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T_4, T_3 and rT_3 levels in serum and cerebrospinal fluid of patients with amyotrophic lateral sclerosis

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Summary. Thyronine (T_4), triiodothyronine (T_3), and reverse-triiodothyronine (rT_3) levels were evaluated in cerebrospinal fluid (CSF) and in serum of 12 patients with definite amyotrophic lateral sclerosis (ALS) by specific radioimmunoassays. Circulating microsomal and thyroglobulin antibodies were also evaluated. In all patients serum levels of T_4, T_3 and rT_3 were within normal limits. In CSF, the rT_3 levels were significantly elevated to 0.118 µg/l (mean), the T_4 levels were not significantly elevated, and the T_3 levels were below the detection limit of 0.03 µg/l. A correlation between the elevated rT_3 levels in CSF and the severity or type of ALS could not be demonstrated by this study. The antithyroid antibodies (thyroglobulin antibodies, microsomal antibodies) showed normal titres and did not suggest disturbances of thyroid autoimmunity in the patients with ALS.

Key words: Amyotrophic lateral sclerosis – Cerebrospinal fluid (CSF) – T_4, T_3, rT_3 levels – Antithyroid antibodies

Introduction

The interest in thyroid function of patients with amyotrophic lateral sclerosis (ALS) has been renewed in light of therapeutic trials with thyrotropin-releasing hormone (TRH). For this reason some basic information concerning the thyroid status in ALS is needed. There are several reports with data on the serum concentrations of total T_3, total T_4, thyroxine-binding globulin (TBG), thyroid-stimulating hormone (TSH), and microsomal and/or thyroglobulin antibody levels in ALS [2, 7, 8]. However, corresponding data from cerebrospinal fluid (CSF) in patients with ALS are lacking. Therefore, we evaluated the concentrations of thyroxine (T_4), triiodothyronine (T_3) and reverse-triiodothyronine (rT_3) in serum and CSF of 12 euthyroid patients with clinical and electrophysiological or (later) autopsy proved ALS. In addition, antithyroid antibodies (thyroglobulin antibodies) were tested to provide a marker for thyroid autoimmunity.

Among the thyroid hormones, T_3 is of substantial importance for normal thyroid function whereas rT_3 has no direct thyreomimetic effect, but is important for regulative functions, i.e. the metabolization of T_4 to T_3 by inhibition of T_3 synthesis from T_4. In generalized diseases, there is a decrease of T_3 serum concentration ("low T_3-syndrome") and simultaneously an increase of rT_3 [10]. This constellation of a low T_3-concentration and a rT_3-concentration in the upper normal limit has been suggested to be an indicator for a non-thyroidal generalized disease. Although studies in rats suggest that T_3 crosses the blood-brain barrier, the source of thyroid hormones in human CSF is not clear [17]. With regard to rT_3 there could be a correlation between CSF and serum concentrations, and it is possible that rT_3 also crosses the blood-brain barrier. On the other hand, there is clear evidence of a local production of rT_3 and T_3 from T_4 conversion in the CNS (5-deiodination of T_4), and in amyotrophic lateral sclerosis there is no disturbance of the blood-brain barrier. Significantly high CSF-rT_3 concentrations have been found in patients suffering from meningitis and cerebrovascular accident [16], and it has been suggested that 5-deiodinating activity is very high in the human brain. However, in cases with meningitis or cerebrovascular accident a disturbance of the blood-brain barrier should be considered. By contrast, elevated rT_3-levels in CSF of ALS patients suggests an effect on 5-deiodinating activity within the CNS.

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Patients and methods

Patients. Each patient gave informed consent for lumbar puncture. All patients had a clinical diagnosis of ALS established by criteria from the history and clinical examination, including electromyography and/or muscle biopsy. Meanwhile, 10 of the patients have died, and in 7 of them the diagnosis of ALS was confirmed by autopsy and neuropathological examination. A total of 12 patients (7 women and 5 men) participated in the study. The age ranged between 26 and 78 years with a mean age of 53.1 years. Clinically, 5 ALS patients were of the conventional type, 3 were of the pseudopolyneuritic type, 3 of the bulbar type, and 1 patient was of the hemiplegic type. All patients were clinically euthyroid with normal laboratory findings of thyroid function in serum, i.e. T_3, T_4, rT_3 and thyroid binding globulin (TBG) levels were normal and all ALS patients were thyroid antibody-negative. Patients with possible thyroid disease were excluded from the study. At the time of lumbar puncture for CSF examination no patients received TRH or other drugs which might affect the thyroid gland.

Methods. The serum concentrations of T_3, T_4, and rT_3 were measured by radioimmunoassay (RIA) shortly after each blood sample was obtained. The sera were tested for the presence of antithyroid antibody activities (antimicrosomal anti-

Table 1. Concentrations of T_4, T_3, and rT_3 in serum and CSF (μg/l): significant elevation of rT_3 in CSF of ALS patients ($P < 0.001$); no significant differences of T_4-concentrations in CSF; T_3 concentrations in serum are significantly higher in ALS patients, but remain within normal limits

	T_4	T_3	rT_3
Control group ($n = 56$)			
mean ± SD			
Serum	81, SD 23	1.05, SD 0.34**	0.16, SD 0.08
CSF	0.91, SD 0.26*	<0.03	0.066, SD 0.027***
ALS patients ($n = 12$)			
mean ± SD			
Serum	95.6, SD 6.6	1.43, SD 0.21**	0.19, SD 0.04
CSF	0.98, SD 0.34*	<0.03	0.118, SD 0.031***
	Not significant*	$P < 0.001$**	$P < 0.001$***

body, antithyroglobulin antibody) by commercial haemagglutination tests.

Radioimmunoassays for T_4, T_3, and reverse T_3 (rT_3) in CSF were performed in barbiturate buffer with the charcoal technique, as described for rT_3 [9]. Blocking of the binding proteins was achieved by addition of 8-aninilino-naphthalene sulphonic acid, corresponding for the RIA for rT_3 in serum [10]. Measurement of T_4, T_3, and rT_3 were performed in CSF samples of the 12 ALS patients. The samples for blood and CSF were taken within 1 h. All CSF samples were examined cytologically, and only clear, blood-free CSF was used.

The control values were taken from prior investigation in 56 healthy volunteers [4]. They are summarized in Table 1. The values given in Table 1 are mean and standard deviation.

Results

The results are summarized in Table 1. In all 12 ALS patients serum concentrations of T_4, T_3, and rT_3 were within the normal limits. The T_3 concentrations in CSF were below the detection limit (0.03 μg/l) as in the control group. T_4 in CSF was normal, except in 3 patients with a clear elevation. By contrast, the rT_3 levels were elevated in CSF, and the mean value (0.118 μg/l) was significantly increased ($P < 0.001$). There was no correlation between the elevation of rT_3 levels in CSF and the severity or duration of ALS. The microsomal and thyroglobulin antibody levels were normal in all patients, i.e. below 1 : 10 for thyroglobulin and below 1 : 100 for microsomal antibodies.

Discussion

A number of conditions are associated with ALS but do not seem to be responsible for the disease. In particular, there is no causative relationship between thyroid function and ALS. Kiessling [8] in 1982 examined thyroid function in 44 patients with ALS and found all patients to be euthyroid and thyroid antibody-negative. Reports on ALS occurring together with hyperthyroidism (Graves disease) have shown that it is a chance association [11, 13]. There are some data supporting involvement of autoimmune mechanisms in ALS [1]. Elevated microsomal and/or thyroglobulin antibody titres and elevated levels of acetylcholine receptor (ACh-R) antibodies have been reported [2, 12]. However, the reproducibility of some of these reports has been questioned, and at present the data implicating immunological abnormalities are inconclusive.

In light of the therapeutic trials with TRH the thyroid function has become of new interest. Engel et al. [3] reported low levels of TRH in the CSF of patients with ALS. These findings have led to the hypothesis that altered TRH function would play a role in the pathogenesis of ALS. By contrast, Mora et al. [15] and Jackson et al. [6] reported normal TRH levels in the CSF of ALS patients. When TRH is given to humans intravenously, serum T_4, T_3, and TSH increase, and the response to i.v. TRH are blunted [14]. Because TRH does not freely cross the blood-brain barrier, alterations of T_4 and T_3 levels in CSF might be different from those in serum. In ALS there is neither an alteration of the blood-CSF barrier nor of the blood-brain barrier. Therefore, the knowledge of T_4, T_3, and rT_3 levels in CSF of patients with ALS could be of fundamental interest. The results, presented here show normal concentrations of T_4 in CSF of euthyroid ALS patients, corresponding with normal serum concentrations. Only in 3 of 12 patients T_4 was increased in CSF, while the serum levels were normal. The T_4 levels in CSF during steady-state distributions in healthy persons can be considered 1/100 of the T_4 concentration in serum [4]. For the concentrations of T_4, T_3, and rT_3 in CSF, a limited permeability of the blood-brain barrier has been considered [5]. Assuming equal rates of permeability of T_4, T_3, and rT_3, the concentrations of T_3 and rT_3 in CSF should be below the detection limit because the serum levels of T_3 and rT_3 are remarkably lower than the T_4 levels. Thus, the T_3 concentration in CSF of ALS patients was below the detection limit of 0.03 μg/l. If the T_3 assay had been more sensitive, perhaps differences would have been found in this assay as well when the CSF was examined. Clearly higher levels were found for rT_3 with an average mean of 0.118 μg/l in CSF of ALS patients. The maximum CSF levels of rT_3 in ALS was 0.20 μg/l, but this is not a specific finding in ALS. Elevated rT_3 levels in CSF have been described in quite different disorders of the central nervous system, e.g. viral and bacterial meningitis and acute cerebrovascular disease [4, 16]. High rT_3 levels in CSF could be a sign of decreased T_3 activity within the CNS, as has been described for serum in severe generalized diseases with the "low T_3 syndrome". Amyotrophic lateral sclerosis is a devastating, progressive disorder, resulting in weakness and muscle atrophies of the extremities and bulbar musculature. Because elevated rT_3 levels have been found at

the beginning and in the terminal state of ALS, a significant correlation between the severity of ALS and rT_3 levels in CSF cannot be demonstrated by our results. A follow-up investigation with repeated measurements of thyroid hormones in CSF in the same patient and in a larger group of ALS patients could be useful to answer this question. So far, the T_4, T_3, and rT_3 levels in CSF presented here suggest that the T_4 metabolism via rT_3 may be relevant to the pathogenesis of ALS because rT_3 in CSF is known to be generated from T_4 by intracellular enzymatic T_4-5-deiodination in various regions of the brain.

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