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Effect of thyroid stimulating hormone on adaptive behaviour in Down's syndrome

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ABSTRACT. Patients with Down's syndrome are particularly vulnerable to the development of both hypothyroidism and Alzheimer's disease. Both hypothyroidism and Alzheimer's disease may be associated with elevated serum concentrations of thyroid stimulating hormone. In a group of institutionalized Down's syndrome patients with normal thyroid function, global scores of ability were higher than in a group of patients with elevated thyroid stimulating hormone levels in the presence of normal T3 and T4. The actual concentrations of thyroid stimulating hormone were shown to be significantly and inversely correlated with scores of global abilities. If these findings are reproducible, the authors believe that thyroid stimulating hormone estimation may provide confirmatory evidence of clinical dementia in this group of mentally handicapped individuals.

INTRODUCTION

Alzheimer's dementia is associated with characteristic histopathological and neurochemical changes, both in the cerebral cortex and sub-cortical structures including the hypothelamus. Such neurochemical changes include reduced activities of choline acetyl transferase (Davies, 1979), noradrenaline (Yates *et al.*, 1981) and a somatostatin (Davies *et al.*, 1982). Neurotransmitters such as acetylcholine, noradrenaline and somatostatin have been shown to control the secretion of pituitary hormones (Reichlin, 1985). Therefore, it is likely that the central changes of neurotransmitters/neurochemicals in Alzheimer's disease (DAT) should be reflected in the basal secretions of pituitary hormones (Christie *et al.*, 1987).

Studies of neuroendocrinal changes in DAT have been few in number, but the majority report changes in several parameters; for example, early escape from the dexamethasone suppression test (Coppen *et al.*, 1983), raised prolactin levels (Samorajski *et al.*, 1982) and reduced sleep-related secretion of growth hormone (Davis *et al.*, 1982). However, these changes are not confined to DAT, and conflicting results have been published in other studies. Christie *et al.* (1987) have recently demonstrated selective changes in the plasma concentrations of thyroid stimulating hormone, growth hormone and oestrogen-stimulated neurophysin (ESN) that are specific to DAT and which can be related to known neurochemical deficits. They reported raised plasma concentrations of growth hormone. This was believed to result in increased growth hormone releasing factor, consequent on the reduced levels of somatostatin seen in DAT. They also found an isolated rise in plasma thyroid

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stimulating hormone values in the presence of normal T3 and T4 concentrations (even when corrected for age- and sex-related changes). They explained this change as resulting from reduced levels of somatostatin in DAT, since somatostatin is known to inhibit TSH. A significant reduction in oestrogen stimulated neurophysin has been found to be of value in discriminating between Alzheimer's disease and other forms of dementia. A combination of these neurochemical abnormalities may lead to the diagnosis of DAT with a sensitivity of 75% and specificity of 86% (Christie *et al.*, 1987). The histopathological changes of Alzheimer's disease are invariably present in subjects with Down's syndrome after the age of 40 years. Therefore, the neuroendocrinal changes seen in the non-handicapped population suffering from Alzheimer's disease may be seen in Down's syndrome subjects with DAT also, since the histopathological and neurochemical changes seen in both conditions probably share an identical aetiological basis. Few studies have been carried out to establish the neurochemical/neuroendocrinal changes in Down's syndrome patients with possible DAT. The only studies reported so far have confirmed similar changes in neurotransmitter concentrations in Down's syndrome with DAT as in the non-handicapped population (Yates *et al.*, 1983).

METHOD

The catchment population consisted of all 41 long-stay patients with a clinical diagnosis of Down's syndrome resident within facilities of the Glenfrith Unit (Mental Handicap Services), Leicester, England. These 41 individuals represent 11·4% of the total number of adults with Down's syndrome within the area served by the Leicestershire Health Authority.

Of the original 41 patients with Down's syndrome, six patients were excluded from the study since they were known carriers of hepatitis B antigen. Two patients with significant autistic traits were excluded. A further single patient refused to take part. Of the remaining 35 patients, 26 had been assessed within the preceeding 6 months by a single investigator using Part I of the American Association of Mental Deficiency's Adaptive Behaviour Scale (ABS). These 26 patients represent the study population. Patient details are summarized in Table 1.

A fasting venous blood sample was taken between 0800 and 0900 h on all 26 patients and sent for analysis of thyroid stimulating hormone (TSH), thyroxine (T4) and tri-iodothyronine (T3) levels.

Table 1 Patient details

Total population of institutionalized Down's syndrome patients	41
Exclusions: carriers of hepatitis-B	6
patient refusal	1
significant autistic traits	2
previous ABS not completed	6
Patients remaining in study	26

On the basis of medical history and laboratory standardized norms (TSH, 0·3–3·8 mU l^{-1}; T4, 54–142 nmol l^{-1}; T3, 0·8–2·5 nmol l^{-1}), patients were divided into three groups: (1) a group with normal thyroid function; (2) a group with treated hypothyroidism; and (3) a group with elevated TSH concentration in the presence of normal T4 and T3.

Subsequently, all patients with either normal thyroid function or elevated TSH levels were assessed using the Vineland Adaptive Behaviour Scales (Survey Form) by a second single investigator who was unaware of the results of the thyroid function test assays or the ABS score.

The effect of TSH level on adaptive behaviour was analysed in two ways. Firstly, scores on the ABS and the Vineland Scales were compared between the group of patients with normal thyroid function and the group with elevated TSH levels (Student's *t*-test). Secondly, correlation coefficients were obtained between TSH levels and adaptive behaviour scores on both the ABS and the Vineland Scales (Pearson product-moment correlation).

RESULTS

Eleven (42%) out of the 26 patients in the study population were shown to have normal T3, T4 and TSH levels. Ten patients (38%) were already receiving treatment for hypothyroidism and were not examined further. Five patients (19%) were found to have elevated TSH levels in the presence of normal T3 and T4. There was no significant difference in the age, sex or institutional histories between the group of Down's syndrome individuals with normal thyroid function and the group with elevated TSH levels in the presence of normal T3 and T4 (Table 2).

For patients in the group with normal thyroid function, the mean TSH level was 2·46±0·84 mU l^{-1}, whilst in the group with elevated TSH levels, the mean TSH

Table 2 Distribution of patients by age, sex and institutional history

Patient group	Number	Male	Female	Mean age (years) (S.D.)	Mean number of years institutionalised (S.D.)
Normal thyroid function	11	9	2	43·09 (±11·47) (range 22–59)	25·82 (±11·72)
Treated hypothyroidism	10	3	7	47·90 (±14·38) (range 27–76)	24·10 (±6·69)
Elevated TSH levels (normal T3 and T4)	5	4	1	47·20 (±10·19) (range 38–65)	30·60 (±8·89)

Table 3 Differences in raw and age-adjusted ABS centile scores

	ABS raw scores			ABS age-adjusted centile scores		
	Normal thyroid function group (mean±S.D.)	Elevated TSH group (mean±S.D.)	Significance (*P*)	Normal thyroid function group (mean±S.D.)	Elevated TSH group (mean±S.D.)	Significance (*P*)*
(I) Independent functioning	71·64 (±14·87)	44·20 (±16·67)	<0·01	33 (±17)	11 (±8)	<0·02
(II) Physical development	20·00 (±2·30)	17·20 (±1·83)	<0·05	38 (±25)	19 (±5)	n.s.
(III) Economic activity	2·67 (±1·92)	0·00 (±0·00)	<0·01	42 (±10)	28 (±2)	<0·02
(IV) Language development	17·27 (±4·89)	8·20 (±3·60)	<0·01	30 (±16)	9 (±5)	<0·002
(V) Numbers and time	3·00 (±2·63)	1·00 (±1·26)	n.s.	31 (±15)	18 (±8)	n.s.
(VI) Domestic activity	8·91 (±4·03)	2·20 (±2·48)	<0·01	64 (±22)	29 (±13)	<0·01
(VII) Vocational activity	4·09 (±4·06)	0·00 (±0·00)	n.s.	39 (±19)	25 (±0)	n.s.
(VIII) Self direction	12·64 (±5·25)	4·20 (±3·49)	<0·01	41 (±17)	10 (±10)	<0·005
(IX) Responsibility	3·82 (±2·25)	1·20 (±1·60)	<0·05	70 (±28)	36 (±20)	<0·005
(X) Socialization	15·00 (±4·18)	10·60 (±3·26)	n.s.	44 (±27)	16 (±20)	n.s.

*n.s.: not significant.

estimation was 6·68±2·20 mU l^{-1}. The difference between mean TSH concentrations is significant at the $P<0·001$ level (Students' t test). For the groups with elevated TSH levels, the mean T4 concentrate was 73·40±8·82 $nmol^{-1}$ and mean T3 concentrate was 1·44±0·25 $nmol^{-1}$. (The laboratory range for T4 and T3 is 54–142 nmol l^{-1} and 0·8–2·5 nmol l^{-1} respectively).

An aggregate score on the ABS was obtained by summating the score for all 10 domains of the ABS. Correlation between this aggregate ABS score and the 'Adaptive Behaviour Composite' of the Vineland Scale was statistically significant ($r=+0·86$; $t=6·309$; $P<0·001$).

Differences in ABS raw scores between the two groups are given in Table 3. On all domains, the group with elevated TSH performed less well than the group with normal thyroid function. Taking into account the differing ages of the patients studied, mean centile scores for each domain were obtained for each group using the normative data for institutionalized mentally handicapped populations as supplied in the ABS manual. Centile scores were lower for the groups of patients with elevated TSH across all 10 domains (Table 3).

The difference between the mean scores (months) obtained in the Vineland Scales

Table 4 Differences in mean scores (months) for the Vineland scales

Domain	Normal thyroid function group	Elevated TSH group	Significance (P)*
Adaptive Behaviour Composite	40·78±19·58	17·53±8·46	<0·05
Communication	32·18±19·26	12·00±6·07	<0·05
Daily living skills	54·85±22·18	27·00±13·02	<0·05
Socialization	35·36±22·00	13·60±9·24	n.s.

*n.s.: not significant.

Table 5 Correlations between ABS domains and actual (TSH) levels

Domains	r	P*
Aggregated ABS score	−0·77	<0·001
(I) Independent functioning	−0·71	<0·01
(II) Physical development	−0·38	n.s.
(III) Economic activity	−0·51	<0·05
(IV) Language development	−0·63	<0·01
(V) Number and time	−0·44	n.s.
(VI) Domestic activity	−0·63	<0·01
(VII) Vocational activity	−0·25	n.s.
(VIII) Self-direction	−0·61	<0·02
(IX) Responsibility	−0·51	<0·05
(X) Socialization	−0·42	n.s.

*n.s.: not significant.

Table 6 Correlation between Vineland scores (months) and actual TSH levels

	r	*P**
Adaptive Behaviour Composite	−0·53	<0·05
Communication domain	−0·45	n.s.
Daily living skills domain	−0·60	<0·02
Socialization domain	−0·50	<0·05

are shown in Table 4. On all domains, mean scores are lower for the group with elevated TSH than for the group with normal thyroid function.

Correlation coefficients were between the actual level of TSH, and the scores obtained from the ABS and Vineland Scales are shown in Tables 5 and 6. Six of the 10 domains of the ABS are significantly but inversely correlated with TSH level, as is the aggregated ABS score. The Adaptive Behaviour Composite and the domains of 'Daily Living Skills' and 'Socialization' of the Vineland Scales are also significantly but inversely correlated with the TSH level.

DISCUSSION

The present results show global differences in adaptive behaviour between institutionalized patients with Down's syndrome who have normal thyroid function and those patients who have elevated blood concentrations of thyroid stimulating hormone in the presence of normal T3 and T4 concentrations. Additionally, the authors have demonstrated an inverse correlation between the actual blood concentration of TSH and global abilities in the present patients, using both the Adaptive Behaviour Scale (AAMD) and the Vineland Scales.

Assessment of thyroid function and of adaptive abilities using the two scales was undertaken blindly by the raters involved. Additionally, a single rater undertook all the ABS assessments, whilst another single rater undertook all the Vineland assessments.

These results refer to small groups of patients from an institutional population. Reservations must be attached to the findings until confirmed by using a larger and more representative study population of Down's syndrome individuals.

The present results are consistent with the findings of Christie *et al.* (1987), who demonstrated that elevated TSH in the presence of normal T3 and T4 could be used as a diagnostic aid in the assessment of dementia in the normal population. These authors additionally showed that the combination of these thyroid function results, when combined with elevated levels of growth hormone and reduced oestrogen stimulated neurophysin activity, gave rise to high degrees of sensitivity and specificity in making the diagnosis of Alzheimer's disease. By this method, they were able to distinguish Alzheimer's disease from other types of dementia.

However, elevated levels of TSH in the presence of normal T3 and T4 levels are

also found in borderline hypothyroidism, where the function of a failing thyroid gland is compensated for by increased production of thyroid-stimulating hormone by the pituitary gland. There is abundant evidence that individuals with Down's syndrome are particularly vulnerable to the development of auto-immune hypothyroidism (Baxter *et al.*, 1975; Mani, 1988; Murdoch *et al.*, 1977; Korsager *et al.*, 1978; Lobo *et al.*, 1980; Hollingsworth *et al.*, 1974; Quinn, 1980; Sare *et al.*, 1978). However, it appears to the present to be unlikely that the current findings are due to the development of hypothyroidism, since it is generally believed that the deleterious effect of hypothyroidism on psychological parameters is due to the failure in the production of thyroid hormones. In the patients with elevated TSH levels, the concentration of T3 and T4 was well within normally accepted limits.

However, patients with Down's syndrome are particularly vulnerable to a presenile dementia that is indistinguishable in terms of neuropathology and neurochemistry from Alzheimer's disease. Malamud (1964) showed that, in patients with Down's syndrome who died after the age of 40 years of age, typical histopathological changes of Alzheimer's disease were present in all brains examined. This finding contrasted with a rate of only 14% in patients who were mentally handicapped as a result of other causes. Such findings were confirmed by Haberland (1969) and Whalley (1982). Recent studies on the genetics of DAT in the general population have employed DNA probes to carry out linkage analysis in familial Alzheimer's disease: they have found that the gene conferring susceptibility to Alzheimer's disease maps not only to chromosome 21 (St George-Hyslop *et al.*, 1987), but also to a region of that chromosome that codes for the amyloid protein gene (Robakis *et al.*, 1987; Tanzi *et al.*, 1987).

In spite of early clinical descriptions (Fraser & Mitchell, 1876; Rollin, 1946; Jervis 1948), criteria for diagnosing the early changes of a dementing process in individuals who are premorbidly suffering from cognitive impairment remain elusive. In individuals with Down's syndrome, there is a marked disparity between the acknowledged presence of histopathological diagnosis of Alzheimer's disease and the recognition of a dementing process.

Miniszek (1986), using the American Association on Mental Deficiency's Adaptive Behaviour Scale (ABS), as in this study, showed that it was possible to identify global differences in adaptive behaviour between 'regressed' and 'non-regressed' older subjects with Down's syndrome.

Wisniewski *et al.* (1978) described a number of significant differences between older and younger Down's syndrome patients, including alterations in personality, apathy, inactivity, changes in affect, loss of self-care skills, vocabulary and temper-tantrums. Zigman *et al.* (1987) studied individuals with Down's syndrome, comparing them with individuals with metal handicap due to other causes. He showed that significant decline in the abilities of Down's syndrome individuals occurred only after the age of 50 years.

Haxby (1989) has recently demonstrated changes in various psychological parameters in middle-aged patients with Down's syndrome which are comparable to those found in the normal population who develop Alzheimer's disease during old age.

If the present results are shown to be reproducible, TSH estimations may form a useful tool in asssisting with a diagnosis of a dementing process in individuals with Down's syndrome. Additionally, the possible aetiological significance of TSH in intellectual decline (both in Alzheimer's disease and hypothyroidism) is raised, in which TSH might be neurotoxic either directly or through an intermediate pathway common to both conditions.

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