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TRH Response Pattern in Adolescent Schizophrenic Males

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Summary: A marked elevation in human growth hormone (GH) following intravenous infusion of thyrotropin releasing hormone (TRH) was seen in three of seven adolescent male schizophrenic patients receiving neuroleptic drugs, and in one of five controls matched for age, sex, and developmental stage, receiving the same drugs. A positive family history for schizophrenia was noted in all three schizophrenic 'responders' but in only one of the remaining patients. The response patterns of thyroid stimulating hormone (TSH), triiodothyronine (T_3), and thyroxine (T_4) following TRH infusion were not significantly different in the two groups. No significant correlations were found between T_3, T_4, TSH, or GH response patterns and age of patient, duration of illness, medication dose or duration, weight change, or hours of sleep preceding testing.

Neuroendocrine strategies, including challenge tests such as the thyroid releasing hormone (TRH) test, are the focus of much current interest in psychiatry. The TRH test involves intravenous injection of synthetic thyrotropin releasing hormone (TRH), and sequential monitoring of serum thyroid stimulating hormone (TSH) levels, triiodothyronine (T_3), and thyroxine (T_4) levels. In psychiatric research this test has been applied to the study of adult patient groups, especially those with affective illness (Loosen & Prange, 1982; Gold *et al*, 1981); much less information is available about adolescent or prepubertal patients. However, two recent reports mention an unanticipated response of growth hormone (GH) following TRH stimulation in adolescent schizophrenic patients (Gil-Ad *et al*, 1981; Weizman *et al*, 1982). The present study was undertaken to further investigate this observation, while controlling for certain previously unattended potential confounding variables.

Method

Consecutive male admissions to two adolescent evaluation units were interviewed. Research diagnostic criteria (RDC) (Spitzer *et al*, 1975) diagnoses were assigned independently by two psychiatrists: a structured interview format (The K-Schedule for Affective Disorders and Schizophrenia Questionnaire) Puig-Antich *et al* (1978) was utilized for symptom assessment and rating. Only those patients with concordant independent diagnoses, who were actively ill, had a minimum duration of illness of six months, and who were felt to meet unequivocal RDC criteria for schizophrenia were included in the study. The identical interview procedure was used to select a small contrast group of males with a diagnosis of conduct disorder matched for age, and developmental stage. Among the schizophrenic patients, five had a diagnosis of undifferentiated subtype; the remaining were paranoid subtype. All schizophrenic patients reported predominant, mood-incongruent, bizarre delusions, or multiple, mood-incongruent auditory hallucinations, or both symptoms. Except for a history of specific reading disability in two schizophrenic subjects, there were no secondary psychiatric diagnoses. No patient met the full criteria for an affective syndrome.

Since advancing age (Martin *et al*, 1977), chronicity of illness, alcohol abuse, recent lithium exposure (Shopsin, 1970), menstrual cycle phase, diet, weight loss, hours of sleep (Green & Kane, 1982), and activing preceding examination have all been raised as potential confounding variables in the TRH test results, the current study was designed to include these restrictions. All patients were male; the age range was restricted to 14–18 years; no patient with concurrent endocrine disease, other medical illness, recent alcohol abuse, or recent lithium exposure was included in the study. All patients had normal baseline thyroid indices, GH levels, blood counts, liver enzyme, and electrolyte values; they had an absence of physical illness, fell within the normal height and weight ranges for age and were in comparable pubertal developmental stages (stage 4 or 5 based upon the Tanner Staging System). All were on a regular hospital diet, and TRH testing was performed only if there was no loss of weight in the preceding week. Six of seven schizophrenic patients, and all control patients were receiving neuroleptic drugs; they received their final dose at 10.00 p.m. on the evening preceding TRH testing. Written consent was obtained from both patient and guardian in all cases. Five schizophrenic patients were on daily oral chlorpromazine regimens; two received 400 mg, two received 600 mg, and one patient received 700 mg daily. One schizophrenic patient received haloperidol, 10 mg orally daily, and one schizophrenic patient received no drugs. In the conduct disorder group, four patients received chlorpromazine, 300 mg per day, and the

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TABLE I

Effect of TRH on T3RU, T4 (μg/dl), and TSH (μIU/ml) in schizophrenic patients and matched controls; means (ranges)

	Baseline	*Post TRH peak*	*Mean increase*
Schizophrenic patients (n = 7)			
T3 =	32% (31%–33%)	33% (31%–35%)	1% (0.4%–2%)
T4 =	7.2 (6.7–7.7)	7.5 (7.1–7.8)	0.2 (0.1–0.4)
TSH =	3.6 (3–4.2)	23.6 (19.7–27.5)	19.9 (16.5–23.3)
Controls (n = 5)			
T3 =	31% (30%–32%)	32% (31%–33%)	1% (0.2%–2%)
T4 =	7.7 (7.4–8.0)	7.8 (7.6–8.0)	0.2 (0–0.4)
TSH =	4.8 (4.3–5.3)	20.5 (18.3–22.7)	15.8 (13.4–18.3)

remaining patient received 400 mg daily. Family psychiatric profiles were drawn up from information gathered during admission interviews with family members, from obtained medical record data and, whenever possible, direct interview of the individual by a psychiatrist.

Following an overnight fast, subjects were restricted to bedrest on the morning of the TRH testing. An indwelling intravenous catheter was inserted at 8.30 a.m.; at 8.59, blood samples for baseline T_3, T_4, TSH, and GH levels were obtained; at 9.00 a.m., 500 mg TRH was administered during a 30 second infusion. This dosage was used to insure maximum stimulation. Blood samples were obtained at 15 and 30 minutes following TRH infusion for determination of T_3, T_4, TSH and GH levels. TSH and GH were measured in duplicate by a radioimmunoassay technique. Group mean calculations were performed to examine for significant group differences in these four indices at baseline, and following TRH stimulation. Individual Pearson correlation coefficients, and significance levels were calculated utilizing the magnitude of change in these indices following TRH and number of hours of sleep preceding examination, chlorpromazine equivalent medication dose, age, duration of illness, and weight change in week preceding the examination.

Results

The mean baseline GH, TSH, T_3 and T_4 levels in the adolescent schizophrenic patients did not differ significantly from those of the control group. However, three of seven schizophrenic patients showed a marked elevation of GH above baseline within the 30 minutes following TRH stimulation. The actual growth hormone increases in these three cases measured 17.8 ng/ml, 18.3 ng/ml, and 19.4 ng/ml, respectively. In contrast, in the remaining schizophrenic patients, the range of growth hormone increases after TRH infusion measured only 0.5–1.6 ng/ml and, in the control group 0.6–2.7 ng/ml.

All three patients with a high GH response (responders) had an unequivocally positive family history for schizophrenia among first degree relatives; one of four non-responder schizophrenics had a questionably positive family history. These three 'responder' patients did not otherwise differ significantly from the remaining schizophrenic patients in respect to age, medication dose or duration of illness. TSH responses among all schizophrenics, and control patients (Table I) were not significantly different. No example of the 'blunted' TSH response pattern, reported in adult patients with major depressive disorder, was seen. Post-stimulation T_3 and T_4 response patterns were not significantly different between the schizophrenic and control group, with both groups showing very slight increases in the 30 minutes following TRH (Table I). No significant correlations at the one in twenty level of significance or below were found between the magnitude of TSH, GH, T_3, and T_4 response patterns and age of patient, duration of illness, medication dose, weight gain in the week preceding test or hours of sleep preceding test.

Discussion

This pilot study demonstrates that TRH testing can be successfully performed in adolescent patients, the patients experienced no side effects, or only mild and transient autonomic symptoms during infusion, although the 500 mg TRH dose was used to insure maximum stimulation. Marked elevation of growth hormone (GH) following TRH stimulation was seen in three of seven schizophrenic patients (responders), and in no control patient. All three 'responder' schizophrenic patients had a positive family history of schizophrenia among first degree relatives: only one of the remaining patients had a positive family history. The response patterns of TSH, T_3, and T_4 were not significantly different between responders, non-responders and controls. No patient showed the 'blunted' TSH response, which has been observed in adult patients with affective illness. This pattern of marked GH elevation following TRH, with absence of TSH 'blunting' in schizophrenic adolescents agrees with two previous reports: the pattern was reported in three of six acute (Gil-Ad, 1981), and five of ten chronic (Weizman, 1982) schizophrenic adolescents. The trend toward this occurring in those with a positive family history for schizophrenia was also noted in those reports.

The design of the present study controlled for the sex, age and pubertal stage of the patient, for weight

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loss during the preceding week and for pretest level of activity. Individuals with endocrine illness, or recent exposure to lithium or alcohol were excluded. No correlations were found between magnitude of TSH, GH, T_3, or T_4 responses and duration of illness, medication dose, weight gain, or hours of sleep preceding exam. In this study drug washout periods were not feasible, therefore, TRH testing was performed while patients were receiving neuroleptic drugs. However, several factors make this an unlikely confounding variable: first, the four nonresponder schizophrenics, and all control patients also received neuroleptics, yet none showed a high growth hormone response. Further, there was a lack of significant correlations between medication dose (as expressed in chlorpromazine equivalent dose) and magnitude of GH or TSH response. A previous study in adult schizophrenics suggested no significant effect of long term neuroleptic use on response to TRH stimulation (Braddock & Blake, 1981). Lastly, in a previous report (Gil-Ad, 1981), TRH testing was performed in a small group of adolescent schizophrenics prior to exposure to neuroleptic drugs, and again after three months of neuroleptic treatment at dose ranges comparable to this study. At both points, the patients showed TSH and GH response patterns identical to those reported here.

The exact pathophysiology of the GH response to TRH stimulation in psychiatric patients is not known, although hypothalamic-limbic dysfunction is often suggested (Weizman *et al*, 1982); equally important, the specificity of these response patterns in adolescent patients is unknown. Growth hormone elevation to TRH stimulation has been reported in certain medical conditions, including acromegaly, and in adult psychiatric patients, especially in a subgroup of those with major depressive disorder (Gold *et al*, 1981).

However, other studies suggest that biological marker findings in child and adolescent patients may not parallel findings in adults (Puig-Antich *et al*, 1982). Therefore, although the results presented here are preliminary in nature, further studies utilizing neuroendocrine strategies in these younger age ranges are warranted. Replication studies, ideally performed following drug free periods, will help to determine the potential research and clinical uses of this procedure.

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