The Hypothalamus-Pituitary-Ovary and Hypothalamus-Pituitary-Thyroid Axes in Spinal Cord–Injured Women

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Sixteen women with spinal cord injury (SCI) underwent studies of the hypothalamus-pituitary-ovary (HPO) and hypothalamus-pituitary-thyroid (HPT) axes with luteinizing hormone (LH) releasing hormone (LHRH) and thyrotropin (TSH) releasing hormone (TRH) stimulation tests during the early follicular phase. The mean interval from injury to participation in this study was 7.5 years (range, 1.5 to 13.1). All subjects were menstruating regularly. Five (35.7%) SCI subjects who were menstruating before injury had postinjury amenorrhea for 1 to 12 months, and the other nine (64.3%) SCI subjects had no interruption of menstruation after injury. Two SCI subjects whose injury occurred in preadolescence proceeded to menarche without any delay. The amount of menstrual flow was noted to be reduced in nine (64.3%) SCI subjects. Two and three SCI subjects had elevated follicle-stimulating hormone (FSH) and prolactin (PRL) levels, respectively. LH responses to LHRH were significantly higher in the SCI group ($P < .001$). Ten (62.6%) SCI subjects had enhanced LH responses to LHRH. The mean TSH, PRL, and FSH responses to TRH and LHRH of the SCI group were not significantly different from those of age-matched controls. However, five (31.2%), four (25.0%), and five (31.2%) SCI subjects had enhanced TSH, PRL, and FSH responses to TRH and LHRH, respectively. Six (37.5%) SCI subjects had a delayed FSH response to LHRH. In total, 13 (81.2%) SCI subjects had at least one axis abnormality. These findings are consistent with the hypothesis that changes of central neurotransmitters may occur after SCI.

THE EFFECT OF spinal cord injury (SCI) on sexual function has been extensively studied in male patients.[1-3] However, few studies have examined female sexual dysfunction after such injury, and most of them have focused primarily on menstruation and pregnancy.[4-9] There are even less hormonal data regarding the hypothalamus-pituitary-ovary (HPO) and hypothalamus-pituitary-thyroid (HPT) axes of SCI females.

Subnormal follicle-stimulating hormone (FSH) levels and a poor estrogenic effect on vaginal epithelium were reported in a group of women with SCI.[6] Previous studies had reported hyperprolactinemia, galactorrhea, and amenorrhea in women with SCI.[10-11] Hyperprolactinemia was also reported in a high percentage of SCI males.[12,13] Elevated gonadotropin responses to luteinizing hormone (LH) releasing hormone (LHRH) stimulation were noted in male SCI patients.[14] It was suggested that hormonal changes in SCI males are due to alterations in central neurotransmitters after SCI. In this study, we examined the menstruation history and HPO and HPT axes in a group of women with complete SCI to test this hypothesis.

SUBJECTS AND METHODS

Fully developed female SCI patients who met the following conditions were recruited for the study. Traumatic SCI occurred more than 6 months before the study, and the current medical condition was stable, without pressure sores, pneumonia, renal failure, or other febrile diseases. No traumatic brain injury or respiratory failure had been associated with the SCI, and there was no prior history of endocrine disorders. Several patients were prescribed magnesium oxide both before and during the study period. Low-dose baclofen (5 mg three times daily) was used by one paraplegic subject. All subjects had normal blood chemistry results including fasting blood glucose, hemoglobin A_{1c}, liver enzymes, serum total protein, and albumin (>3.5 g/dL); anemia was not present (hemoglobin > 12 g/dL). Subjects with a urinary tract infection were treated with antibiotics before each blood sampling for endocrine studies. The age of the subjects varied from 18.9 to 43.9 years, with a mean of 32.7. The interval between injury and the time of study varied from 1.5 to 13.1 years, with a mean of 7.5. The level of injury varied from C6 to L1, and all lesions were complete. Two patients had cervical, 13 thoracic, and one lumbar injury; two were quadriplegic and 14 paraplegic. Two subjects were injured before menarche, with the onset of menarche occurring at 12 and 13 years, and presently are menstruating regularly. Four subjects were married, and the rest were single. One (case no. 9) had a normal delivery 15 years after SCI. Menstrual histories after SCI were elicited from the subjects retrospectively.

Fifteen normally menstruating age-matched females were recruited as controls. They ranged in age from 20.1 to 43.0 years, with a mean of 32.5. They were taking no medications and did not smoke tobacco or drink alcohol.

Endocrinologic Studies

All subjects, including normal controls, were studied in the early follicular phase, ie, 1 to 3 days after the first day of menstruation. The study was performed between 8 and 9 AM after an overnight fast. After taking two basal blood samples (15 minutes apart), LHRH 100 μg and thyrotropine (TSH)-releasing hormone (TRH) 400 μg were administered by intravenous (IV) bolus. To avoid mixing, 0.5 mL normal saline was injected after each releasing hormone was administered. Subjects remained supine throughout, and blood was sampled for FSH, LH, TSH, and prolactin (PRL) at −15, 0, 20, 40, 60, 90, and 120 minutes after injection. In addition, 2 mL serum from three basal samples taken on consecutive days were pooled to obtain the basal hormone levels listed in Table 1.

Radioimmunoassay

All of the hormones were assayed by commercial radioimmunoassay (RIA) kits: thyroxine (T_4), 3′,3,5-triiodothyronine (T_3), TSH, FSH, LH, PRL, and cortisol by the Amersham (Buckinghamshire, England) RIA kit; corticotropin (ACTH) by the Nichols (San Juan

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Submitted February 9, 1995; accepted December 4, 1995.

Supported by Grant No. NSC83-0412-B002-201 from the National Science Council, Republic of China.

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0026-0495/96/4506-0009$03.00/0

Table 1. Baseline Serum Hormone Levels in Women With SCI

	T_3 (nmol/L)	T_4 (nmol/L)	TSH (mU/L)	GH (μg/L)	FSH (IU/L)	LH (IU/L)	PRL (pmol/L)	Cortisol (μmol/L)	Estradiol (nmol/L)
SCI subjects (n = 16)	1.51 ± 0.23	102 ± 13	1.68 ± 0.73	2.16 ± 2.22	10.9 ± 9.8	4.8 ± 2.7*	556 ± 344	0.34 ± 0.11	0.32 ± 0.05*
Controls (n = 15)	1.54 ± 0.31	87 ± 12	1.45 ± 0.65	1.75 ± 1.78	11.4 ± 2.4	6.8 ± 2.5	502 ± 233	0.29 ± 0.08	0.28 ± 0.03
Reference value	1.16-3.39	58-161	0.45-4.5	<5	6-15	2-18	90-850	0.14-0.70	0.07-0.37

NOTE. Values are means ± SD and ranges.

*P < .05, SCI v controls by Student's t test, which does not reach statistical significance with Bonferroni correction (P must be <.05/9 = .0055 to be significant).

Capistrano, CA) high-sensitivity ACTH RIA kit; growth hormone (GH) by the Nichols high-sensitivity GH RIA kit; and estradiol by the Biodata (Allentown, PA) RIA kit. All these commercial kits had been used previously in our laboratory with interassay and intraassay variations of less than 10%. All basal and stimulated hormone measurements were performed in the same assay.

Statistical Analysis

The results of baseline hormone levels are expressed as the mean ± SD (Table 1), and LH responses to LHRH are expressed as the mean ± SE (Fig 1).

Baseline hormone levels of subjects with SCI and normal controls were compared by Student's t test with Bonferroni correction. TSH, PRL, FSH, and LH responses to TRH and LHRH of SCI subjects and normal controls were first compared by repeated-measures ANOVA with post hoc pairwise comparison (Scheffe's test). The nonparametric Mann-Whitney test was also used to compare the LH response to LHRH of SCI subjects and normal controls at various time points with Bonferroni correction. Both approaches had similar results. The areas under the curve of hypophyseal hormone response to LHRH and TRH were also compared with the nonparametric Mann-Whitney test. Linear regression was used to analyze the correlation between the peak response or the area under the curve of the LH response to LHRH with serum estradiol level. Statistical analysis was performed using the computer statistical package SPSS/4.0 (SPSS, Chicago, IL) and SAS/6.04 (SAS Institute Cary, NC)

RESULTS

Nine (64.3%) of 14 SCI subjects who menstruated before injury had no interruption of the menstruation cycles. The other five SCI subjects were amenorrheic for 1 month to 1 year after injury. Eleven (78.5%) SCI subjects noted no change in cycle interval, whereas three noted a shortening in cycle interval. Nine (64.3%) SCI subjects noted a decrease of menstrual flow, and five noted no change of flow.

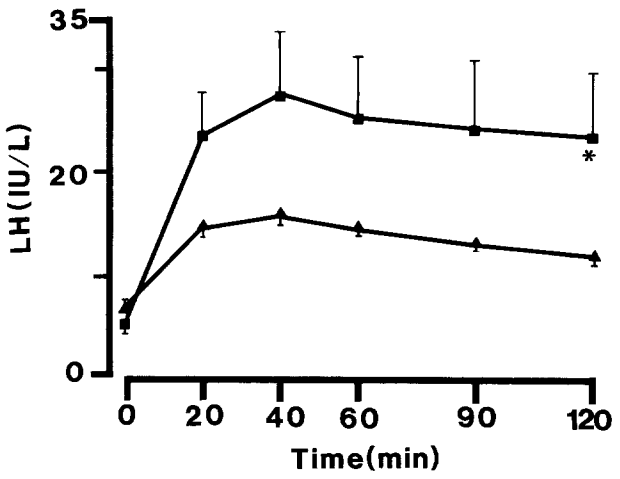

Fig 1. LH responses (mean ± SE) to LHRH 100 μg IV in 16 SCI females (■) and 15 age-matched normal controls (▲). *P < .008 v normal controls.

The mean basal serum hormone levels of SCI subjects and normal controls are shown in Table 1. All subjects had normal serum T_4, T_3, TSH, cortisol, GH, LH, and estradiol levels. The serum LH level of SCI subjects was lower than that of normal controls (4.8 ± 2.7 v 6.8 ± 2.5 IU/L, P = .042 by Student's t test, which does not reach statistical significance after Bonferroni correction). The serum estradiol level of SCI subjects was higher than that of normal controls (0.32 ± 0.05 v 0.28 ± 0.03 nmol/L, P = .045 by Student's t test, which does not reach statistical significance after Bonferroni correction). Other basal serum hormone levels were not significantly different between the SCI group and normal controls. There were two (cases no. 11 and 15) SCI subjects who had elevated FSH levels (43.7 and 20.8 IU/L, respectively). There were three (cases no. 1, 2, and 15) SCI subjects with T7-L1 injuries who had elevated PRL levels (932, 1,456, and 864 pmol/L, respectively). The body mass index (BMI) of SCI subjects was not significantly different from that of normal controls (19.1 ± 2.0 v 19.9 ± 1.5 kg/m^2).

LH responses to LHRH stimulation are shown in Fig 1. LH responses of SCI subjects were significantly higher than those of normal controls (P < .001). Ten (62.6%) SCI subjects had enhanced LH responses to LHRH (Fig 2). The area under the curve of LH responses to LHRH for SCI subjects is significantly higher than that for normal controls (2,759 ± 1,548 v 1,578 ± 246 IU · min/L (mean ± SD, P < .05). In contrast, FSH responses to LHRH for SCI subjects are not significantly different from those for normal controls (not shown). However, five (31.2%) SCI subjects had elevated FSH responses to LHRH. Six (37.5%: cases no. 1, 2, 6, 8, 9, and 14) SCI subjects (one also with elevated FSH responses) had delayed FSH responses to LHRH (Fig 3).

TSH and PRL responses to TRH for SCI subjects were not significantly different from those for normal controls. However, five (31.2%) and four (25%) SCI subjects had elevated TSH and PRL responses to TRH, respectively (Figs 4 and 5).

Six (37.5%: cases no. 1, 11, 12, 13, 14, and 15) SCI subjects had both HPO and HPT, and seven (44%: cases no. 2, 4, 5, 6, 8, 9, and 16) had HPO axis abnormalities. In total, 13 (81%) SCI subjects had at least one axis abnormal-

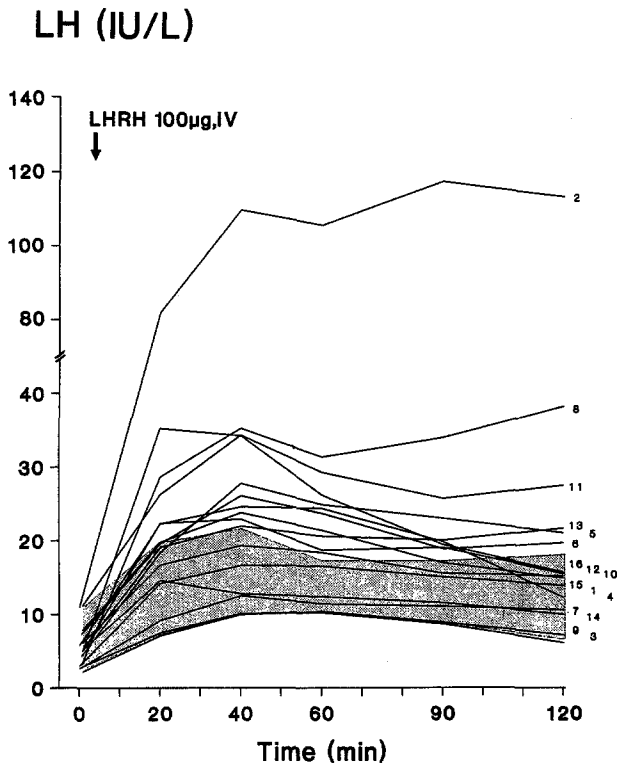

Fig 2. Enhanced LH responses to LHRH in 9 SCI females. (▨) Range of normal LH responses obtained from 15 normal controls. Numbers at right indicate the assigned number of each SCI subject.

ity. Among six SCI subjects who had both HPO and HPT abnormalities, there were five paraplegics with T3, T4, T7, T11, and T12(2) injury and one quadriplegic (case no. 13) with C6 injury.

There was no significant correlation between the peak response and the area under the curve of the LH response to LHRH and serum estradiol level.

DISCUSSION

Although our SCI subjects had enhanced hypophyseal hormone responses to releasing hormones, they were menstruating regularly. These abnormalities therefore probably had little effect on fertility. Similar findings had been reported previously. Cooper and Hoen[4] reported a 3- to 6-month interval of amenorrhea following SCI, with the eventual return of a scanty and irregular flow, in a group with paraplegia; Comarr[5] surveyed 25 SCI females and reported that 50% had no posttraumatic amenorrhea and most of the other subjects resumed their cycles within 6 months of injury. He concluded that most women with regular preinjury cycles will remain regular, and that regularity may return for those whose cycles were irregular preinjury. Also, women nearing menopause may become amenorrheic after SCI. Dysmenorrhea was not found after SCI. Durkan[6] noted an absence of menses ranging from 9 months to 10 years after SCI in seven SCI females. FSH levels were subnormal, and vaginal-smear results showed a poor estrogenic effect. Axel[7] studied 38 SCI females and found that 22 had temporary amenorrhea of an mean of 5 months' duration. Sixty-eight percent of these women had the same cycle length, and 60% had the same flow duration. Fifty-six percent reported no change in pain, 22% reported an increase, and 22% reported a decrease. Reame[8] studied 20 SCI women and noted that the level of SCI did not influence cycle length, duration of menses, or serum concentrations of gonadotropins and ovarian hormones. One of the most extensive retrospective studies was reported by Charlifue et al.[9] Among 218 SCI females, 60% reported amenorrhea postinjury; the median time until return of normal menses was just over 5 months. By 12 months, 89% were menstruating, and at 3 years postinjury, only one had not resumed menses. The majority reported little or no change in menstrual regularity, duration, or intensity.

The finding of transient amenorrhea and reestablishment of preinjury menstrual pattern in this study is consistent with previous studies.[4-9] Scantier mense were noted in nine SCI subjects, and this finding is consistent with that of Cooper and Hoen.[4] Two SCI subjects who suffered the injury in preadolescence proceeded to menarche without any delay. One subject (case no. 11) with T3 injury had prolonged amenorrhea of 1 year's duration, but the etiology was unclear. Berezin et al[10] reported on six SCI subjects who developed hyperprolactinemia, galactorrhea, and amenorrhea a mean of 10 months after injury. Excluding three

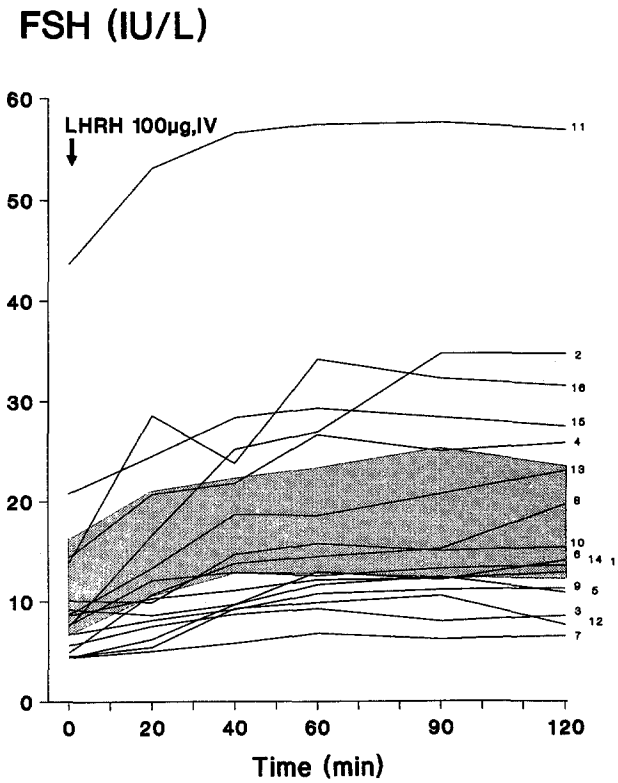

Fig 3. Enhanced FSH responses to LHRH in 5 SCI females. (▨) Ranges of normal FSH responses obtained from 15 normal controls. Six SCI females had a delayed FSH peak after LHRH injection. Case no. 2 had both enhanced and delayed FSH responses. Numbers at right indicate the assigned number of each SCI subject.

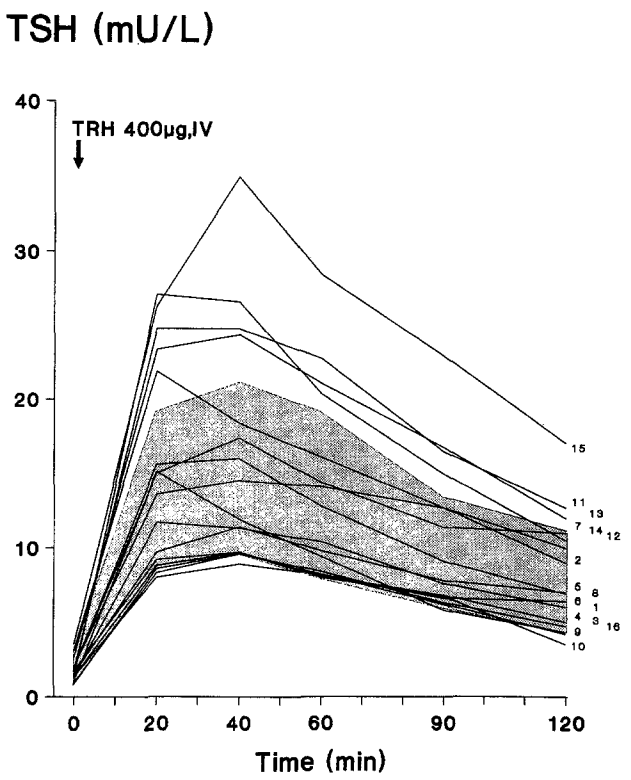

Fig 4. Enhanced TSH responses to TRH in 5 SCI females. (▨) Range of normal TSH responses obtained from 15 normal controls. Numbers at right indicate the assigned number of each SCI subject.

SCI subjects who were pregnant or who delivered within 4 months of injury, the other three subjects had no evident neurophysiologic cause of hyperprolactinemia except SCI. A central mechanism such as a concussion of the pituitary stalk and/or alteration of endorphin metabolism was suggested.[10] However, our subject did not have galactorrhea or breast engorgement during her amenorrheic period. Serum PRL level was not measured at that time. Since most studies were retrospective, underestimation of menstrual changes may have occurred, since the injuries had happened a long time before the studies.

Previously, an increased prevalence of hyperprolactinemia and elevated PRL response to TRH was found in a group of male SCI subjects.[14] In this study, there were 18.7% (three of 16) and 25% (four of 16) SCI females with hyperprolactinemia and an enhanced PRL response, respectively. Since hypophyseal hormone responses to hypothalamic releasing hormones are modulated by neurotransmitters,[16] our findings are consistent with the notion that changes of central neurotransmitters may occur after SCI.[1-4] In our recent study, a suppressed hypothalamus-pituitary-somatotrope axis was noted in a group of male SCI subjects, and reduced central dopaminergic tone was suggested.[17] Recently, alterations of central nervous system endorphin,[18] substance P,[19] serotonin,[20] dopamine,[14,21] and gamma-aminobutyric acid[22] levels after SCI were reported in animals and men.

Enhanced gonadotropin responses to LHRH have been reported in a group of SCI males.[14] Similarly, in our study, there were 62.6% (10 of 16) SCI females with an enhanced LH response to LHRH and 62.6% (10 of 16) with an enhanced or delayed FSH response to LHRH. The delayed appearance of gonadotropin peak response to LHRH is highly suggestive of a hypothalamic disorder within the HPO axis. In this study, the mean BMI of SCI subjects was not significantly different from that of normal controls. BMI is a surrogate measure of fat mass, but it is a relatively poor measure of adiposity in SCI subjects. SCI subjects were found to have greater adiposity even in the presence of a lower BMI as compared with normal controls.[22] To what extent body adiposity may influence gonadotropin responses is unclear, but our SCI subjects were menstruating regularly during the study period.

Despite the high prevalence of abnormalities of the HPO axis, the fertility rate and miscarriage rate in sexually active SCI women are the same as in the general population.[23-25] Serum estradiol is higher in the SCI group, but still within the normal range. The significance of this finding is unknown. There is also no correlation between LH response to LHRH and basal estradiol level. Enhanced LH response to LHRH was found to be correlated with sperm count in SCI males and was believed to be a mechanism to preserve fertility in SCI males.[14] The physiologic meaning of the enhanced LH response to LHRH in SCI females is unclear. The difference of the effect of SCI on male and female SCI subjects with regard to fertility may be due to the suscepti-

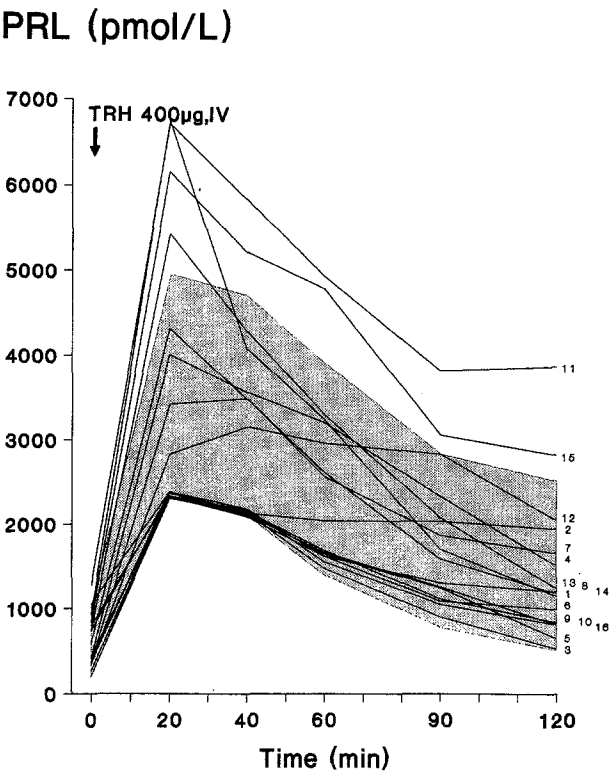

Fig 5. Enhanced PRL responses to TRH in 4 SCI females. (▨) Range of normal PRL responses obtained from 15 normal controls. Numbers at right indicate the assigned number of each SCI subject.

bility of the testes to peripheral insult. Thus, the testes are very sensitive to even a mild degree of hyperthermia,[26,27] and scrotal hyperthermia is very common in SCI males, due to prolonged sitting in wheelchairs.[28] Furthermore, prostatitis and epididymitis, which are common in SCI males, may have a deleterious effect on male sexual function.[1]

A smaller but significant percentage (25.8%) of SCI males had an enhanced TSH response to TRH.[14] Similarly, there were 31.3% (five of 16) SCI females with an enhanced TSH response to TRH in this study. All of these SCI subjects had normal thyroid function. The physiologic meaning of this finding is unclear.

In conclusion, this study demonstrated that there is a high prevalence of HPO axis abnormalities in SCI females, as previously reported in SCI males. Although the mechanism is not clear, these findings are consistent with the hypothesis that changes of central neurotransmitters may occur after SCI.

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