Growth Hormone Response to Thyrotropin Releasing Hormone in a Pellagrin

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Abstract

An abnormal hyperresponse of GH to intravenous injection of TRH in a 66-year-old female pellagra patient with typical 3'D's was reported. Diagnosis of pellagra was mainly based on her clinical course and manifestations, although serum levels of nicotinic acid and serotonin were within the normal range. Serum vitamin A and B2 levels were low. However, these findings did not exclude the diagnosis. The abnormal GH response to TRH observed in this patient was decreased at 2 months and thoroughly disappeared at 10 months after admission. GH response to arginine showed an exaggerated and sustained response on admission, decreased at 2 months and showed an almost normal pattern at 10 months after admission. TSH and prolactin response to TRH were normal throughout the clinical course. LH and FSH response to LH-RH were exaggerated, suggesting post-menopausal hypogonadism. Cortisol response to ACTH showed slightly sustained reactions at both times of the provocation. Oral glucose tolerance test revealed a slight impairment in this patient. These results suggest that pellagra is one of the disorders which exhibit an abnormal hyperresponse of GH to intravenous administration of TRH.

Although it is well known that thyrotropin releasing hormone (TRH) stimulates both thyrotropin (TSH) and prolactin (PRL) release from the anterior pituitary in normal subjects (Anderson et al., 1971; Bowers et al., 1971; Jacobs et al., 1971), it also has been reported that in some pathological conditions such as acromegaly or gigantism (Irie and Tsushima, 1972; Schalch et al., 1972; Faglia et al., 1973), primary hypothyroidism (Hamada et al., 1976), anorexia nervosa (Maeda et al., 1976), mental depression (Maeda et al., 1975), chronic liver diseases (Panerai et al., 1977), alcoholic hepatitis with cirrhosis (Zanboni and Zanboni-Muciacia, 1977), liver cancer (Kamijo et al., 1980), chronic renal failure (Gonzalez-Barcena et al., 1973; Hasegawa et al., 1975), insulin dependent diabetes mellitus (Ceda et al., 1982), and isolated TSH deficiency (Miyai et al., 1976), TRH is able to stimulate growth hormone (GH) release.

Recently, we studied a patient with pellagra whose GH release from the pituitary was abnormally stimulated by TRH administration. This paper deals with some endocrinological aspects of a pellagra patient with severe psychiatric disturbance.
Case report

A 66-year-old female was admitted to our hospital because of gait disturbance, hand tremor and dementia. She became delirious several months before her admission. She had watery diarrhea and, in the week prior to admission, she was unable to sit upright. She also had mild hypertension and mild diabetes mellitus, which had been kept well under control. However, because of poor understanding of diet control of her diseases, her eating habits had tended to be extremely unbalanced, low in proteins especially animal proteins and fats. Proteins from soybean had been taken to some extent.

On admission, height: 150 cm, weight: 29 kg. The patient had no active move-

Fig. 1. Clinical course and treatment. *Panvitan (Takeda Chemical Industries, Co.) was used. This preparation contains 15 mg of nicotinic acid per gram. The normal levels are 1) 50–300 IU/dl, 2) 7–8 µg/dl, 3) 0.56–0.78 mg/dl and 4) 0.04–0.34 µg/ml, respectively.
ment or spontaneous speech, but responded briefly to questions by opening the eyes. The tendon reflexes were symmetrically exaggerated in the legs and bilateral Babinski signs were elicited. Muscle rigidity and coarse tremor were found in the upper extremities. Dark brownish pigmentation with a distinct border was found on the dorsal aspect of the hands and feet. Erosions were found in the genital region.

The urinalysis findings were normal. The red-cell count was $390 \times 10^4/\mu l$; the white cell count was 7800/μl; hemoglobin was 12.2 g/dl. The erythrocyte sedimentation rate was 6 mm/h. Blood urine nitrogen was 16 mg/dl; blood sugar 80 mg/dl. Serum Na⁺ was 144 mEq/l; K⁺ 3.1 mEq/l; Cl⁻ 105 mEq/l. GOT was 19 U; GPT 5 U; ALP 7.5 K-K-U; LAP 90 G-B-U. Total protein was 6.3 g/dl (albumin 60.6%); total cholesterol 177 mg/dl; triglyceride 89 mg/dl. All these values were almost within the normal range.

Resin sponge T₃-uptake was 28%; thyroxine (T₄) 7.7 μg/dl; triiodothyronine (T₃) 60 ng/dl; TSH 3.9 μU/ml TBG 22 μg/ml. These values of thyroid function tests were within the normal range except that of T₃ in which the normal range was 80–180 ng/dl by our method.

The serum vitamin A concentration was under 10 IU/dl (normal 50–300), vitamin B₂ 2.4 μg/dl (normal 7–8), nicotinic acid 0.60 mg/dl (normal 0.56–0.78) and serotonin 0.19 μg/ml (normal 0.04–0.34).

Results of a CT-scan of the skull were normal. Electro-encephalogram showed a tendency to diffuse slow wave and no laterality.

A treatment with intravenous and oral administration of nicotinamide and multivitamin preparation was begun at 2 weeks after admission. The treatment and clinical course are summarized in Fig. 1.

The patient was discharged at 4 months after admission. As a multivitamin preparation, Panvitan® (Takeda Chemical Industries, Co., Osaka, Japan) was used. This preparation contains 15 mg of nicotinic acid per each gram.

### Table 1. Endocrine tests

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<th>Time in minutes</th>
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<th>15</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>180</th>
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<td>12.0</td>
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<tr>
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<td>Cortisol (μg/dl)</td>
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<td>38.0</td>
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<tr>
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<td>161</td>
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<td>30.6</td>
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M*: months after admission.
## Materials and Methods

TRH (a synthetic TRH, Hirtomin\textsuperscript{R}, Takeda Chemical Industries, Co., Osaka, Japan, 500 µg, i.v.) test, and arginine (arginine-glutamate, Arginate\textsuperscript{R}, Morishita Pharmaceutical Co., Osaka, Japan, 0.5 g arginine/kg of body weight, d.i.v. for 30 min.) loading test were performed on admission, 2 months after and 10 months after admission. ACTH (a synthetic 1-24corticotropin, Cortrosyn\textsuperscript{R}, Daiichi Pharmaceutical Co., Tokyo, Japan, 250 µg, i.v.) test, LH-RH (a synthetic LH-RH, LH-RH Tanabe\textsuperscript{R}, Tanabe Pharmaceutical Co., Osaka, Japan, 100 µg i.v.) test and 75 g oral glucose tolerance test were carried out on admission and again 2 months after admission. All these endocrine tests were performed early in the morning under the fasting condition.

Blood samples were collected according to the time schedule shown in Table 1 and the serum was frozen at $-20^\circ$C until assayed. Serum levels of hormones were determined by radioimmunoassay using the following kits: GH, cortisol and immunoreactive insulin (IRI): Eiken Labs, Tokyo, Japan; LH, FSH and PRL: Daiichi RI Labs, Tokyo, Japan; TSH: Dainabot RI Labs, Tokyo, Japan.

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**Fig. 2.**

a. (left) Effects of TRH (500 µg i.v., indicated by the arrow) on the serum GH in a pellagrin. $\bullet-\bullet$, $\circ-\circ$, $\circ-\circ-\circ$ indicate GH response to TRH on admission, 2 months after and 10 months after admission, respectively.

b. (right) Effects of arginine infusion (0.5 g/kg of body weight, for 30 minutes, indicated by the dotted rectangle) on the serum GH in a pellagrin. The hatched area indicates the normal range of the GH response in our laboratory. Other symbols are the same as Fig. 2a.
Results

GH responses to TRH are shown in Fig. 2a. GH release was markedly stimulated on admission after a single injection of synthetic TRH with a peak of 24.2 ng/ml at 30 min. This stimulation was decreased to approximately half at 2 months after admission with a peak of 12.2 ng/ml at 60 min. This abnormal hyperresponse of GH to TRH thoroughly disappeared and GH response to TRH in this patient showed a normal pattern at 10 months after admission. GH response to arginine showed exaggerated and sustained reaction on admission and diminished to almost half at 2 months and returned to a normal pattern at 10 months after admission (Fig. 2b).

As shown in Table 1, TSH and PRL responses to TRH were within the normal range throughout the clinical course of this patient. LH and FSH responses to LH-RH showed exaggerated reactions, which were usually seen in post-menopausal women, both on admission and 2 months after admission. Cortisol responses to synthetic ACTH showed a slightly sustained reaction at both times of the provocation. Glucose tolerance in a 75 g oral glucose tolerance test was slightly impaired in this patient and the insulino-genic index (Δ IRI/Δ blood sugar) values at 30 min. were 0.37 on admission and 0.14 at 2 months after admission, respectively.

Discussion

In the present paper, it is demonstrated that TRH abnormally stimulated GH release in a patient with pellagra, who showed typical signs and symptoms; diarrhea, dermatitis and psychiatric disturbance and that this abnormal hyperresponse of GH to TRH disappeared following recovery from the disease. Since GH response to arginine was enhanced, it was suggested that not only the abnormal but also the normal GH releasing mechanism was stimulated in this patient. It has been reported that TRH has no significant influence on GH release in normal subjects, but has a stimulatory influence in some pathological conditions such as cited above. Pellagra with clinically typical manifestations including psychiatric disturbance should be added to these conditions.

One may suppose that this is a case of a patient with protein calorie malnutrition and multiple vitamin deficiency who exhibited a ‘paradoxical’ GH response to TRH injection. However, total protein in the serum was almost within the normal range. This is probably related to taking soybean protein to some extent. As Dickerson and Wiryaanti (1978) mentioned, pellagra should be considered as a complex of metabolic disorders. The etiology of the disease is complicated and there is some doubt as to whether the human disease is a pure nicotinic acid deficiency. These support the finding that the abnormal hyperresponse of GH to TRH observed in this patient is due to pellagra. Although both nicotinic acid and serotonin levels in the serum were within the normal range, these normal levels did not exclude pellagra. Vitamin A and B2 levels in the serum were low. It is not possible to definitely determine whether the ‘paradoxical’ GH response in this patient is caused only by nicotinic acid rather than multiple vitamin deficiency. It would have been necessary to have treated this patient solely with nicotinamide to decide this issue clearly.

The mechanism of TRH-induced GH release in this patient is considered to be due to (1) the abnormality in the GH secreting cell with altered cellular receptors, (2) the abnormality of the GH secreting mechanism at the level of hypothalamus or at the higher level in the central nervous system. GH increase in this patient was observed 15 min. after the TRH injection, just as observed in acromegaly (Irie and
Tsushima, 1972). This seems to indicate that the GH secreting abnormality in this patient was present at the level of the pituitary. However, changes in the cellular receptors such as acromegaly is unlikely in this patient.

In mental depression and anorexia nervosa, in which impaired GH response to usual challenges (Sacher et al., 1972) and non-specific release of GH by TRH (Maeda et al., 1975; Maeda et al., 1976) are present, a disturbance of brain serotonin (Ashcroft et al., 1966; Shaw et al., 1967) and/or brain catecholamine (Barry and Klawans, 1976) metabolism has been suspected. GH responses to insulin induced hypoglycemia in the depression was significantly less than that in normal subjects, suggesting the normal GH releasing mechanism is at least not enhanced (Maeda et al., 1975).

In hepatic failure, a disturbance of brain serotonin turnover due to an increased passage of tryptophan from the plasma into the brain has been postulated (Munro et al., 1975).

In insulin dependent diabetics, it has been reported that GH paradoxically responds to TRH injection (Ceda et al., 1982). However, this response was not so obvious as the reaction of GH to TRH observed in this patient. There are some patients with non-insulin dependent diabetes, who exhibited a 'paradoxical' GH response to TRH (Ieiri et al., unpublished data). In these patients, there is a significant negative correlation between the net increase in GH after TRH and arginine injection (Ieiri et al., unpublished data).

In renal failure, a decrease in TSH and/or TRH clearance may contribute to the sustained elevation in serum GH levels after TRH administration (Gonzalez-Barcena et al., 1973). However, decreased clearance as a cause of increased GH levels after TRH in this patient was unlikely since no sign of renal failure was observed.

Estrogens may be an another cause of hyperresponse of GH to TRH. Carlson et al. (1973) reported that the basal level of GH was increased after a treatment with diethylstilbestrol in man, but GH response to TRH was not altered by the treatment. The serum estrogen level was not examined in this patient, but the estrogen level in this patient was considered to be below the normal level, since LH and FSH responses to LRH were high and exaggerated as usually seen in postmenopausal women.

In pellagrins with psychiatric disturbances, it has been postulated that serotonin activity in the brain was decreased (Raghuram and Krishnaswamy, 1975; Dickerson and Wiryanti, 1978). Since brain biogenic amines including serotonin have been considered to be closely related to the control of GH secretion (Weiner and Ganong, 1978), certain changes in serotonin or other biogenic amines may be involved in the abnormal secretory mechanism of GH in pellagra. These changes in biogenic amines might be present in this patient and caused the abnormal increase in GH in response to TRH, although no available evidence for the activity of biogenic amines in the central nervous system was obtained in this patient except the normal serum level of serotonin.

Although the reciprocal relationship between cortisol and serotonin has been reported, cortisol response to ACTH has been reported to be normal in pellagrins suggesting a normal pituitary-adrenal axis (Krishnaswamy, 1971). In this patient, the cortisol response to ACTH showed a slight sustained reaction, and failed to return to near the basal level 120 min. after the ACTH stimulation. Krishnaswamy (1971) did not show the time course of the cortisol alteration after the ACTH stimulation.

Intravenous glucose tolerance test in pellagrins has been reported to be normal (Prinsloo et al., 1971a). Prinsloo et al., (1971b) reported that adult pellagrins showed a slightly diminished oral glucose tolerance. Insulinogenic index (ΔIRI/ΔBS) at 30 min.
has been calculated on admission: 0.74; after admission: 1.14, respectively in Prinsloo's report (Prinsloo et al., 1971b). The index in this patient was 0.17 on admission and 0.14 two months after admission, showing a lower value than that in Prinsloo's report.

In summary, an abnormal hyperresponse of GH to TRH in a pellagrin was described. This is probably due to some changes in GH secreting mechanism in the hypothalamus or the higher levels in the central nervous system. These changes in the GH secreting mechanism resemble those reported previously in depression, anorexia nervosa, liver diseases and diabetes mellitus. However, it seems that the mechanism(s) responsible for the abnormal GH response to TRH observed in this patient is different at least partially from that of disorders reported previously, in which TRH is able to stimulate GH secretion.

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