6, 21–23) and the 17β-hydroxysteroid dehydrogenase (5), these findings may demonstrate an increased signaling through the TNF-receptor pathway, leading to observed hormonal changes.

In conclusion, TRAPS is an interesting disease permitting investigation of a possible influence of the TNF-signaling pathway on hormonal cascades in vivo in humans. In our TRAPS patient, acute hormonal changes in the febrile attack phase indicate that TNF may play an important role. Whether or not these hormonal changes influence symptoms during the attack phase remains to be established.

Acknowledgments

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References


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